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Exoskeleton-assisted upper limb rehabilitation after stroke: a randomized controlled trial

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ABSTRACT

Objectives: The upper-limb exoskeleton training program which is repetetive and task-specific therapy can improve motor functions in patients with stroke. To compare the effect of an upper-limb exoskeleton training program with Bobath concept on upper limb motor functions in individuals with chronic stroke.

Methods: Participants were randomly assigned to exoskeleton group (EG, $n = 12$) or to Bobath group (BG, $n = 12$). Interventions were matched in terms of session duration and total number of sessions and performed 2 times per week for 6-weeks. Primary outcome was Fugl-Meyer-Upper Extremity (FMA-UE). Secondary outcomes were Modified Ashworth Scale (elbow and wrist flexor muscles), Motor Activity Log-30 which is consist of two parts as an amount of use (AOU) and quality of movement (QOM), and The Nottingham Extended Activities of Daily Living (NEADL) index.

Results: After 12-sessions of training, the mean (SD) FMA-UE score increased by 5.7 (2.9) in the EG, and 1.9 (1.5) points in the BG ($p < .05$). In total, 40% of participants (5/12) demonstrated a clinically meaningful improvement (≥5.25 points) in the FM-UE, while none of the participants reached MCID score in the bobath group. Changes in the AOU, QOM, and NEADL were significantly larger in the EG compared to BG ($p < .05$). 7/12 (58.33%) of participants for AOU and 5/12 (42%) of participants for QOM in the EG showed that clinically meaningful change. 5/12 of participants (42%) in the EG demonstrated ≥4.9-point increase in NEADL score.

Discussion: High-intensity repetitive arm and hand exercises with an exoskeleton device was safe and feasible. Exoskeleton-assisted training demonstrated significant benefits in improving upper limb functions and quality of life in individuals after stroke.

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Stroke rehabilitation; upper extremity; exoskeleton; Bobath; motor function

Introduction

Stroke is the second leading cause of death and long-term adult physical disability, with an incidence of 25.7 million people worldwide [1,2]. Recovery after stroke is often incomplete leaving more than two-third of survivors with moderate to severe upper extremity motor impairment [3]. Abnormal synergies, increased muscle tonus, loss of coordination, and muscle weakness [4] are commonly manifested after stroke and negatively linked with performance in daily activities [5,6] and quality of life [7].

Treatment dosage is critical in attaining better functional outcomes [8]. High-intensity, repetitive movement practices via robotic-assisted therapy have shown to be promising adjunct modalities to standard rehabilitation [9–11] A 2018 Cochrane review (45 randomized controlled trials, 1619 participants) reported that electromechanical and robot-assisted arm training may help to improve arm functions, arm muscle strength, and activities of daily living (ADLs) [12]. Similarly, in a recent review (41 randomized controlled trials, 1916 stroke patients), when compared to dose-matched conventional therapy, robot-assisted training has shown better outcomes in recovery of arm impairment [13]. However, when comparing the robot-assisted training with conventional training, there are several factors that should be considered for interpreting variations across studies e.g. variations in robotic devices, content of conventional therapy, active training time, total treatment dosage as well as variations in stroke size, location, time since injury, and baseline impairment level. These factors are considerably limiting generalization of outcomes and reproducibility of protocols across rehabilitation clinics. Especially, the techniques in conventional therapy protocols can highly vary and range from specific neurodevelopmental approaches to compensatory training protocols with limited focus on functional movement training. In this regard, Bobath concept based on neurodevelopmental principles is standardized method in stroke rehabilitation and commonly used in clinical practices [14].

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In this study, we hypothesized that exoskeleton-assisted training might have an effect on the improvement of upper extremity motor functions in patients with chronic stroke. To test this hypothesis, we used exoskeleton-assisted arm training to evaluate the effectiveness and compare it with the Bobath concept, standardized for this study, in the recovery of upper limb motor functions in chronic stroke survivors.

