

Hybrid Robot-Assisted Gait Training for Motor Function in Subacute Stroke: A Single-Blind Randomized Controlled Trial

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Research

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Abstract

Background:

Robot-assisted gait training (RAGT) is a practical treatment adjunctive to conventional rehabilitation to provide high-intensity repetitive training for patients with stroke. The robot models designed are usually either the end-effector type or the exoskeleton type. We developed a novel hybrid RAGT system that combines the advantages of both types.

Objective:

This randomized controlled trial (RCT) evaluated whether the novel RAGT system was beneficial and assessed long-term effects (at the 3-month follow-up) for nonambulatory patients with subacute stroke.

Methods:

This trial recruited 40 patients with subacute stroke who were equally randomized to receive conventional rehabilitation or 15 add-on RAGT sessions. We assessed lower-extremity motor function, balance, and gait performance by using the following tools: active range of motion (AROM), manual muscle test (MMT), the Fugl-Meyer Assessment (FMA) lower-extremity subscale (FMA-LE) and total (FMA-total), Postural Assessment Scale for Stroke (PASS), Berg Balance Scale (BBS), Tinetti Performance Oriented Mobility Assessment (POMA) balance and gait subscores, and the 3- and 6-m walking speed and Timed Up and Go (TUG) tests. These measurements were performed before and after the intervention and at the 3-month follow-up.

Results:

Both groups demonstrated significant within-group changes in the AROM, MMT, FMA-LE, FMA-total, PASS, BBS, POMA, TUG, and 3- and 6-m walking speeds before and after intervention and at the 3-month follow-up ($p < 0.05$). Only FMA-LE ($p = 0.014$) and total ($p = 0.002$) scores differed significantly between groups (RAGT vs. control).

Conclusion:

Although the novel hybrid RAGT was beneficial, no powerful evidence supported its effectiveness relative to the control group in substantial leg dysfunction after stroke.

Trial Registration:

The study was registered with an *International Standard Randomized Controlled Trial Number*, ISRCTN, ISRCTN15088682. Registered 16 September 2016, Retrospectively registered <https://www.isrctn.com/ISRCTN15088682>

Introduction

Stroke continues to be a leading cause of mortality and morbidity globally [[1]]. Functional disabilities caused by motor impairment are the most common problems after stroke. Approximately 60% of patients lose their walking function immediately after stroke [2], and 20% are still unable to walk independently 1 year later [3]. Assisted walking affects the quality of life, and recovery of walking ability is a critical goal of rehabilitation.

Conventional physical and occupational therapy programs have facilitated poststroke neurological and functional recovery. However, these recoveries are usually unpredictable and suboptimal, warranting new strategies to enhance poststroke recovery. Robotic-assisted gait training (RAGT) was introduced as a new treatment to improve walking recovery; this system is available in end-effector (e.g., Gait trainer GI I [4] and the G-EO system [5]) and exoskeleton types (e.g., Lokomat [6]), both of which are commonly used to provide programmable gait training during rehabilitation [7]. RAGT is ideal for use as an adjunctive treatment to traditional rehabilitation programs. Lokomat was reported to be more effective than treadmill gait training in improving walking ability, balance, and balance confidence and restoring symmetrical gait patterns with gait discrepancies in patients with chronic stroke [8]. Another type—the hybrid assistive limb robot suit—improved maximum walking speed in patients with subacute stroke compared with the control group [9]. RAGT with alternating stepping movements was noted to induce physiological muscle activations pattern and improve motricity index and Medical Research Council scores in patients with subacute stroke and healthy controls [10].

RAGT was developed based on the hypothesis that a task-specific repetitive approach may help motor learning and facilitate functional recovery[11, 12]. It was designed to provide high-intensity repetitive work and reduce manpower requirements; a patient can practice 1000 steps within 30 min, which cannot be offered by a physiotherapist [4]. Although its beneficial effects on ambulation function after stroke have been controversial, two Cochrane systematic reviews have indicated that patients with stroke who received RAGT in combination with physiotherapy in the first 3 months after stroke were more likely to achieve independent walking than those without RAGT, but the authors recommended more trials to evaluate the parameters of device type, training frequency, and duration [7, 13].

Studies have continued the recommendations of Cochrane review for different models of RAGT, different intensities of treatment protocol, and different onset phases after stroke [14–19]. Progressive reduction in assistance force control during RAGT combined with conventional physiotherapy may yield greater benefit for subacute patients with severe disabilities [16, 17, 19]. The beneficial effects of RAGT and technology-assisted gait training (TAGT) with body weight support (BWS) were inconsistent in terms of ambulation function (Functional Ambulation Category), balance (Berg Balance Scale [BBS]), and gait (speed, kinematics); however, RAGT and TAGT with BWS were not significantly superior to traditional rehabilitation [14, 15, 18].

