

Effect of Robot-assisted Rehabilitation to Botulinum Toxin A Injection for Upper Limb

Disability in Patients with Chronic Stroke: a Case Series and Systematic Review

Koichi Hyakutake^{1,2}, Takashi Morishita¹, Kazuya Saita³, Hiroyuki Fukuda^{1,2}, Hiroshi Abe¹,

Toshiyasu Ogata⁴, Satoshi Kamada², Tooru Inoue¹

¹*Department of Neurosurgery, Faculty of Medicine, Fukuoka University, Fukuoka, Japan*

²*Department of Rehabilitation Medicine, Fukuoka University Hospital, Fukuoka, Japan*

³*Department of Psychosocial Rehabilitation Graduate School of Biomedical and Health Sciences Hiroshima University, Hiroshima, Japan*

⁴*Department of Neurology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan*

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Corresponding author: Takashi Morishita, M.D., Ph.D. Department of Neurosurgery, Fukuoka University Faculty of Medicine, Nanakuma 7-45-1, Jonan ward, Fukuoka 814-0180, Japan. Phone: 81-92-801-1011. Fax: 81-92-865-9901. E-mail: tmorishita@fukuoka-u.ac.

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Abstract

Combining single-joint hybrid assistive limb (HAL-SJ) with botulinum toxin A (BTX-A) therapy is novel and has great therapeutic potential for the rehabilitation of stroke patients with upper limb paralysis. The purpose of this observational case series study was to evaluate the effect of BTX-A and HAL-SJ combination therapy on different exoskeleton robots used for treating upper limb paralysis. The HAL-SJ combination received a BTX-A injection followed by HAL-SJ-assisted rehabilitation for 60 min per session, 10 times per week, during 2 weeks of hospitalization. Clinical evaluations to assess motor function, limb functions used during daily activities and spasticity were performed prior to injection, at 2-weeks post-treatment intervention, and at the 4-month follow-up visit. The total Fugl-Meyer assessment-upper limb (FMA-UE), proximal FMA-UE, action research arm test (ARAT), Motor Activity Log (MAL) and Disability Assessment Scale (DAS) showed a statistically significant difference, and a large effect size. However, the FMA distal assessment at 2-weeks post-treatment intervention showed no significant difference and a moderate effect size. The FMA-UE scores of the extracted systematic review articles showed that our design improved upper limb function. The change in the total FMA-UE score in this study showed that, compared to previous reports in the exoskeletal robotic therapy group, our combination therapy had a higher score than five of the seven references. Our results suggest that BTX-A

therapy and HAL-SJ combination therapy may improve upper limb function, similar to other treatment methods in the literature.

Introduction

Longitudinal studies have reported a 30-66% incidence of upper extremity dysfunction in patients with chronic stroke.^[1-4] More specifically, upper extremity spasticity after stroke often causes limitations in activities of daily living (ADL), which can reduce the quality of life by affecting appearance, hand hygiene, and dressing ability.^[5,6] A wide variety of treatments, such as botulinum therapy, is available for rehabilitating upper limb dysfunction in post-stroke spastic paralysis patients.^[5,6] Because botulinum therapy is very effective, combination therapies that include it result in significant improvements in upper limb function.^[7-10] Many botulinum combination therapies include electrical stimulation therapy, repeated transcranial magnetic stimulation therapy, and robot therapy.^[9,11,12] Among these, combined upper limb support robot therapy has gained attention in recent years.^[13]

Stroke upper limb support robots include exoskeleton and end-effector types.

Among the end-effector types, Reo Go therapy system (Motorika Medical Ltd, Israel) improves upper limb function when used in combination with botulinum therapy.^[12] In contrast, the exoskeleton-type single-joint HAL (HAL-SJ, Cyberdyne Inc., Japan) system has been developed based on the “interactive biofeedback” theory. The lightweight and compact

exoskeleton-type upper limb robot reads the wearer's intention as a potential signal and operates a small power unit to assist the flexion/extension movement of the elbow joint (Figure 1).^[14-16] HAL-SJ has been reported to be effective in numerous clinical studies.^[14,15,17-19]

Botulinum toxin A (BTX-A) therapy and HAL-SJ combination therapy are effective for upper limb spastic paralysis in patients with chronic stroke.^[17] In this study, we investigated the clinical outcomes of a larger cohort of study subjects to further evaluate the effect of this combination therapy. We also investigated the effect of robot rehabilitation therapies by a systematic review to address the efficacy of our combination therapy.

Materials and Methods

Study design

In this study, we included patients with chronic stroke who received BTX-A therapy between December 2014 and March 2018. The patients were recruited as outpatients in the hospital. We calculated that 10 patients should be enrolled before starting the present study. Previous studies have suggested that to accurately estimate treatment outcomes, pilot studies should enroll 10-40 patients per group.^[20] This study included patients aged 20-85 years, who were ischemic or hemorrhagic with chronic stroke, and experienced paralysis in an upper limb with spasticity more than 6 months after stroke occurrence. Patients with severe pain on the

paralyzed upper limb, those who could not follow the instructions owing to cognitive impairment or aphasia, and those who received intrathecal baclofen therapy one year before their enrolment in the study were excluded.