Material and methods

Participants

This was a single-center, prospective, randomized controlled study. Thirty hemiparetic chronic stroke subjects were recruited between January and July 2019 from an outpatient rehabilitation clinic. Participants were enrolled if they had (a) diagnosis of ischemic or hemorrhagic stroke confirmed by MRI and/or CT; (b) aged between 18 and 85; (c) scored <3 points in Modified Ashworth Scale (MAS) for select upper extremity muscles; (d) at least 6-month post-stroke. Participants were excluded if they presented (a) history of uncontrolled cardiovascular co-morbidities (severe hypertension, coronary artery disease); (b) cognitive impairment that will interfere with following training instructions (Mini Mental State Examination <24); (c) concurrent orthopedic and neurologic diseases that may affect upper extremity movement; (d) other behavioral problems that will interfere with study participation.

Gpower 3.1 software was used while calculating the sample size of the study. When the alpha error was calculated as 0.05 and the power of the study as 80%, it was determined that at least 18 patients should be included totally in this study. The study of Liao et al. [15] was referenced to calculate the sample size.

Thirty patients (16 male, 14 female) were randomly assigned by using an envelope randomization technique to the exoskeleton group (EG; $n = 15$; 9 male, 6 female) and to the Bobath group (BG; $n = 15$; 7 male, 8 female).

All participants signed an informed consent that was approved by the Clinical Research Ethics Committee of Marmara University Faculty of Medicine (approval number 09.2019.146), Istanbul, Turkey. This trial was registered in ClinicalTrials.gov with NCT04353622 registration number.

Exoskeleton training

Exoskeleton-assisted training consisted of active and active-resistive movements with the ExoRehab X device (HoustonBionics, Inc. CA, USA). The device's structure allowed to isolate movements to single-joint while all other joints were locked. In total, four video games were used to practice elbow flexion/extension, forearm pronation/supination, wrist ulnar/radial deviation, and wrist flexion/extension. The cognitive load of the games was minimal, which allowed participants easily focus on the movement practice. While participants moved their joints to play the games, the sensors on each joint simultaneously recorded movement and provided a final report/feedback on the number of successful hits, time spent on each movement, and maximum range of motion achieved per joint.

During training, participants were comfortably seated in a chair with back support, and adjustable straps were used to minimize compensatory trunk movements. The height of the exoskeleton was adjusted so that both shoulder heights were symmetrical and the elbow, wrist anatomical joints were aligned with the mechanical joints (Figure 1). Three different resistance modules were used to adjust level of difficulty in a specific movement. These modules were designed to create resistance proportional to the speed of the movement. Participants actively trained for 40–60 min each day, 2 days per week, for 6 weeks and on average performed 1800–2000 movements.

Bobath training

The Bobath training group received neurodevelopmental exercises based on Bobath concept. The aim of this concept is to regain motor control and function of the hemiparetic side after stroke without promoting compensation [16].

The exercises were bilateral upper extremity movement (performing functional movements with both hands such as cleaning the desk with a towel, water-drinking), external rotation of the arm in horizontal abduction, weight transfer to affected arm, shoulder mobilization (with push-pull and external rotation), arm control training against antigravity. Additionally, hand and arm functions that include movements of scapular protraction, shoulder flexion, elbow and wrist extension, finger opposition and extension were trained with and without objects (cups, balls, boxes, sticks) for ~15 min.

The training was delivered by a senior physical therapist who had minimum of 5 years of experience using Bobath techniques for stroke rehabilitation.

On average 20 repetitions were practiced per movement, repeated in three sets. Total number of repetitions in a given session was about 300 movements. Treatment sessions were scheduled on non-consecutive days and performed 40–60 min each session, 2 times per week over 6 weeks.

Outcome measures

The primary outcome measure was Fugl-Meyer Assessment-Upper Extremity (FMA-UE) motor

Figure 1. Applicationof exoskeleton training with the ExoRehab X device (HoustonBionics,Inc. CA, USA).

score. The FMA-UE is an impairment-based measurement of upper extremity movements. The 33 items in the subscale asses the movements, reflexes and coordination of the shoulder, elbow, forearm, wrist and hand. Each item is rated between 0 and 2 (total score ranges 0–66), with a higher score representing better performance [17]. A difference of minimum 5.25 points change in FMA-UE was considered as clinically important [18].

