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Combined effects and timing of robotic training and botulinum toxin on upper limb spasticity and motor function: a single-blinded randomized controlled pilot study

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Abstract

Background This study aimed to evaluate the combined effects of robotic training (RT) and botulinum toxin (BTX) injections on motor function and spasticity in individuals with post-stroke upper limb spasticity (ULS). We also sought to investigate the optimal timing of RT and BTX administration.

Methods Forty-two participants with chronic stroke-induced ULS were initially enrolled and randomized into four groups: Group B4R4 (RT + BTX at 4 weeks [W4]), Group B0R0 (RT + BTX at baseline [W0]), Group B0R4 (BTX at W0, RT at W4), and Group B4R0 (RT at W0, BTX at W4). Clinical assessments and robotic kinematic evaluations were performed at W0, W4, and 8 weeks (W8). The primary outcome was the Fugl-Meyer assessment (FMA) score, and secondary outcomes included the modified Ashworth scale (MAS) of the elbow and kinematic parameters, such as spectral arc length, mean speed, hand path ratio, and movement deviation in various tasks. Changes in outcome measures over time were analyzed using a linear mixed-effects regression model or ordinal logistic regression.

Results Of the 42 participants, 40 completed the study. From W0 to W4, Group B0R0 exhibited the most favorable outcomes in terms of spasticity (MAS-elbow flexor and extensor) and kinematic variables, suggesting that the combined application of BTX and RT is superior to sole interventions in improving motor function and spasticity. From W0 to W8, Group B0R4 demonstrated the most substantial improvements in FMA scores and kinematic parameters, indicating that the combined use of BTX and RT, particularly when RT is initiated 1 month after BTX injection, results in superior functional outcomes compared to other intervention timings.

Conclusions The combination of RT and BTX is more effective in enhancing motor function and reducing spasticity in individuals with ULS than either intervention alone or no intervention. Furthermore, the timing of RT relative to BTX injection plays a critical role in maximizing therapeutic benefits in individuals with stroke and ULS, given the distinct modes of action of each intervention.

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Trial registration clinicaltrials.gov NCT02228863. The study was retrospectively registered on August 23, 2014.
Keywords Upper limb, Robotic rehabilitation, Botulinum toxin, Stroke, Rehabilitation, Motor function, Spasticity

Background

Upper limb spasticity (ULS), a prevalent impairment following a stroke, is associated with significant functional limitations and can hinder recovery during rehabilitation [1]. Botulinum toxin (BTX) is considered the standard first-line treatment for focal ULS. It inhibits acetylcholine release at neuromuscular junctions to reduce muscle overactivity and involuntary contraction. Additionally, BTX decreases afferent input and gamma motor neuron excitability, attenuating the stretch reflex. These combined effects make BTX effective in alleviating spasticity, improving range-of-motion, and facilitating rehabilitation outcomes.

Systematic reviews have established that BTX reduces muscle tone and increases the range of motion; however, evidence regarding its effects on active upper limb function remains limited [2, 3]. This discrepancy suggests that while BTX effectively addresses spasticity, additional interventions targeting motor function are necessary to translate these effects into tangible improvements in active function. Therefore, it is critical to utilize adjunct interventions alongside BTX injections to enhance functional outcomes. Systematic reviews have recommended combining BTX administration with other interventions for individuals with post-stroke ULS [4, 5].

Several adjunctive interventions combined with BTX have shown promising effects on upper limb function in individuals with chronic stroke, including modified constraint-induced movement therapy, active task-specific training, and electrical stimulation [6–8]. Notably, robot-assisted upper limb training (RT) is a promising adjunct intervention owing to its high-intensity, precise, task-specific repetitions. Despite this, the combined use of RT and BTX (RT + BTX) for improving upper limb function has been explored in only a limited number of randomized controlled trials (RCTs) involving individuals with stroke. Pennati et al. [9] were the first to compare RT + BTX with RT alone and found that while motor function improvement (measured by the Fugl-Meyer assessment [FMA] and the Box and Block test) was greater in the RT group, spasticity reduction was more pronounced in the RT + BTX group, although statistical analysis was not performed. Nonetheless, they concluded that the effects of the two interventions were equivalent. Gandolfi et al. [10] compared RT + BTX with conventional treatment (CT) plus BTX (CT + BTX) and demonstrated that the RT + BTX group showed greater improvements in muscle strength than the CT + BTX group, although there were no significant between-group differences in FMA scores or spasticity. Paolucci et al. [11] compared RT + CT with RT + BTX and found that the RT + BTX group exhibited better outcomes in the Box and Block test, Frenchay arm test, and spasticity than the RT + CT group.