In our previous single-arm study, seven patients were treated with combination therapy using BTX-A injection and robot rehabilitation between December 2014 and November 2015.^[17] The present study includes three patients who received the HAL-SJ combination therapy from the period between November 2015 and March 2018. All participants provided written informed consent, and our Institutional Review Board approved the study (approval number: U20-01-009). Patient characteristics are summarized in Table 1.

BTX-A (BOTOX, GlaxoSmithKline, Brentford, UK) was injected in the paralyzed upper limb of each patient based on the severity of spasticity. The dose was set to a maximum of 240 units, as determined by the upper limit set in our health insurance.

HAL-SJ is an exoskeleton-type upper limb support robot weighing 1.5 kg. The attachment consists of a brachial and forearm supporter, and the trigger electrodes are attached to the biceps brachii and triceps brachii. The wearable robot reads the potential signal according to the wearer's will, and the small power unit assists the joint movement. A controller is used to adjust the movement of the robot. The amount of assistance can be adjusted by the patient on a scale from 0 to 100 according to their upper limb function level. The balance of flexion/extension can also be adjusted. In addition, the state of flexors and

extensors is displayed as a waveform on the controller monitor, which can be confirmed by the therapist and the patient, thus making it possible to visualize the movement of the upper limbs (Figure 1). In the HAL-SJ combination group, patients used the HAL-SJ during each session after receiving a BTX-A injection. The period consisted of 60 minutes per hospital session, 10 times a week, and continued for 2 weeks. The patients also received task-specific ADL training in addition to HAL-SJ training. After 2 weeks of the intervention, patients were instructed to perform home exercises. These exercises included a passive range of motion and the use of the upper limb as much as possible in daily life.

We evaluated outcome measures at baseline (T0), 2-weeks post-treatment intervention (T1) and at 4-month follow-up (T2) after BTX-A injection. Previous studies have reported that the pharmacological effects of BTX-A in patients with spasticity last for 3-4 months. Therefore, our analysis used data from the 4-month follow-up period.^[21,22] Upper limb function was assessed by the Fugl-Meyer assessment-upper limb (FMA-UE, range 0-66).^[23] The action research arm test (ARAT, range 0-57) was used to evaluate ADL.^[24] Limb functions used during daily activities were assessed using the Motor Activity Log (MAL, range: 0-5),^[25] and spasticity was assessed using the Disability Assessment Scale (DAS, range 0–12).^[26]

Statistical analyses

The pre-treatment, 2-week post-treatment, and 4-month follow-up-comparisons in the evaluation of the upper extremity, use of impaired upper limb and spasticity were performed using the Wilcoxon test. The effect size index r was also calculated. r indicates the effect size (0 to 1), where 0.1 indicates a small change, 0.3 indicates a moderate change, and 0.5 indicates a large change. SPSS version 21.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The statistical threshold was set at $P < 0.05$.

Systematic Review

This study is based on the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement, and database searches based on search formulas, primary screening, and secondary screening conducted in the procedure of analysis. The search formula was created following an agreement by the authors, occupational therapist, and physician. Primary and secondary screening and analysis were performed by the authors and the physician.

A systematic search of the literature for studies related to upper limb exoskeleton structure robots for chronic stroke until December 31, 2020 was conducted using the PubMed database. Search terms were “chronic stroke and robotics,” “chronic stroke and robotics and rehabilitation,” and “chronic stroke and exoskeleton robotics and upper extremity.”

Eligibility criteria include targeting patients with chronic stroke, targeting upper limb paralysis, and evaluation of upper limb function FMA or ARAT. Exclusion criteria were acute or subacute stroke patients, wrist or finger robots, upper limb function evaluation other than FMA and ARAT, and articles from Books and Document, Clinical Trial, Meta-analysis, Review, and Systematic Review. In this study, we focused on comparing the effects of improving upper limb function when other exoskeleton structure robots were used instead of the control group.

In the primary screening, only randomized controlled trial (RCT) designs were extracted from the articles obtained using the search formula, and articles that met the criteria were extracted after reading the title and summary. In the secondary screening, these papers were confirmed, and the studies that met the criteria were extracted as the final research papers. Data pertaining to authors, study designs, number of subjects, evaluation scales used, methods, and main results of the studies were extracted (Figure 2).

Results

Baseline Characteristics

In this study, 10 patients (four females; mean: 64.0 ± 9.1 years; mean interval from stroke onset: 36.0 ± 43.0 months) receiving HAL-SJ combination were included. Of the 10 patients, 6 had ischemic stroke, 4 had hemorrhagic stroke, and all were right-handed. Stroke lesions

were found in the left and right hemispheres of the brains of three and seven patients, respectively. Of the six patients with ischemic stroke, four had ischemic lesions in the corona radiata, and the others had lesions in the putamen and middle cerebral artery. Of the four patients with hemorrhagic stroke, two had lesions in the thalamus and the others had lesions in the parietal subcortex and putamen.

Demographic data and clinical characteristics are shown in Table 1. The baseline mean total FMA-UE value was 25.4 ± 13.0 . The mean proximal and distal FMA-UE values were 19.9 ± 7.4 and 5.5 ± 6.9 , respectively. The baseline mean ARAT value was 11.3 ± 16.6 . The baseline mean MAL value was 6.2 ± 3.7 . The mean amount of use (AOU) and the mean quality of movement (QOM) values were 0.6 ± 0.8 each. The baseline mean DAS value was 6.2 ± 3.7 .