Secondary outcome measures were MAS, motor activity log (MAL) and the Nottingham Extended Activities of Daily Living (NEADL). The MAS allows for quantification of spasticity from passive muscle stretching. Elbow and wrist flexor muscles were graded on a scale from 0 to 4, where a score of 0 indicates normal muscle tone and a score of 4 indicates rigidity of the limb joint in flexion or extension [19]. One-point change was indicated clinically meaningful according to expert opinion; because no minimal clinically important difference (MCID) for MAS was determined in the literature [20].

The Motor Activity Log-30 (MAL-30) is a self-reported measure of upper extremity use. Thirty questions are designed to quantify the amount of use (AOU) and quality of movement (QOM) of paretic arm during everyday tasks. The score ranges from 0 to 5 with higher scores indicating higher engagement in daily activities and better movement performance [21]. A change of at least 0.5 on the MAL scale before and after treatment was considered clinically meaningful [22].

The NEADL was used to assess disability in ADLs. It is composed of 22 activities, subdivided into four subscales: mobility, kitchen, domestic, and leisure activity [23]. In each item, there are four answer options ranging from 0 to 3 (0 = not at all, 1 = with help, 2 = on my own with difficulty, 3 = on my own). The total score range is between 0 and 66. Higher scores indicate higher level of independence in performing daily activities. A 4.9-point change was indicated clinically meaningful [24].

All assessments were performed by a blinded assessor at baseline before randomization and at after last treatment.

Data analyses

SPSS version 23.0 statistics program was used to analyze the data obtained from the study. The suitability of the data for normal distribution was evaluated with the Shapiro–Wilk test. To assess the homogeneity of the two groups, we used the Mann–Whitney *U* test for independents samples and Fisher's exact test for the categorical variable. Independent samples *T*-test for variables with normal distribution and Mann–Whitney *U* test for non-normally distributed variables were used to compare the treatment effect between the EG and BG. To analyyze the effect of treatment types separately, we used the paired samples *T*-test for

variables with normal distribution and Wilcoxon test for non-normally distributed variables. The significance level was determined as $p < 0.05$.

Results

Of the 30 patients randomized, 6 (3 in EG, 3 in BG) dropped out of the study. Two patients experienced new medical problems during the treatment period; one patient moved to another city in EG. One patient had transportation problems, and the other two patients had familial/companion problems in BG. The study was completed with 24 patients between January and July 2019 (Figure 2). Groups were balanced for sex, age, type of stroke, time since stoke onset, and baseline arm function. Demographics and key characteristics of participants are presented in Table 1.

After 6 week-training, arm impairment as measured with FMA-UE improved significantly in both groups (EG: $p = 0.001$, BG: $p = 0.001$). The mean ± SD change in the primary outcome measure was 5.7 ± 2.9 in the exoskeleton-assisted training group compared to 1.9 ± 1.5 in the bobath group. When groups were compared the change in the EG was significantly higher compared to BG ($p = 0.001$), (Table 2). In