The results of these RCTs were inconsistent despite the hypothesis that RT + BTX would have synergistic effects compared to RT or BTX alone. Additionally, the comparisons across these RCTs were not uniform; RT + BTX was compared to RT, CT + BTX, or RT + CT, making it challenging to assess the effectiveness of RT + BTX relative to the sole interventions of BTX or RT. Therefore, an RCT comparing the combined effects of RT and BTX to those of RT alone, BTX alone, or no intervention is warranted.

Notably, the mode of action of BTX has not been adequately considered in study designs. BTX begins to take effect 2–3 days after intramuscular injection, with maximal effects observed approximately 2 weeks post-injection, influencing the outcomes of adjunct interventions [11]. It is hypothesized that RT, when initiated 1 month after BTX injection—after the effects of BTX have reached their peak—may be more effective in recovering motor function than RT performed on the day of BTX injection when the effects of BTX are not yet fully realized. However, the timing of BTX administration relative to RT varied in previous RCTs, ranging from 1 to 3 days before RT, 7 days before RT, or with no clear description of the injection date [9–11]. Given the high cost of both BTX and RT, it is critical to establish an optimal schedule for RT that takes into account the timing of BTX's effects.

The primary aim of this study was to examine the contribution of RT + BTX, RT, and BTX to upper limb function in individuals with chronic stroke and ULS. The secondary aim was to explore the effects of combined RT and BTX based on the timing of each intervention. To this end, we designed a four-arm RCT in which participants received RT + BTX, RT, BTX, or no additional intervention during the first four weeks. In the subsequent 4 weeks, each group received no intervention, BTX, RT, or RT + BTX, respectively, ensuring that the total amount of intervention was the same across groups. Results from the first 4 weeks addressed the primary aim, which focused on the effectiveness of each intervention, whereas results from the full 8 weeks were used to assess the secondary aim, which explored the combination of interventions and the timing of their administration. Furthermore, we conducted kinematic assessments using rehabilitation robots, which have the advantage of collecting kinematic data from embedded sensors without the need for additional external devices. Kinematic assessments are sensitive to subtle changes in

motor function and are capable of capturing meaningful findings and more precise measurements that are not obtained with conventional clinical outcomes [12, 13].

Methods

Study design

This study was a single-blinded, randomized, controlled pilot trial involving individuals with chronic stroke, conducted at a single rehabilitation hospital between March 2014 and February 2017. Participants were randomly allocated to one of four groups based on a computer-generated random sequence that combined BTX and RT. Table 1 outlines the intervention structure across two periods (W0–W4 and W4–W8) for the four groups. The group names were designed to indicate the start time of the two interventions. This design facilitates a comparison of the effects of BTX injections and RT, either alone or in combination, across different timeframes, providing insights into the effectiveness and timing of these interventions. Allocation was carried out by consecutively opening sealed, opaque envelopes containing the group names from a plastic container. This study was approved by the Institutional Review Board of the Rehabilitation Hospital (NRC-2014-01-005) and registered at clinicaltrials.gov (NCT02228863). All participants provided written informed consent before enrollment. Additionally, all groups received 30 min of conventional therapy for the affected upper limb, which included range-of-motion exercises, strengthening exercises for the affected upper extremity, and basic activities of daily living (ADL) training. This therapy was administered 5 days a week throughout the study period.

Participants

Individuals with stroke who were admitted to a rehabilitation hospital and exhibited functional deficits and ULS were consecutively screened to determine whether they met the inclusion criteria: (1) age > 19 years; (2) hemiplegia secondary to cerebral infarction or hemorrhage, as confirmed by medical records or brain imaging; 3) ≥ 6 months since the first onset of stroke; 4) spasticity of the affected elbow flexor with a modified Ashworth scale (MAS) score of 1 + or higher; 5) muscle strength in the affected shoulder and elbow flexor/extensor, as measured by the Medical Research Council scale, of 2 or 3; and 6) moderate or severe impairment, defined as a baseline FMA-upper extremity score ≤ 45 [14]. The exclusion criteria were as follows: (1) severe orthopedic conditions or a history of upper limb impairment, including fractures or orthopedic surgeries; (2) contracture in the affected shoulder or elbow joints; (3) prior treatments for ULS, including BTX, alcohol or phenol neurolysis, intrathecal baclofen therapy, or surgery; (4) contraindication for BTX treatment; (5) affected upper limb pain ≥ 5 on the numeric rating scale; (6) neurological disorders other than stroke; and (7) inability to follow simple instructions or cooperate with outcome measure-related tasks owing to cognitive impairment or aphasia.