Clinical Outcomes

Comparison of the pre-treatment, 2-week post-treatment, and 4-month follow-up results of HAL-SJ combination therapy showed a significant difference in the evaluation of the upper extremity, use of impaired upper limb and its spasticity, though with some exceptions. The measured mean and standard deviation values (P -values compared with baseline) from the evaluation items of the HAL-SJ combination at 2-week post-treatment and 4-month follow-up were as follows: total FMA-UE values were 28.0 ± 12.9 ($P = 0.012$, $r = 0.79$) and $29.4 \pm$

13.9 ($P = 0.011$, $r = 0.80$), respectively; proximal FMA-UE values were 22.0 ± 7.1 ($P = 0.012$, $r = 0.80$) and 22.5 ± 7.1 ($P = 0.017$, $r = 0.76$), respectively. The distal FMA-UE values were 6.0 ± 6.9 ($P = 0.180$, $r = 0.42$) and 6.9 ± 7.9 ($P = 0.041$, $r = 0.65$), respectively. The ARAT values were 12.8 ± 17.3 ($P = 0.017$, $r = 0.76$) and 15.3 ± 20.0 ($P = 0.018$, $r = 0.75$), respectively. MAL-AOU values were 1.1 ± 1.1 ($P = 0.008$, $r = 0.84$) and 1.5 ± 1.4 ($P = 0.012$, $r = 0.80$), respectively. MAL-QOM values were 1.3 ± 1.3 ($P = 0.008$, $r = 0.84$) and 1.3 ± 1.4 ($P = 0.012$, $r = 0.80$), respectively. DAS values were 4.5 ± 2.4 ($P = 0.017$, $r = 0.76$) and 3.8 ± 2.7 ($P = 0.018$, $r = 0.75$), respectively (Figure 3).

Based on the analysis, the results showed improvement in the pre-treatment, 2-week post-treatment, and 4-month follow-up-comparison. The total FMA-UE, proximal FMA-UE, ARAT, MAL-AOU, MAL-QOM and DAS endpoints showed a statistically significant difference ($P < 0.05$), and the effect size was large. However, the FMA distal assessment (compared to baseline vs post-treatment) showed no significant difference ($P = 0.180$), and the effect size was moderate.

Review results

Of 477 articles, 241 were excluded for not having a RCT design by automation tools, 193 were excluded after reading the title and abstract, and 17 were duplicate records, all of which were removed during the first screen. Out of the 25 remaining articles, 18 were excluded for

the following reasons: the target disease was not chronic stroke (1), the devices were not exoskeleton robots (16), and FMA and ARAT were not used for evaluation (1). Overall, 7 studies that used exoskeleton robotics for chronic stroke upper limb paralysis met the inclusion criteria and were subject to critical review.^[27-33] Details of each study are shown in Table 2. The FMA-UE scores of the extracted articles showed that most of the literature improved upper limb function.^[27-33] In the exoskeleton robotics therapy group, the total FMA score improved from 2.1 to 12.4, while ARAT score improved from 10.9 to 11.1.^[27-33]

Discussion

We investigated the clinical outcomes of a larger cohort of study subjects to further evaluate the effect of BTX-A therapy and HAL-SJ combination therapy. We also investigated the effect of robot rehabilitation therapies by a systematic review to address the efficacy of our combination therapy. The evaluation of upper limb function (which consisted of FMA total score, proximal FMA score, and ARAT score) in the HAL-SJ combination showed significant improvement in the pre-treatment-, 2-week post-treatment, and 4-month follow-up-comparison results. When we compared the change in upper limb functional assessment of our study with those of other exoskeletal robots extracted from the systematic review, we found that our combination therapy showed a similar or increased change. Increased change is usually more formal. However, the distal FMA score showed no significant improvement

in the pre-treatment and post-treatment comparison results. On the other hand, limb functions used during daily activities and limb spasticity evaluation results showed a significant difference in the comparison results.

Many papers related to botulinum therapy have reported that botulinum combined therapy and rehabilitation improve upper limb spastic paralysis in the chronic stage of stroke patients.^[7-12] One of these studies also reported a combination of botulinum therapy and upper extremity robotic therapy.^[12] Similarly to these reports, in our study, the HAL-SJ combination showed significantly improvement in upper limb function in our study.

Our systematic review paper was extracted to compare the results of this study with those of studies on other exoskeleton robotics therapies. The FMA-UE scores of the extracted articles showed that several therapies improved upper limb function.^[27-33] In the literature review of exoskeleton robotics therapy, the total FMA score improved from 2.1 to 12.4, and the ARAT score improved from 10.9 to 11.1.^[27-33]

The results of the BTX-A and HAL-SJ combination therapy in this study can be compared with those in previous literature. The subjects in each article differed in severity of upper limb function, duration of intervention, and intervention protocol, and only the FMA-UE and ARAT were used to assess upper limb function. However, our combination therapy showed higher scores than five of the seven studies on exoskeleton robot therapy.^[27-33] These

results suggest that the combination therapy used in this study can produce positive changes in upper limb function.