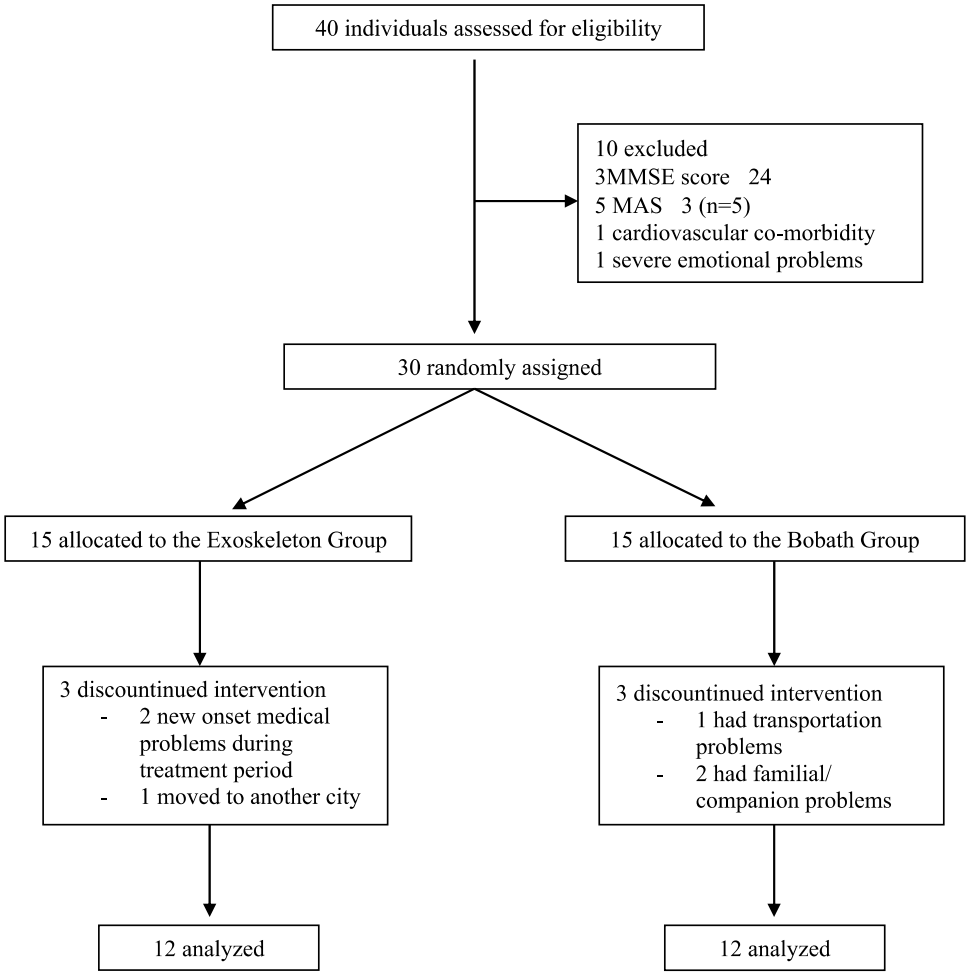

Figure 2. CONSORT diagram of study enrollment.

Table 1. Demographics and baseline functions of participants in both group.

Characteristics	Exoskeleton group (n = 12)	Bobath group (n = 12)	p Value
Age (years)	57.3 (12.1)	66.7 (10.5)	0.053
Male, *n* (%)	9 (75)	5 (42)	0.214
BMI (kg/m^2)	27.3 (5.1)	25.8 (2.6)	0.488
Time after stroke (years)	3.9 (3.0)	4.8 (4.0)	0.579
Stroke-affected arm, *n* (%)			0,400
Right	3 (25)	6 (50)	
Left	9 (75)	6 (50)	
Stroke type, *n* (%)			1,000
Ischemic	11 (91)	10 (83)	
Hemorrhagic	1 (9)	2 (17)	
MMSE	25.4 (2.6)	26.08 (2.6)	0.543

Data presented as mean (standard deviation) unless otherwise indicated. EG: exoskeleton group; BG: Bobath group; SD: standard deviation; BMI: body mass index; MMSE: Mini Mental State Examination; *$p < 0.05$.

Table 2. Clinical outcome measures.