Recently, several studies have evaluated the effects of RAGT in patients with stroke [20–25]. A Cochrane review proposed that RAGT combined with physiotherapy increased gait velocity and odds of participants being able to walk independently [21]. However, some studies have reported that the improvement was

not superior to that of conventional treatment, even when delivered as an add-on to routine rehabilitation in the subacute phase of stroke [20, 23], whereas others have demonstrated beneficial effects compared with physiotherapy alone on clinical functional outcomes and gait pattern [22, 24, 25]. Our group previously demonstrated changes in the Fugl-Meyer Assessment (FMA), Postural Assessment Scale for Stroke (PASS), BBS, and Barthel Index (BI) scores after an RAGT intervention, indicating substantial improvements in neurological status, balance, and the activities of daily living [26].

The clinical effects on different types of RAGT have been inconsistent and follow-up checks are lacking. We therefore proposed a randomized controlled trial (RCT) with a novel hybrid RAGT system and a 3-month follow-up to explore the treatment effects (lower-extremity motor function, balance, and gait) following subacute stroke.

Methods

Participants

The participants were recruited if they had a first-ever supratentorial stroke in the past 10–60 days, displayed substantial leg disabilities (e.g., a Brunnstrom Stage [BS] of I–III in the paretic leg), and were unable to stand or walk independently even with orthosis included (e.g., a functional ambulation classification score of 0–1). Participants were excluded if they had substantial spasticity over the affected leg, severe osteoarthritis, or walking disabilities before the stroke. Accordingly, 43 patients with stroke were recruited from the neurological, neurosurgical, and rehabilitation departments of Shuang Ho Hospital. All patients were randomly assigned 1:1 in a block of four to the experiment or control group after providing informed consent. The patient inclusion flowchart is presented in Fig. 2. The study protocol was approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB No. N201509027) and was explained to all participants before their participation. All participants provided written informed consent. The study was registered with an International Standard Randomized Controlled Trial Number (Trial ID: ISRCTN15088682).

Stroke characteristics

Basic participant characteristics, including stroke information and comorbidities, were obtained from a chart review. Information about lesion location and stroke type was obtained from brain computed tomography or magnetic resonance imaging (MRI). The pretreatment assessment included the National Institutes of Health Stroke Scale (NIHSS), modified Ashworth scale (MAS), modified Rankin Scale (MRS), and Brunnstrom Stage (BS).

Device

The RAGT (MRG-P100, HIWIN) is a hybrid of end-effector and exoskeleton systems, which consist of a three-point (i.e., knees, pelvis, and abdomen) support system, an electrically driven transfer system, and an intelligent monitor system (Figure.1)[26]. The three-point support system (nonsuspension system) included abdominal support and supportive kneecaps. The transfer system included a retractable ramp

plate and an electric body lifting device. The intelligent monitor system (Celeron B810 1.60 GHz 1.88 GB, 32 GB hardware, Microsoft NET Framework 4) included settings for the individual user's basic data, thigh (upper leg) and calf (lower leg) lengths, and training parameters and functions for monitoring vital signs. When standing on the machine, the patient's abdomen contacted the abdominal support from the front. The hip block from the rear prevented the patient from falling backward. The knee pad/support from the front avoided knee buckling. Without a suspension harness, which is frequently used in commercial RAGT systems, the three-point support (abdomen, hips, and knees) enables the patient to receive weight-bearing training in a more comfortable environment. The three-point support was designed to help the patient maintain an upright position during gait training. Without the suspension harness, the system has the advantage of easy mounting and dismounting, avoiding the discomfort caused by the harness suspension and hence providing intensive training in a relatively comfortable condition. The peddling cycle is driven by two coordinating footplates and secured by the exoskeleton modules. Development of the desired peddling trajectory was based on the pedal trajectory of an elliptical trainer, and the elliptical-shaped trajectory was shown to have joint kinematics similar to those of a normal walking pattern [27]. The RAGT program predetermines trajectories according to different leg lengths. With a certain leg length, the trajectory can be adjusted automatically using a desired step length, which is presented as the percentage of the maximal step length that is preset by the RAGT program. With a given leg length, the trajectory can be adjusted to different step lengths. In the case of RAGT, the step length represents the maximal anterior–posterior displacement of the foot during a peddling cycle. The peddling rate can be set from 1 to 10, corresponding to a walking speed of 0.066–0.917 km/h. The user's weight is limited to 135 kg. The system is easy to set up and saves the labor for PT-dependent procedures, which is in line with human's expectations toward a robot. All patients were able to tolerate the high intensity (e.g., 100% of maximal step length and a peddling rate of 10) through the progression of training.