Numerous studies have shown the effectiveness of botulinum therapy in improving spasticity.^[7,34–38] The results of spasticity evaluation in this study showed improvement in DAS, suggesting that the spasticity-improving effect was maintained in ADL even after the effect of botulinum therapy disappeared. Previous studies have suggested that administration of BTX-A injections to the proximal muscles of the upper limbs, such as the shoulders and elbows, may improve upper limb function.^[39,40] Therefore, this effect may lead to an improvement in upper limb paralysis.

The MAL score improved both post-treatment and 4-month follow-up. The minimum clinically important difference (MCID) in this score has been reported to be 0.5 after chronic stroke.^[41] In the present MAL evaluation results, it was above 0.5. This indicated that the program motivated patients to use the affected limb even after completion of the 2-week treatment program. Previous studies have reported that the recovery of motor function after stroke depends on the level of use of the affected limb.^[42] Therefore, it may have enhanced the effect of improving upper limb function and spasticity.

In previous studies, the effectiveness of rehabilitation using HAL-SJ was examined to analyze the aspects of upper limb function and brain function in clinical settings using patients with subacute and chronic stroke.^[15,17] Saita et al. found that robot-assisted

rehabilitation using HAL-SJ increased the number of elbow flexion repetitions as an immediate effect of upper extremity training in subacute stroke patients, suggesting that the HAL-SJ interaction may promote brain plasticity.^[15] Furthermore, despite using an end-effector-type upper limb robot, the combination of conventional intervention and robot treatment is more effective in improving upper limb function (shoulder/elbow) than the conventional intervention alone.^[43]

However, when comparing the sites of upper limb function based on the FMA results in this study, the HAL-SJ combination significantly improved only in the proximal region and not in the distal region. HAL-SJ is an exoskeleton structure consisting of an upper arm mounting part and a forearm supporter, so it is difficult to use for distal rehabilitation.^[44-46]

The results of this study suggest that rehabilitation with HAL-SJ after injection of BTX-A toxin may improve upper limb function. However, this study has important limitations. This case observation study was compared with previous studies without establishing a control group. In addition, the sample size of this non-randomized study was small. Furthermore, the comparison with previous studies is not a comparison by effect size. Therefore, in future studies, the reproducibility of these results should be confirmed in randomized controlled trials with control groups and increased patient samples.

The BTX-A and HAL-SJ combination therapy significantly improved upper limb function in patients with chronic stroke. Our results suggest that BTX-A therapy and HAL-SJ

combination therapy may improve upper limb function, similar to other treatment methods in the literature. Although this may show a greater effect when this combination program is compared with other exoskeleton structure robots therapies for upper limb paralysis, more rigorously designed studies are needed to validate the results.

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Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

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Figure legends

Figure 1. HAL-SJ. (A)HAL-SJ attachment (B)The controller showing the bioelectrical signal (BES). Monitor indicates flexor and extensor muscles.

Power Unit has visual feedback function in the elbow joint on the lateral side. The light - emitting diode shows colors of red, green, and yellow depending on the upper limb coordination.

Figure 2. Study flow diagram

Figure 3. Upper limb function assessment, use of impaired upper limb, and affecting of muscle tone in ADL

Box plots were created to display change in upper limb function in both the BTX-A therapy and the HAL-SJ combination group before (T0) and after 2 weeks (T1) after treatment (T2).

All panels show within-group. Fugl-Meyer assessment-upper limb (FMA-UE) results are displayed as total (A), proximal (B) and distal (C) ARAT (D) scores. Use of impaired upper limb was measured using the Motor Activity Log (MAL), AOU: amount of use (E-1), QOM: quality of movement (E-2), and spasticity was measured using the Disability Assessment Scale (DAS) (F) scores.