	Exoskeleton group				Bobath group				
	Pre-treatment mean (SD)	Post-treatment mean (SD)	Change (Δ) mean (SD)	Within group *p*	Pre-treatment mean (SD)	Post-treatment mean (SD)	Change (Δ) mean (SD)	Within group *p*	Between group *p*
FMA-UE	27.8 (9.1)	33.5 (9.1)	5.7 (2.9)	0.001*	31.7 (14.9)	33.6 (14.4)	1.9 (1.5)	0.001*	0.001*
NEADL	31.8 (13.3) Med (%25; %75)	38.3 (12.6) Med (%25; %75)	6.5 (6.2) Med (%25; %75)	0.004*	27.4 (18.7) Med (%25; %75)	28.8 (18.9) Med (%25; %75)	1.4 (0.9) Med (%25; %75)	0.001*	0.017*
MAS									
Elbow	2 (1; 2)	1 (1; 1)	1 (1; 0)	0.008*	2 (1; 2)	1 (1; 1.75)	0 (1; 0)	0.046*	0.229
Wrist	2 (1; 2)	1 (1; 2)	0 (1; 0)	0.046*	1 (1; 2)	1 (0.25; 1)	0 (0.75; 0)	0.083	0.660
MAL-30									
AOU	1.13 (0.7; 1.8)	1.69 (1.2; 2.7)	0.56 (0.3;0.7)	0.003*	1.02 (0.4; 2.8)	1.25 (0.6; 3.0)	0.18 (0.1; 0,2)	0.002*	0.002*
QOM	1.07 (0.6; 1.9)	1.46 (1.2; 2.6)	0.43 (0.9;0.9)	0.002*	1.17 (0.4; 3.0)	1.40 (0.5; 3.2)	0.16 (0.1; 0,2)	0.003*	0.001*

MAS: Modified Ashworth Scale; FMA-UE: Fugl-Meyer Assessment Upper Extremity; MAL-30: Motor Activity Log-30; AOU: amount of use; QOM: quality of movement; NEADL: Nottingham Extended Activities of Daily Living; *$p < 0.05$.

total, 40% of participants (5/12) demonstrated a clinically meaningful improvement (≥5.25 points) in the FM-UE, while none of the participants reached MCID score in the Bobath group.

The changes in primary and secondary outcomes post-treatment are shown in Table 2.

The MAS scores demonstrated significant decrease in elbow flexors in both groups (EG: $p = 0.008$, BG: $p = 0.046$), and in wrist flexors for only the EG (0.046). Group comparison did not reveal significant difference (Elbow $p = 0.229$, wrist $p = 0.660$) (Table 2).

Here, 9/12 (75%) participants in the EG demonstrated 1 point or more decrease in elbow, and 5/12 (42%) in the wrist MAS score. On the other hand, 5/12 of participants (42%) in the BG demonstrated ≥ 1-point decrease in elbow, and 3/12 (25%) in the wrist MAS score.

The MAL subscales AOU and QOM demonstrated significant improvement in both groups (AOU, EG: *p*