Intervention

All patients participated in conventional inpatient rehabilitation programs (100 min), including physiotherapy and occupational therapy. The conventional inpatient rehabilitation programs, which involved transfer, sit to stand, static and dynamic balance training, ambulation training, and functional training, were individually tailored to the functional status of each patient. The RAGT session (30 min) was added to conventional inpatient rehabilitation sessions, which were performed five times a week for 3–4 weeks (a total of 15 sessions). Interventions included 15 daily sessions of 30 min of RAGT training with a physical therapist (PT). The 30 min of training included 5 min of warm-up, followed by 20 min of workout, and 5 min of cool-down. The intensity of the warm-up and cool-down was set to 30% of the maximal step length and a speed of 3 for all sessions. The training intensity progressed by increasing the step length by 10% and peddling rate by 1 for every subsequent session if no discomfort was reported until the maximal intensity (i.e., a ratio of 100% and peddling rate of 10) was achieved. PTs settled down on the machine (e.g., from sitting in the wheelchair to standing on the footplate of the RAGT), and typed in the anthropometric data after measuring the length of the thigh and calf; then, they input the training parameters including the training duration, step length, and speed through the intelligent monitoring system. In the control group sessions, 30 min of conventional inpatient rehabilitation was added, and the

sessions were performed five times per week for 3–4 weeks (totally 15 sessions) to match the time in the experimental group.

Outcome measurements

We evaluated lower-extremity motor function, balance, and gait performance as outcome measures. The tools used to assess these were the following: active range of motion (AROM), manual muscle test (MMT), lower-extremity subscale and total FMA (FMA-LE and FMA-total scores, respectively), PASS, BBS, Tinetti's Performance Oriented Mobility Assessment (POMA) balance and gait subscores, and 3-m and 6-m walking and Timed Up and Go (TUG) tests. These measurements were performed before and after intervention and at the 3-month follow-up.

Lower-extremity motor function was assessed using the AROM, MMT of the quadriceps muscle, and lower-extremity subscale of FMA-LE [28]. The postural control and balance were assessed using PASS [29], POMA balance subscore, and BBS [30]. The gait performance was assessed using POMA gait subscore, 3-m walk, 6-m walk, and TUG. The BI assesses the independence of ADLs [31]. The outcome measurements were performed at the pretest, posttest, and 3-month follow-up. In addition, vital signs (e.g., heart rate, blood pressure, and blood O₂ saturation) of the patients were monitored during each session. Any discomfort perceived during or after the interventions was recorded.

Blinding

An independent assessor, who was blinded to study setup, participant recruitment, and group assignment, assessed all outcomes at an offsite location. The participants were instructed to avoid mentioning anything about their intervention to the assessor or to each other.

Statistical analysis

G*Power (version 3.1.9.2, Heinrich-Heine-Universität, Düsseldorf, Germany) was used to calculate the required sample size. According to a similar study [23], to satisfy an α level of 0.05 and a power of 0.95, a minimum of 20 participants were required in each group. The participants who achieved a change in a score of 6 on FMA-LE would perceive a meaningful recovery of lower-extremity function [32]. For between-group comparisons of participant characteristics, the chi-square test was used to compare categorical variables (sex ratio, DM, stroke type, affected hemisphere), and the one-way analysis of variance (ANOVA) was used to compare continuous variables (age, onset time, NIHSS, BS, MRS, BI, and MAS). The within- and between-group differences at three time points (preintervention, postintervention, and 3-month follow-up) were assessed using repeated-measures ANOVA. The differences between the RAGT group and the control group in terms of AROM, MMT, FMA-LE, PASS, POMA balance subscore, and BBS at the three time points were analyzed using one-way ANOVA and Fisher's least significant difference (LSD) post hoc test. POMA gait subscore, 3-m walk, 6-m walk, and TUG were analyzed using Mann–Whitney U test and Wilcoxon signed-rank test for within- and between-group comparisons at two time points (postintervention and 3-month follow-up). Furthermore, we adjusted for the effects of age on postural

stability and sensory integration. The criterion for entry into the model was set at $p = 0.05$. All statistical analyses were performed using SPSS v19 (IBM, Chicago, IL, USA).

Results

Three patients with stroke were excluded because of inability to understand simple instructions ($n = 1$) and inability to comply with 15 sessions ($n = 2$). Finally, 40 participants (20 RAGT and 20 control) met the eligibility criteria. The flowchart of participant enrollment is indicated in Fig. 2. All participants were recruited from an acute stroke care setting approximately 10 days after stroke. Their clinicodemographic information is presented in Table 1. All participants were nonambulatory at recruitment, as indicated by the mobility scale and BS in the paretic leg (RAGT: 2.6 ± 1.0 , Control: 2.8 ± 0.8); thus, all patients had substantial leg paralysis and marked disabilities. The mean age ($p = 0.50$), sex ratio ($p = 0.50$), DM ($p = 0.50$), stroke type ($p = 0.60$), affected hemisphere ($p = 0.10$), onset time ($p = 0.29$), NIHSS ($p = 0.77$), BS ($p = 0.50$), MRS ($p = 0.50$), BI ($p = 0.50$), and MAS ($p = 0.50$) of the patients in the two groups (RAGT and control) were not significantly different (Table 1).