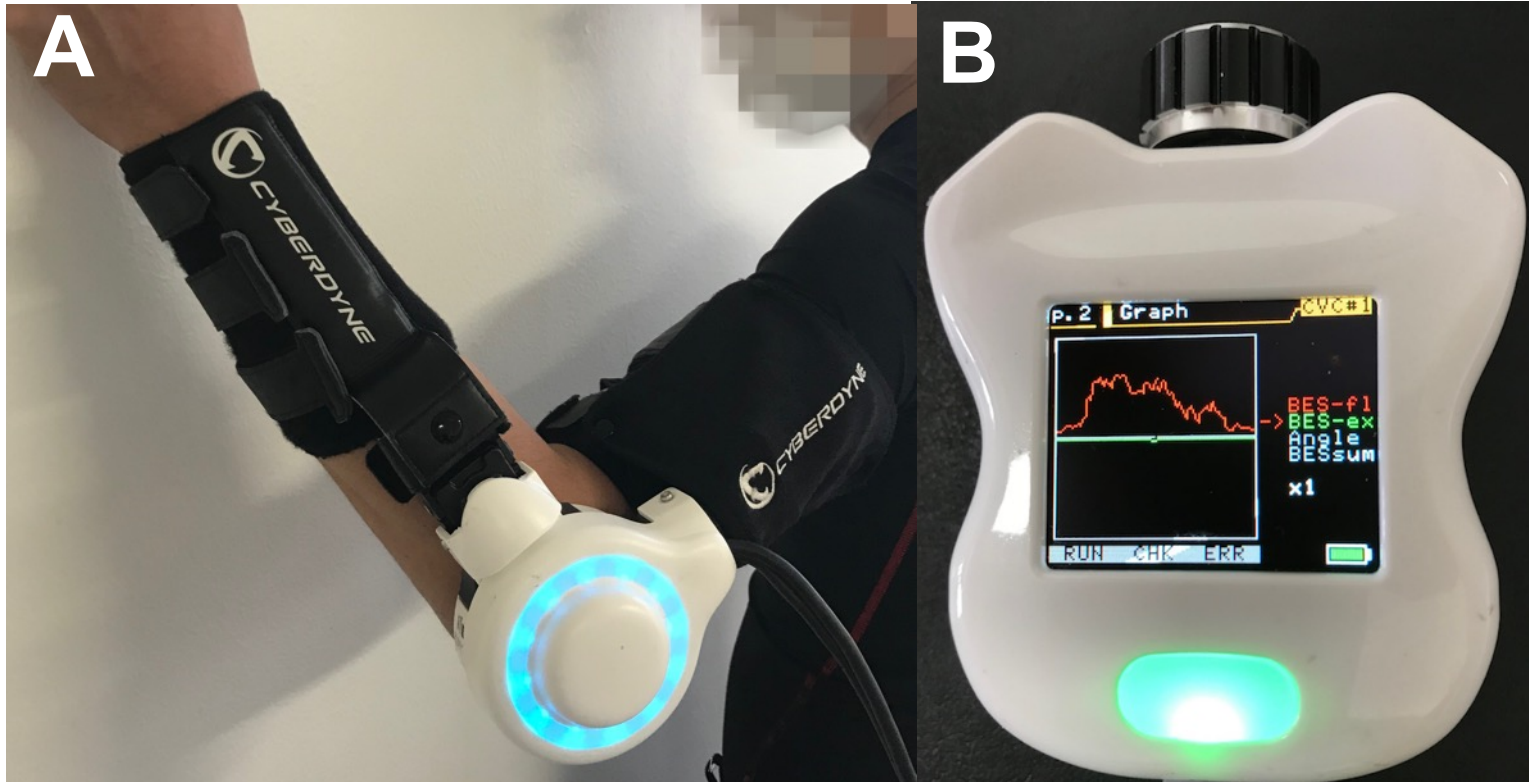


Fig.1. HAL-SJ. (A)HAL-SJ attachment (B)The controller showing the the bioelectrical signal(BES). Monitor indicates flexor and extensor muscles. Power Unit has visual feedback function in the elbow joint on the lateral side. The light - emitting diode shows colors of red, green, and yellow depending on the upper limb coordination.