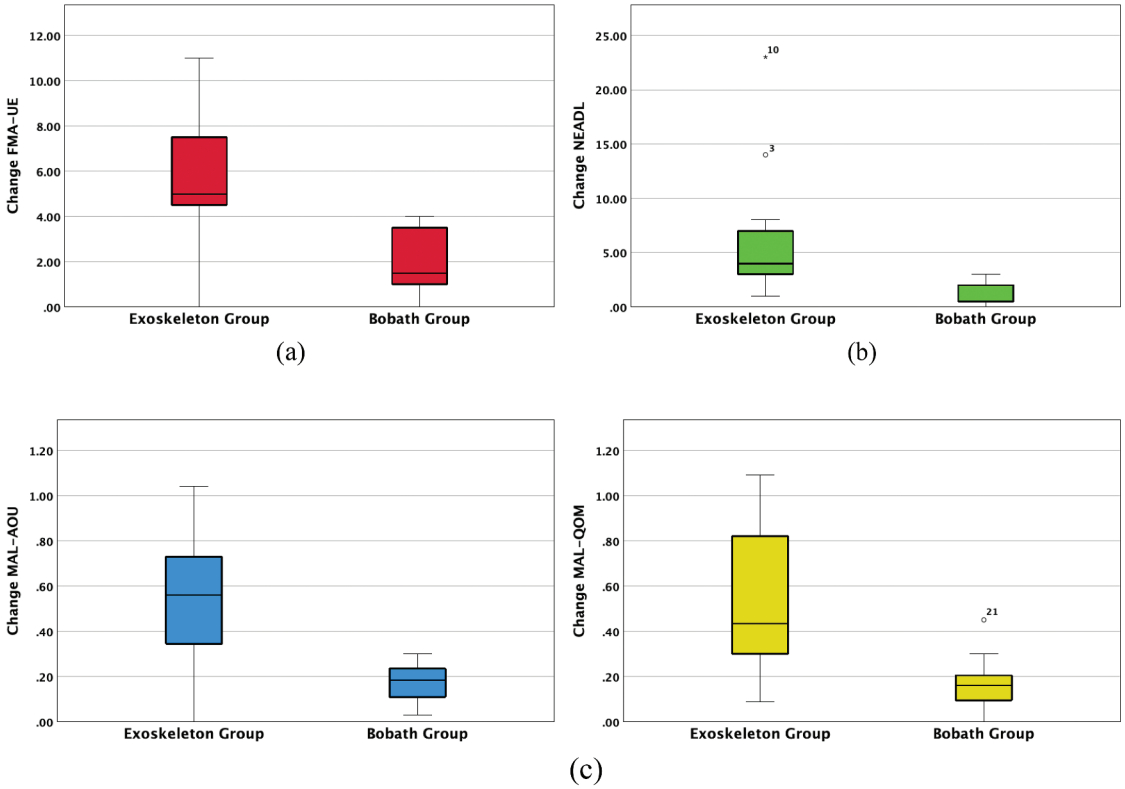

Figure 3. Fugl-Meyer Assessment-Upper Extremity (FMA-UE; mean ± SD), motor activity log-amount of use (MAL-AOU; mean±SD), and motor activity log-quality of movement (MAL-QOM; mean ± SD), Nottingham Extented Activities of Daily Living (NEADL; mean ± SD). After 6 week training: (a) changes in FMA-UE score are 5.7 (2.9) in exoskeleton group (EG) and 1.9 (1.5) in bobath group (BG); (b) changes in NEADL score are 6.5 (6.2) in EG and 1.4 (0.9) in BG; (c) changes in MAL-AOU score are 0.5 (0.3) in EG and 0.2 (0.8) in BG, changes in MAL-QOM score are 0.5 (0.3) in EG and 0.2 (0.1) in BG.

= 0.003, BG: $p = 0.002$; and QOM, EG: $p = 0.002$, BG $p = 0.003$). When groups were compared, change in both AOU and QOM were significantly higher in the EG (AOU: $p = 0.002$; for QOM: $p = 0.001$) (Table 2, Figure 3). Clinically meaningful change (0.5 MCID) was observed in 7/12 (58.33%) of participants for AOU and 5/12 (42%) of participants for QOM in the EG, while MCID change was not observed in the BG.

Similarly, significant group difference was identified on NEADL. The EG had greater increase in NEADL score (6.5 ± 6.2) compared with the BG (1.4 ± 0.9); $p = 0.017$. 5/12 of participants (42%) in the EG demonstrated ≥4.9-point increase in NEADL score.

There was no adverse event related to the use of exoskeleton device.

Discussion

Results of this study demonstrate that both exoskeleton-assisted therapy and Bobath therapy provide improvement in motor functions and quality of life in chronic stroke. When compared with the BG, participants in the exoskeleton-assisted therapy group demonstrated better outcomes in motor function and performance in daily activities.

In addition, high-intensity repetitive arm and hand exercises with an exoskeleton device was safe and feasible. There was no device related adverse events. Participants in both groups successfully completed all treatment and assessment sessions.

Our FMA-UE findings showed that participants in both groups had treatment-related improvements in their motor functions. However, the number of participants exceeding MCID was much higher in the group trained with exoskeleton than the conventional treatment (5/12 versus 0/12) with mean FMA-UE score gains of 5.7 points in the EG, exceeding 5.25-point of MCID for FMA-UE in chronic stroke [18]. Our observation is consistent with previous randomized controlled studies, systematic reviews and meta-analysis that has shown higher dose of therapy produces overall larger improvement in motor functions [10,25–28].

The optimal dose for post stroke arm rehabilitation has not been established. Higher doses of movement practice are linked to better outcomes in motor performance [29]. The amount of practice patients receiving during a conventional upper limb task-specific therapy session, however, is significantly lower (~32 repetitions), which may not be adequate to facilitate neuroplastic changes according to previous animal and human plasticity studies [30]. On the other hand, with robotic-assisted therapy protocols hundreds of arm movements per session are easily achievable, which totals to over several thousands of repetitions over the course of whole therapy program [15,31,32]. Participants in the EG practiced on average 1900 movements while participants in the BG performed on average 300 movements per session.