Table 1

Participant characteristics in the RAGT group ($n = 20$) and the control group ($n = 20$) at baseline

	RAGT	Control	P value
Age (years)	54.1 ± 8.6	56.5 ± 12.9	0.50
Sex (female/male)	6/14	5/15	0.50
DM (yes/no)	5/15	2/18	0.20
Type (hemorrhagic/ischemic)	14/6	14/6	0.60
Affected hemisphere (L/R)	13/7	8/12	0.10
Mean onset time (days)	25.8 ± 26.5	34.7 ± 25.5	0.29
NIHSS	12.3 ± 6.0	11.8 ± 5.7	0.77
BS	2.6 ± 1.0	2.8 ± 0.8	0.51
MRS	4.5 ± 0.5	4.5 ± 0.5	1.0
BI	29.3 ± 18.4	33.0 ± 13.8	0.47
MAS	0.2 ± 0.7	$0.4 \pm .8$	0.53
Note. Values are expressed as mean \pm SD or number. *Group differences were analyzed with either chi-square test or independent <i>t</i> test.			
Abbreviations: DM: Diabetes mellitus; NIHSS: National Institute of Health Stroke Scale; BS: Brunnstrom Stage; MMT: Manual Muscle Testing; MRS: Modified Rankin Scale; BI: Barthel Index; MAS: Modified Ashworth Scale			

ADL improved after RAGT and conventional inpatient rehabilitation. BI at preintervention (RAGT: 29.3 ± 18.4 , control: 33.0 ± 13.8), postintervention (RAGT: 47.3 ± 23.3 , control: 50.3 ± 22.8), and the 3-month follow-up (RAGT: 75.0 ± 25.4 , control: 74.5 ± 23.3) did not differ significantly ($p = 0.73$). Whether the participants continued to receive rehabilitation after discharge to maintain effects at the 3-month follow-up was recorded. We noted that 16 of 20 (80%) in the RAGT group and 17 of 20 (85%) in the control group were in the rehabilitation treatment ward at the 3-month follow-up, and the difference was not significantly different. BS in the paretic leg increased after RAGT and control (conventional inpatient rehabilitation) in both groups, but the between-group difference was not significant at any time point: preintervention (RAGT: 2.6 ± 1.0 , control: 2.8 ± 0.8), postintervention (RAGT: 3.3 ± 0.9 , control: 3.4 ± 0.7), and 3-month follow-up (RAGT: 3.9 ± 1.0 , control: 3.7 ± 0.7) ($p = 0.24$).

The scores of lower limb function, measured using MMT ($p < 0.001$), AROM ($p < 0.001$), FMA-LE ($p < 0.001$), and FMA-total ($p < 0.001$) significantly improved in both the RAGT and control groups after 15 sessions of intervention (Table 2). MMT ($p = 0.645$) and AROM ($p = 0.873$) were not significantly different between the RAGT and control groups after 15 sessions of intervention or at the 3-month follow-up. Notably, the scores of FMA-LE ($p = 0.014$) and FMA-total ($p = 0.002$) were significantly different between the RAGT and control groups before and after the 15-session intervention and at the 3-month follow-up. The higher scores of FMA-LE indicated that RAGT (preintervention: 7.0 ± 4.7 , postintervention: 12.5 ± 5.8 , follow-up: 16.5 ± 7.2) improved lower limb motor function compared with the controls (preintervention: 8.1 ± 4.9 , postintervention: 11.5 ± 6.3 , follow-up: 13.2 ± 5.9). The higher FMA-total scores indicated that RAGT (preintervention: 11.4 ± 5.4 , postintervention: 17.3 ± 6.9 , follow-up: 21.4 ± 8.1) improved lower limb motor function (including coordination function) compared with the controls (preintervention: 11.7 ± 5.7 , postintervention: 15.8 ± 7.3 , follow-up: 17.8 ± 7.0). The results of the post hoc test (LSD) revealed that the FMA-LE and FMA-total scores did not significantly differ between the RAGT and control groups. The POMA balance subscore, PASS, and BBS significantly improved in both groups. The POMA balance subscore ($p = 0.562$), PASS ($p = 0.548$), and BBS ($p = 0.394$) were not significantly different between the groups at postintervention or 3-month follow-up. The higher scores of POMA balance, PASS, and BBS improved the balance function.

Table 2

Within- and between-group comparisons of lower limb motor function and balance in the RAGT group (n = 20) and control group (n = 20) at preintervention, postintervention and 3-month follow-up

	RAGT (n = 20)				Control (n = 20)				P ^b value
	Pre	Post	3-month follow- up	P ^a value	Pre	Post	3-month follow- up	P ^a value	
MMT	1.7 ± 1.3	2.7 ± 1.5	3.5 ± 1.2	< 0.00*	1.8 ± 1.3	2.5 ± 1.4	3.3 ± 1.0	< 0.00*	0.645
AROM	25.0 ± 31.0	43.8 ± 35.6	61.8 ± 34.4	< 0.00*	26.5 ± 28.6	41.8 ± 35.1	60.3 ± 27.8	< 0.00*	0.873
FMA-LE	7.0 ± 4.7	12.5 ± 5.8	16.5 ± 7.2	< 0.00*	8.1 ± 4.9	11.5 ± 6.3	13.2 ± 5.9	< 0.00*	0.014*
FMA-total	11.4 ± 5.4	17.3 ± 6.9	21.4 ± 8.1	< 0.00*	11.7 ± 5.7	15.8 ± 7.3	17.8 ± 7.0	< 0.00*	0.002*
POMA balance subscore	3.2 ± 3.5	8.1 ± 5.6	12.1 ± 4.6	< 0.00*	3.9 ± 3.7	7.9 ± 5.8	11.6 ± 4.8	< 0.00*	0.562
PASS	17.1 ± 7.3	25.4 ± 8.3	31.2 ± 5.7	< 0.00*	17.3 ± 9.3	23.6 ± 9.6	30.5 ± 6.7	< 0.00*	0.548
BBS	8.2 ± 8.4	22.8 ± 16.7	38.6 ± 15.5	< 0.00*	8.8 ± 9.7	22.4 ± 17.8	34.5 ± 17.0	< 0.00*	0.394