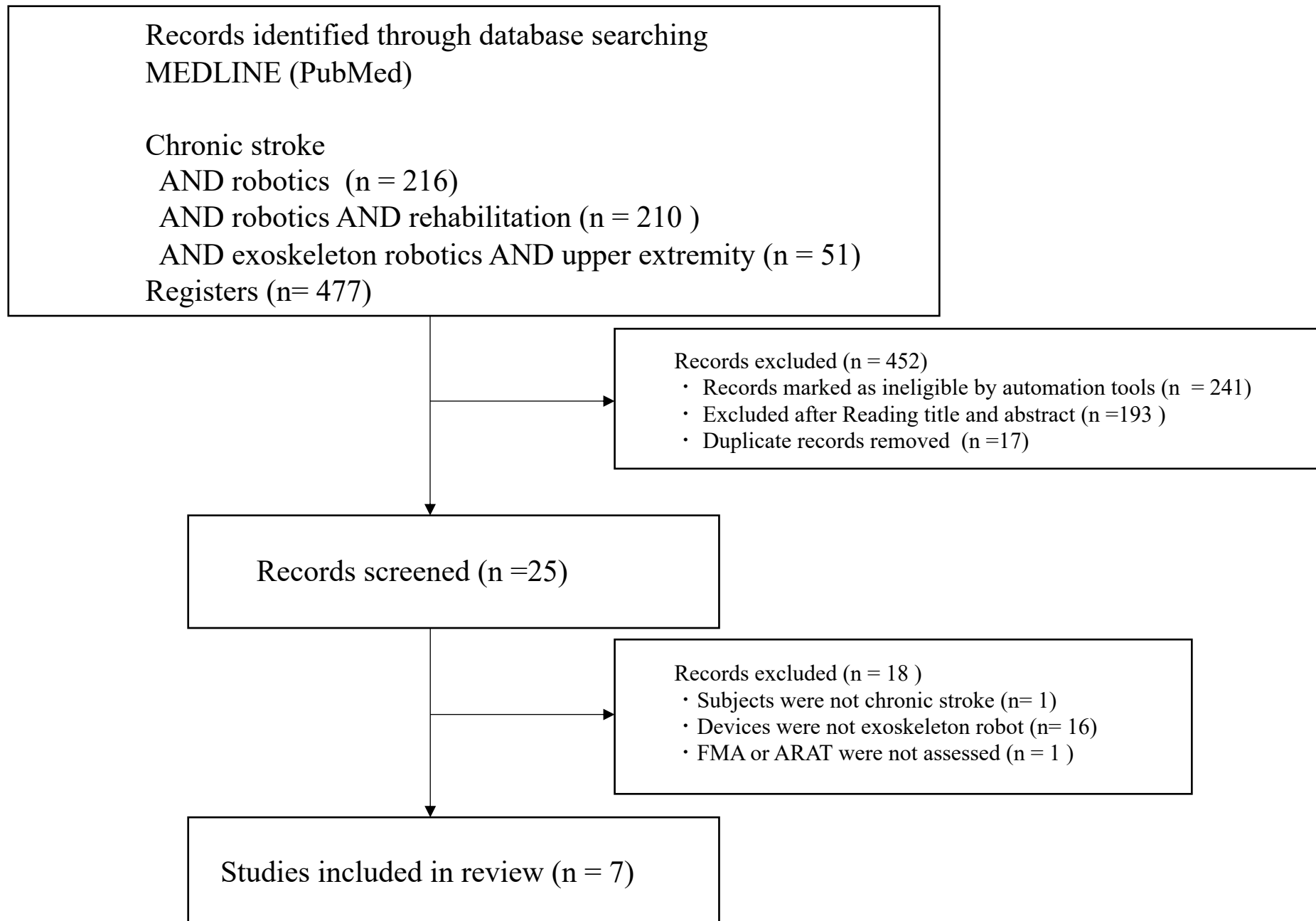
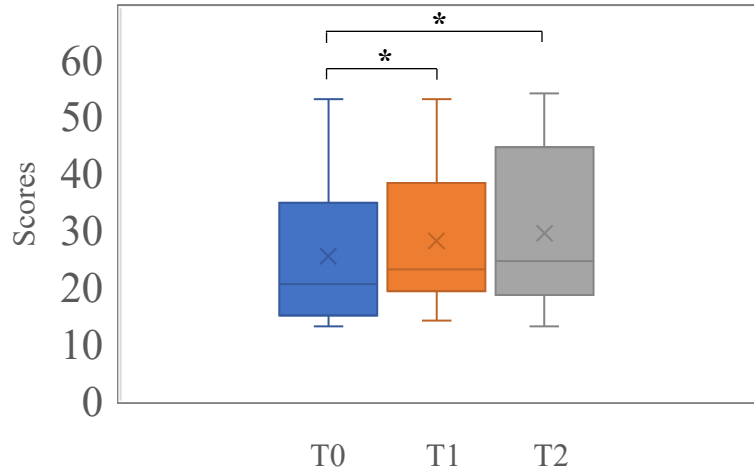
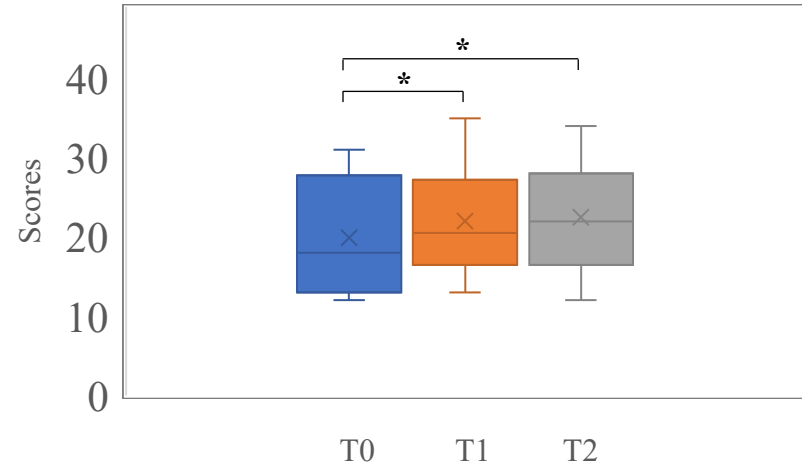