In addition to massed motor practice, participants in the EG had a variety of task choices via video games compared to a more single task exercise in the BG. Studies have shown that video games can be more engaging and motivating to complete a set of exercises and produce higher number of repetitions than conventional exercise therapy [33] and provide higher adherence to therapy [34].

How robotic-assisted training affects muscle tone is still controversial. While conventional therapy inherently incorporates physical contact between the therapist and limb muscle and hence therapist carefully sets the movement pace, this immediate feedforward control with most exoskeleton devices is not available. Therefore, the type of device, the type of movement being exercised, and the pace of each movement in each treatment protocol may contribute to controversial results on muscle tone [10,35]. In our study, patients in both EG and BG demonstrated significant reduction in tone, with higher reduction in the elbow for EG. %75 of the participants in the EG demonstrated ≥1 point decrease in elbow. Our findings agree with previous studies that have shown similar effects on muscle tone with robotic-assisted training [36,37]. Despite the lack of touch for immediate muscle feedback in the EG, a therapist assessed muscle tone before each training session and adjusted the range of motion and speed for each game accordingly. On the other hand, MAS is very tester-dependent. Despite great efforts in standardizing the testing protocol and minimizing inter and intra-rater variations, several other factors such as positioning of the limb during testing, total time to passively move the joint within available range, and finally individual differences in forces applied by the tester should be carefully considered when comparing different study results [38]. In the current study, the MAS was applied by the same therapists and a standardized protocol was followed to avoid external factors as mentioned above.

The improvement in motor function skills is likely associated with an increase in the amount of upper extremity use. Although both groups increased the frequency of arm use in everyday activities and demonstrated improvement in movement quality, exoskeleton training produced a better outcome when compared to Bobath training. The latter is especially noteworthy, since improvement in movement smoothness a prominent metric of movement quality, has commonly attributed to benefits of robotic-assisted training in stroke [39,40] and spinal cord injury population [41–43]. Moreover, smoothness has been associated with recovery rather than compensatory movement skills [44]. In addition, there is substantial evidence that kinematic measures of movement smoothness correlates significantly with clinical measures of impairment

and function [45–47] as well as qualitative movement quality. Lack of quantified kinematic measurement is limitation of the current study, but anecdotally participants in the EG reported that they could start to use their impaired arms more naturally (referring to more smooth joint movements) in some daily activities such as washing faces with both hands, preparing a snack or, chopping vegetables and fruits on the board.

Since the limitations of motor performance negatively affect the ADLs [6], it is necessary to consider the impact of any intervention on the ADLs in stroke patients. The NEADL is one of the scales to assess ADLs in stroke patients and used to reveal the possible improvements after any treatment strategy by means of ADLs. In the current study, the NEADL measurements showed that EG had more significant improvement than BG after a 6-week rehabilitation process.

Hung et al. [48] found the effect of robot-assisted therapy on ADLsg similar to our study. In their experimental design they used three groups receiving upper extremity therapeutic interventions including robotic rehabilitation for different implication times. Since robot-assisted treatments include repetitive and rhythmic arm movement patterns this treatment approach may have a significant impact on ADLs due to improvements in motor functions [48]. Another study by Hsieh et al. performed a similar robot-assisted threapy design with the current study and it was found that robot-assisted therapy was more helpful in participating in ADLs [49]. There is limited study in the robot-assisted stroke rehabilitation literature using NEADL to assess ADLs. Therefore, comparison of our NEADL scores with the previous studies are limited. However, in studies using Barthel Index, another widely used ADL scale in stroke, it has been observed that exoskeleton-assisted upper limb rehabilitation has positive effects on ADL [10,50,51].

Our results support that high-intensity repetitive movement training produces better outcomes in recovery of upper extremity motor impairment, performance in daily activities. Exoskeleton devices are safe and feasible in delivering repetitive movement practices. However, randomized controlled trials with larger sample size are warranted to confirm these preliminary results.

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