Note. Values are expressed as mean ± SD. ^aWithin-group difference at preintervention and postintervention. ^bBetween-group difference at preintervention, postintervention, and 3-month follow-up. *P<0.05 by repeated-measures ANOVA for the within-group and between-group comparisons.

Abbreviations: MMT: Manual Muscle Testing; AROM: Active Range of Motion; FMA-LE: Fugl-Meyer Assessment Lower Extremity (Hip/Knee/Ankle); FMA-total: Fugl-Meyer Assessment Lower Extremity total (Hip/Knee/Ankle, coordination/speed); POMA balance subscore: Tinetti Performance Oriented Mobility Assessment Balance; PASS: postural assessment scale for stroke; BBS: Berg Balance Scale.

All participants were nonambulatory at preintervention. At postintervention, one and four patients in the RAGT and control groups, respectively, could walk independently and seven and four patients, respectively, could walk with an assistive device. At the 3-month follow-up, these numbers increased to 7 and 3 and 8 and 13 in the RAGT and control groups, respectively. However, at no time point was any between-group difference in these numbers significant. The POMA gait subscore and 3-m walking, 6-m walking, and TUG tests significantly improved in both groups from postintervention to the 3-month follow-up, except for the POMA gait subscore in the control group at 3 months (Table 3). The POMA gait subscore ($p = 0.44$), 3-m walking test ($p = 0.88$), 6-m walking test ($p = 0.72$), and TUG test ($p = 0.72$) were not significantly different between the groups at postintervention or between postintervention and the 3-

month follow-up ($p = 0.06$, 0.57, 0.74, and 0.65, respectively). The POMA gait subscore increased from postintervention to the 3-month follow-up in the RAGT group but decreased in the control group, and the between-group difference tended toward significance ($p = 0.066$). (Notably, higher POMA gait subscores indicate improved gait performance, whereas lower values of 3-m walking, 6-m walking, and TUG tests indicated improved gait velocity and agility.)

Table 3
Within- and between-group comparisons of gait performance in the RAGT and control groups at postintervention and 3-month follow-up

	RAGT			Control			P^b value	P^c value
	Post (n = 8)	3-month follow-up (n = 15)	P^a value	Post (n = 8)	3-month follow-up (n = 16)	P^a value		
POMA_Gait	7.4 ± 2.1	8.4 ± 2.8	0.02*	7.1 ± 3.1	6.6 ± 3.2	0.11	0.44	0.06
3 m (s)	17.2 ± 11.9	12.9 ± 13.7	0.01*	14.8 ± 8.0	12.7 ± 8.4	0.02*	0.88	0.57
10 m (s)	52.2 ± 36.4	41.5 ± 46.3	0.04*	41.9 ± 22.5	37.9 ± 25.9	0.02*	0.72	0.74
TUG (s)	48.7 ± 32.6	35.3 ± 27.1	0.03*	39.4 ± 19.3	37.1 ± 22.8	0.02*	0.72	0.65

Note. Values are expressed as mean ± SD. ^aWithin-group difference at 3-month follow-up. ^bBetween-group difference at postintervention. ^cBetween-group difference at 3-month follow-up. * $P < 0.05$ by Mann–Whitney U Test and Wilcoxon Signed-Rank Test for the within-group and between-group comparisons between two time points. Abbreviations: POMA_Gait: Tinetti Performance Oriented Mobility Assessment Gait; 3 m: 3-m walk test; 10 m: 10-m walk test; TUG: Timed Up and Go.

Discussion

We investigated the effectiveness of a novel 15-session RAGT intervention add-on to a conventional rehabilitation program over 3–4 weeks. To the best of our knowledge, this is the first RCT that applies a hybrid RAGT system (combined end-effectors and exoskeleton) to gait cycle training to improve gait performance. All patients completed the interventions without any major issues. Significant within-group improvements in AROM, MMT, FMA-LE, balance function, and gait performance were noted at all times points. However, significant improvements in RAGT compared with control group were noted only in FMA-LE and FMA-total scores. Notably, POMA gait subscore improved from postintervention to the 3-month follow-up in the RAGT group and regressed in the control group, and the different was almost significant. This study demonstrated that this novel RAGT was beneficial in improving gait performance in patients with severe leg paralysis after stroke, with the effects continuing for 3 months after the intervention.