Fig 2. Study flow diagram

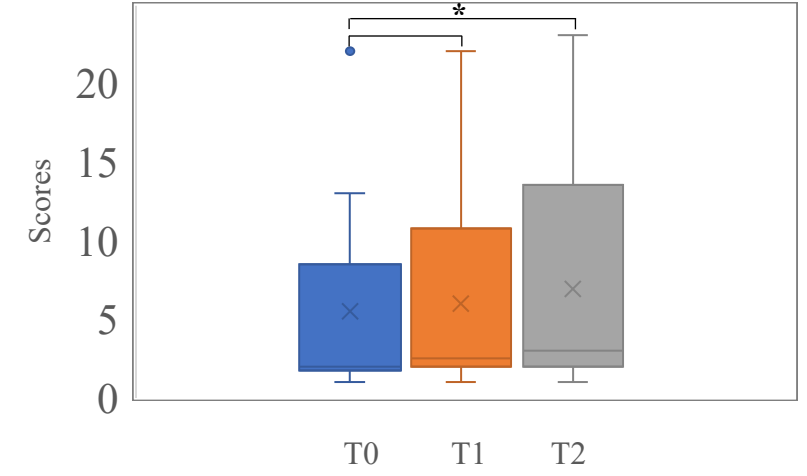
(A) Total FMA - UE



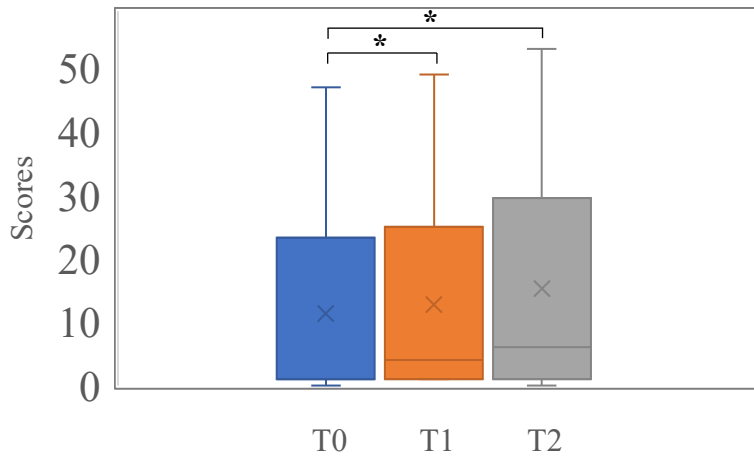
(B) Proximal FMA - UE



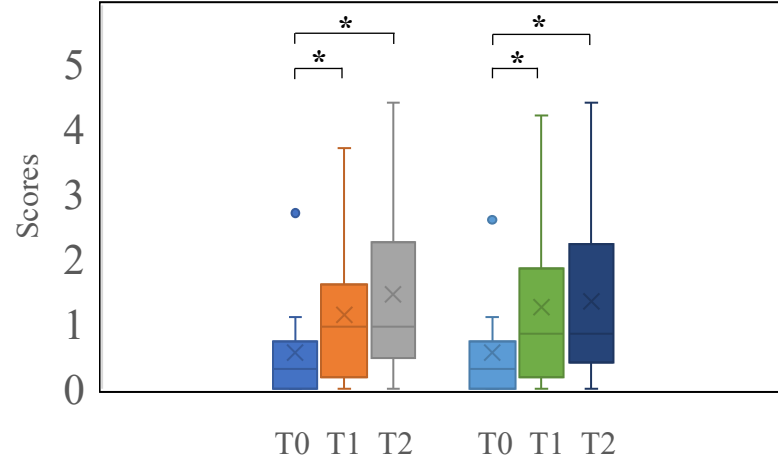
(C) Distal FMA - UE



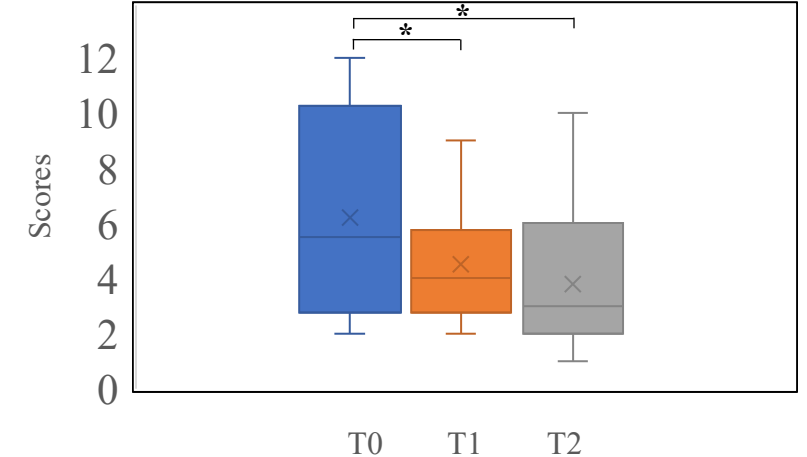
(D) ARAT



(E-1) MAL - AOU (E-2) MAL - QOM



(F) DAS



* $p < 0.05$

Fig 3. Upper limb function assessment, use of impaired upper limb and affecting of muscle tone in ADL

Table 1. Demographics and clinical characteristics in HAL-SJ combination group

Case	Age	Sex	Handedness	Diagnosis	Lesion location	Interval from onset	MMSE	BTX-A	Injection sites
	(years)					(months)	(scores)	(units)	
1	65	M	R	Hemorrhage	Rt. thalamus	37	20	240	PM,LD,Bi,Bra,PT
2	64	M	R	Hemorrhage	Lt. thalamus	131	26	200	Bi,Bra,Tri,PT,FCR,FDS,FDP,FPL
3	68	F	R	Hemorrhage	Rt. parietal subcortex	9	26	100	PM,Bi,Bra,Tri,PT,FCR
4	46	F	R	Hemorrhage	Lt. putamen	7	27	150	PM,Bra,Tri,FCR,FDS,FDP
5	68	M	R	Ischemic	Rt. corona radiata	10	30	150	PM,LD,Bi,Bra,Tri
6	52	F	R	Ischemic	Rt. putamen	13	29	200	PM,Bi,Bra,Tri,FCR,FDS,FDP,FPL
7	61	F	R	Ischemic	Rt. corona radiata	35	30	240	PM,LD,Bra,Tri,PT,FCR,FDS,FDP,FPL
8	79	M	R	Ischemic	Rt. corona radiata	14	27	240	PM,LD,Bra,PT,FCR,FCU,FDS,FDP
9	68	M	R	Ischemic	Rt. corona radiata	8	28	130	PM,LD,Bi,PT,FCR
10	69	M	R	Ischemic	Lt. MCA lesion	96	N/A	240	PM,LD,Bra,Tri,FCR,FCU,FDS,FDP
Mean	64.0					36.0	27.0	189.0	
(±SD)	±9.1					±43.0	±3.0	±52.8	

MCA: middle cerebral artery, MMSE: mini mental state examination, BTX-A: Botulinum toxin A, PM: pectoralis major, LD: latissimus dorsi, Bra: brachialis, Bi: biceps brachii, Tri: triceps brachii, FCR: flexor carpi radialis, FCU: flexor carpi ulnaris, FDS: flexor digitorum superficialis, FDP: flexor digitorum profundus, PT: pronator teres

Table 2. Review of Exoskeleton Robotics Rehabilitation

Study	Design	Sample	Device Employed	Protocol Times of Session	Outcome	Follow-up	Results (FMA and ARAT)/ (ΔE- ΔC)
Sarah J et al. 2009	RCT(vs Conventional treatment group)	E:14(T-WREX Group) C:14(Standard care and home exercise)	T-WREX	Twenty-four 1-hour treatment sessions, approximately 3 times per week for 8 to 9 weeks	FMA, ROM, MAL	6-month follow-up	The T-WREX group maintained a significant improvement in FMA compared to the control group at 6 months. (FMA ΔE 3.3- ΔC 2.2)
Milot MH et al. 2013	RCT(single joint robotic training vs multijoint functional robotic training)	single joint robotic training:10 multijoint functional robotic training:10	BONES	3 sessions /week for 60 minutes per session for eight weeks for a total of 24 sessions	BBT, FMA, WMFT, MAL, MAS, Strength	3-month follow-up	Training with the robotic exoskeleton resulted in significant improvements in the FMA at the 3 month follow-up. There was no difference between multijoint functional and single joint robotic training programs in terms of disability and activity area. (FMA ΔE 3.0- ΔC 4.0)
Byl NN et al. 2013	RCT(TSRT-PT vs TSRT-URO vs TSRT-BRO)	TSRT-PT:5 TSRT-URO:5 TSRT-BRO:5	UL-EX07	2 sessions /week for 6 weeks of training(18h)	ROM, Strength, Pain, FMA	6-weeks follow-up	After 6 weeks of training, all subjects showed significant improvement in FMA. Each training group significantly improved FMA score without significant differences between the groups. (FMA ΔTSRT-PT6.0- ΔTSRT-URO4.0- ΔTSRT-BRO3.8)

Stephen J Page et al. 2013	RCT(vs Usual care RTP)	Myomo:8 RTP:8	Myomo	30-minutes 3 days/week for 8 weeks	FMA, SIS, COPM,	8-weeks follow-up	After the intervention, the robot group showed an increase in the Fugl-Meyer score. All endpoints showed greater score changes. (FMA ΔE 2.1- ΔC 2.2)
Verena Klamroth et al. 2014	RCT(vs conventional therapy)	E:38 (robotic therapy and Conventional therapy) C:35(Conventional therapy)	ARMin	therapy sessions of 45 minutes or more were conducted three times a week for eight weeks (24 sessions total)	FMA, WMFT, MAL, MAS, SIS, Strength	34-weeks follow-up	The robotic treatment had significantly improved motor function of the affected area as measured by the FMA-UE, compared to patients who received conventional treatment. (FMA ΔE 3.25- ΔC 2.47)
Qiuyang QIAN et al.2019	RCT(EMG-driven NMES-robotic systems hand group vs Sleeve group)	E:15 (hand group) C:15 (Sleeve group)	EMG-driven NMES-robotic hand and sleeve	20 sessions of robot-assisted UE training, 3 to 5 sessions/week, with a maximum intensity of 1 session/day (1 hour for each session of movement task)	FMA, MAS	7-weeks follow-up	Providing robotic support to either the distal part of the finger or the proximal part of the elbow and wrist was effective in improving the motor function of the UE. (FMA ΔE 13.3- ΔC 12.4) (ARAT ΔE 10.9- ΔC 11.1)
Stephanie Hyeyoung Lee et al. 2020	RCT(EE group vs Exo group)	E:19 (EE group, robotic training) C:19(Exo group robotic training)	InMotion2 Armeo Power	30 minutes of active therapy 5 days a week for 4 weeks [total 20 sessions] along with conventional occupational therapy (30 minutes of therapy [total 20 sessions])	FMA, WMFT, BBT, SIS	6-weeks follow-up	The EE robotic intervention was superior to the Exo robotic intervention in terms of activity. (FMA ΔE 3.8- ΔC 2.4)

Abbreviations: E, experimental group; C, control group; RCT, randomized controlled trial; ROM, range of motion; FMA, Fugl-Meyer assessment; MAL, Motor Activity Log; MAS, Modified Ashworth Scale; BBT, Box and Block Test; WMFT, Wolf Motor Function Test; TSRT-PT, actual task specific repetitive training (TSRT) working with a physical therapist (PT); TSRT-URO, virtual TSRT guided by the UL-EX07 used unilaterally; TSRT-BRO, virtual TSRT guided by the UL-EX07 used bilaterally; RTP, repetitive task specific practice; SIS, stroke impact scale; COPM, Canadian Occupational Performance Measure; DAS, Disability Assessment Scale; PDS, Posttraumatic Diagnostic Scale; VAS, Visual Analog Scale; HSP, Hemiplegic shoulder rehabilitation; SSNB, Suprascapular nerve block; MRC, Medical Research Council; EMGs, electromyography surface; ARAT, Action Research Arm Test; UE, upper extremity; EMG, electromyography; NMES, neuromuscular electrical stimulation; EE, end-effector-type; Exo, exoskeleton-type.