According to previous studies evaluating the effect of RAGT as an add-on to conventional physiotherapy, patients with (subacute or chronic) stroke exhibited improved ambulation function, lower-extremity motor function, balance, and gait performance both immediately postintervention and at follow-up, and these improvements were superior to those conventional physiotherapy [14, 16, 17, 19, 21, 22, 24, 25, 33]. By contrast, some studies have shown that training effects in locomotion function, activities of daily living, and gait were not superior to those of conventional stroke training in patients with subacute stroke [15, 18, 20, 23]. Our RCT focused on the effectiveness of the novel hybrid RAGT system, which provides high repetitions and intensity (step length and gait velocity), in improving motor function, balance, and gait performance in patients with stroke both immediately after the 15-session intervention and at the 3-month follow-up. All participants were nonambulatory at preintervention. The number of RAGT and controls with improved ambulation function (independent or assisted walking) was approximately equally at the immediate and 3-month follow-up. The central drive of participants may be a better indicator of functional recovery because active participation is the key to successful rehabilitation. The balance and gait performance were the same in both groups; this may be because the control group performed dynamic postural control and gait adjustment more actively than passive RAGT. We also observed that the number of participants that improved to independent walking status in the RAGT group ($n = 7$) was higher than that in the control group ($n = 3$), indicating a higher opportunity to recover independent activity function through RAGT intervention at the 3-month follow-up. This was also indicated by the score change of POMA gait subscore from postintervention to 3-month follow-up between the RAGT and control groups. The balance component (PASS and BBS) and motor function component (FMA-LE) performance of the participants of previous studies was worse than that of our study participants, which may influence the extent of progress after RAGT.

The end-effector and exoskeleton RAGT types have their own advantages and disadvantages. Current end-effector products with the body suspended allow for a high degree of spatial freedom of movement of the legs, which makes the trajectory unsecured. For a stroke patient with poor control of the paretic leg (e.g., poor activation of the knee extensor or unintentional hip rotation caused by spasticity), physical assistance provided by a PT is usually required to help control the knee or adjust the leg and trunk position to secure the gait trajectory [4, 5]. By contrast, the exoskeleton of the RAGT secured the desired gait trajectory and automation provided high-intensity repetitive training in safe conditions and reduced PT manpower. However, the complex design of the current commercial exoskeleton-type systems may make it inconvenient to set up. According to our previous pilot study, this RAGT system was feasible, safe, and beneficial when applied to nonambulatory patients who have sustained significant leg dysfunction following stroke. Unlike other types of commercial RAGT products, the gait trajectory is driven by the end-effector and secured by the exoskeleton. This hybrid RAGT combines the advantages of both systems. This system was designed for use in patients who have sustained severe leg dysfunction, with the active control of the paretic leg being insufficient to facilitate conventional standing or ambulation training. This feature may have led to providing excessive support, resulting in a lower degree of freedom in biomechanics. In other words, the participants probably did not have the opportunity to challenge their postural control, thereby somewhat diminishing the training benefits.

Although the RAGT provided passive gait training, active participation by the patient can be encouraged by the PT to actively contract the leg muscles (e.g., quadriceps, iliopsoas, and gluteal muscles) during the gait cycles. During passive gait training, the proprioceptive receptors at the joints (e.g., tendons and ligaments) produced sensory input in the weight-bearing position to the cerebral sensory cortex through complex neural connections; the proprioception sense was significantly higher than that in the non-weight-bearing position [34]. Thus, RAGT can be seen as a sensory stimulation intervention that may affect neural plasticity after a stroke; intentionally enhancing motor recovery after a stroke has been tried [35–41]. Although the sensory and motor systems function differently, these two components are tightly linked. For example, sensory feedback is required to properly control body movements, especially during tasks requiring proficiency and dexterity. Moreover, somatosensory deficits can influence motor learning, with worse motor recovery occurring in those with more severe sensory loss following stroke [42, 43]. Animal and human studies have shown that sensory input may be connected to brain plasticity and affect the corticomotor excitability of the target area [35, 36, 40, 44–47]. Transcranial magnetic stimulation studies have shown that the excitability of the motor cortex increased by applying sensory electrical stimulation to the corresponding body region on the contralateral side, or reduced by deprival of sensory inputs from the contralateral extremity [36, 38, 45, 48]. With respect to proprioceptive modalities, both functional MRI and transcranial magnetic stimulation studies have shown that sessions of continuous passive motion of a joint affect cortical excitability [39, 49]. These neurophysiological findings encourage further clinical trials to explore the clinical effects of RAGT as a proprioceptive intervention on functional performance. VR-augmented RAGT resulted in high acceptability and motivation, reduced drop-out rate, and extended training time compared with standard RAGT [50].

Study limitations

First, the research design and RAGT in this study were rigorous when electromyography of the bilateral lower extremity was not recordable. However, we proposed that peddling cycling training may enhance the proprioception input of the lower extremity, but not only muscle unit firing. Second, the lack of positive results in this study did not support the effectiveness of the RAGT, but several issues warrant mentioning. For example, the performance of participants in the balance component (PASS and BBS) and motor function component (FMA-LE) should include more severe deficits, which may influence the extent of progress after RAGT. Moreover, the selection criteria of patients with stroke (e.g., patients with subacute stroke with severe functional impairments) should be carefully considered for RAGT treatment. Third, other essential technical issues and doses should be considered in future studies.

Implications for clinical practice

This study investigated the effectiveness of a novel hybrid RAGT system aimed as an add-on to a routine inpatient rehabilitation program to improve lower-extremity motor function, balance, and gait following subacute stroke. Whether this system helps to improve the neuromotor recovery of the paretic leg requires further evaluation. This study demonstrated that RAGT is suitable and beneficial for patients with subacute stroke and substantial leg dysfunction.

Implications for research

This single-blind RCT evaluated the clinical effectiveness of a novel hybrid RAGT for patients with stroke. We found that the central drive was difficult to quantify, so future studies can measure muscle activation and energy expenditure during RAGT as a proxy of training intensity. Although our results were not very satisfactory, our findings, including the dose and technical issues, can be valuable for future studies. However, after RAGT is proven as a practical treatment solution, our results may encourage future RCTs to explore the effectiveness of RAGT combined with brain stimulation or VR augmentation.

Conclusions

This study demonstrated that the novel hybrid RAGT add-on inpatient rehabilitation was not superior to conventional intervention immediately and at the 3-month follow-up after subacute stroke. However, we observed some indication of a beneficial effect (FMA-LE scores) of RAGT on lower-extremity motor function.

Abbreviations

Robot-assisted gait training (RAGT); Randomized Controlled Trial (RCT); Active Range Of Motion (AROM); Manual Muscle Test (MMT); Fugl-Meyer Assessment (FMA) Lower-Extremity subscale (FMA-LE); Postural Assessment Scale for Stroke (PASS); Berg Balance Scale (BBS); Tinetti Performance Oriented Mobility Assessment (POMA); Timed Up and Go (TUG); Technology-Assisted Gait Training (TAGT); Postural Assessment Scale for Stroke (PASS); Barthel Index (BI); Berg Balance Scale (BBS); ANalysis Of Variance Analysis (ANOVA)

Declarations

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Authors' contributions

YNL, SWH and LFL contributed to the idea for research or article/hypothesis generation and planning the methods to generate hypothesis. HCC, YNL, LFL and YCK contributed to the supervision and responsibility for the organization and course of the project and manuscript preparation. HCC, YNL and LFL contributed to the supplying financial resources, equipment, space, and personnel vital to the project. YCK, HCC, SWH and LFL contributed to the responsibility for biological materials, reagents, and referred patients. YCK, LFL and WSJ contributed to the responsibility for conducting experiments, managing patients, organizing, and reporting data. YCK, LFL and WSJ contributed to the responsibility for

presentation and logical explanation of results. YNL, SWH and LFL contributed to the responsibility for creation of the entire or a substantial part of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was conducted at Taipei Medical University Hospital, and the study protocol was reviewed and approved by the Joint Institutional Review Board of Taipei Medical University (approval number: TMU-JIRB N201509027). The potential risks and benefits of participation in this study were explained to each participant in advance. All participants provided signed informed consent before participation.

Consent for publication

All participants provided signed informed consent for the publication of this study.

Conflicts of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Figures

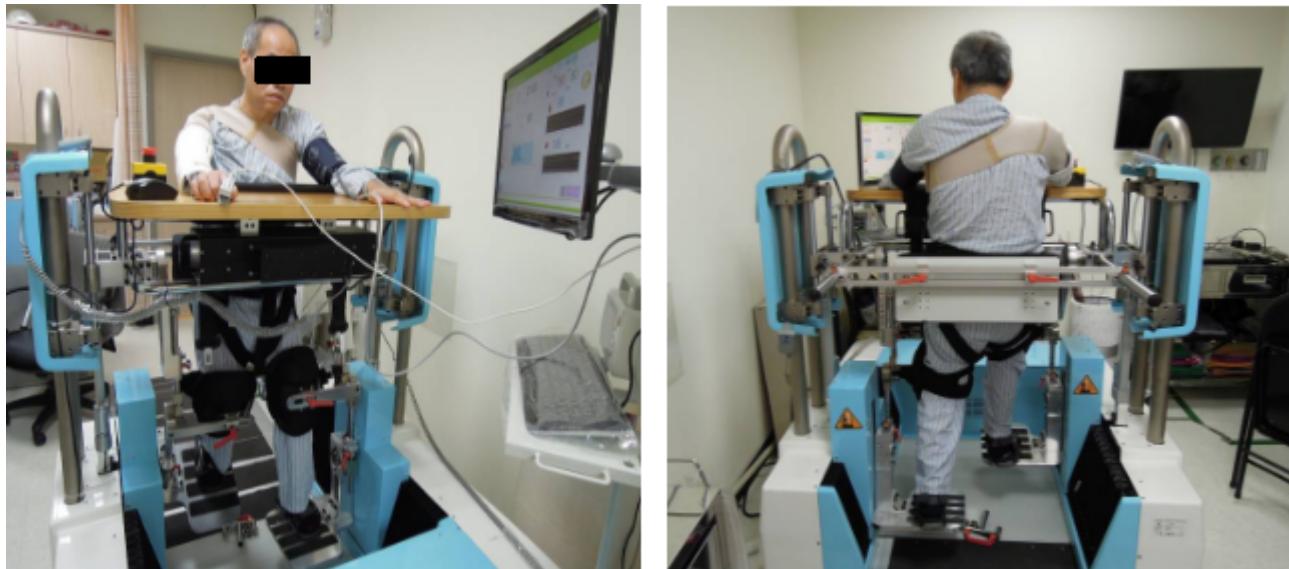


Figure 1

Photographs of frontal and back views of actual use of the Robot Assisted Gait Training (RAGT).

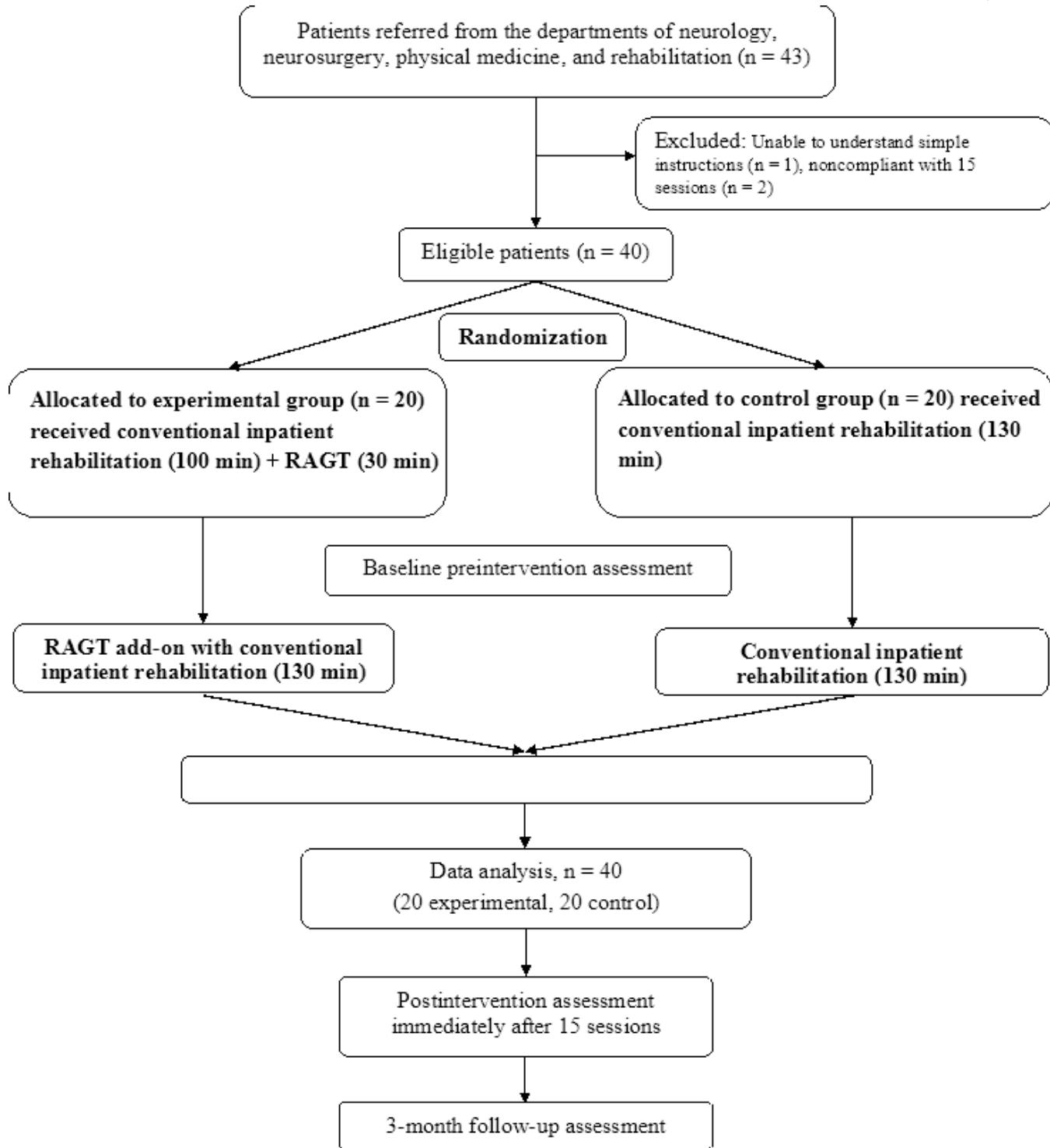


Figure 2

Flowchart depicting patient enrollment