Table 1 Description of four groups

	W0–W4	W4–W8
B4R4	No additional intervention	BTX injection at W4 & robot-assisted upper limb training from W4 to W8
B0R0	BTX injection at W0 & robot-assisted upper limb training from W0 to W4	No additional intervention
B0R4	BTX injection at W0	Robot-assisted upper limb training from W4 to W8
B4R0	Robot-assisted upper limb training from W0 to W4	BTX injection at W4

Robot-assisted upper limb training

We administered RT using the InMotion ARM (Interactive Motion Technologies, Inc., Watertown, MA, USA), a robotic device specifically designed for clinical rehabilitation to improve proximal upper limb movements. Participants were seated with their trunk restrained by a 5-point seatbelt to limit compensatory movement while their affected arm was placed in an armrest attached to the robotic handle. They were instructed to perform planar reaching by moving the robot handle from a central target to one of eight peripheral targets positioned equally around a circle with a 14-cm radius, guided by visual cues on a monitor in front of them. The central target on the monitor represented the center of the robotic handle's workspace. Participants were directed to perform the task comfortably without a time constraint. Participants received RT in the active-assistive mode, completing 640 repetitions of planar reaching (approximately 30 min) per day, five times a week, for 4 weeks, totaling 20 sessions of robotic intervention under the supervision of research physical therapists.

BTX administration

Participants received BTX (onabotulinumtoxin A, Botox; Allergan, an AbbVie Company, Irvine, CA, USA) injections. BTX was diluted in a standardized manner, with each vial (100 U) diluted in 2 mL of normal saline (5 U/0.1 mL). An experienced physiatrist conducted clinical assessments of upper limb function and selected the target muscle(s) from the elbow flexors (brachialis, biceps brachii, brachioradialis, or pronator teres), determining the dosage based on the spasticity pattern, severity, and the participant's body weight. BTX injections were administered under ultrasonographic guidance (ACCUVIX XG; Medison, Seoul, Korea). The total BTX dose did not exceed 300 U per participant.

Outcome measurements

The initial evaluations (clinical and robotic kinematic assessments) were performed immediately after participants were assigned to one of the groups, prior to any interventions, regardless of the specific intervention schedule assigned to each group (W0). The second and third assessments were conducted in the same manner at 4 weeks (W4) and 8 weeks (W8) after the initial evaluations. For Group B4R4, the initial evaluation occurred before the intervention period from W0 to W4, the second assessment was performed prior to BTX and RT, and the third assessment was conducted after the completion of BTX and RT.

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Clinical assessments

The primary outcome measure was the change in upper extremity FMA scores (FMA-total, 33 items; 0–66). The FMA is a stroke-specific, performance-based motor impairment scale, with higher scores indicating less motor impairment [15]. Additionally, we assessed the FMA-proximal score (shoulder, elbow, and forearm movements; 18 items; 0–36). Spasticity was evaluated using the MAS, where a higher grade indicates greater spasticity [16]. To standardize the grading of spasticity, MAS grades were converted as follows: 1 + to 2, 2 to 3, 3 to 4, and 4 to 5, whereas grade 1 remained unchanged. Spasticity was assessed for elbow flexors (MAS-EF, 0–5) and elbow extensors (MAS-EE, 0–5). We also assessed participants' quality of life using the Stroke Impact Scale (SIS, version 3.0), focusing on domains relevant to our intervention: hand function, ADL, instrumental ADL, and social participation [17]. The scores from these three domains were combined to calculate a composite SIS score, and the SIS-recovery score was also used. Adverse events that occurred during the intervention were monitored.

Robotic kinematic assessment

To assess body function and structure, we conducted robotic evaluations of upper limb kinematics using the same robot employed in the intervention. A point-to-point evaluation test was performed, capturing kinematic data from the central point to each of the eight peripheral targets and vice versa (Fig. 1). During the point-to-point assessment, the robotic system guided the arm to the central origin point at the start of the evaluation. Movements were then performed independently by the participant without robotic assistance, following a sequential clockwise order through predefined targets. This sequence was repeated five times, resulting in 80 arm movements. Participants were instructed to perform the task at a comfortable speed. This protocol ensured a standardized assessment of arm movement performance. The robot recorded various kinematic parameters, including position, direction, distance, time, and applied force, while controlling the participant's arm in a horizontal plane. Subsequently, kinematic features—namely spectral arc length measure (SPARC, movement smoothness) [18], mean speed (MeanSp, movement speed), hand path ratio (HPRatio, movement efficiency) [19, 20], and movement deviation (MovDev, movement accuracy) [21]—were calculated using MATLAB (R2019b, MathWorks Inc, Natick, MA, USA) (Table 2). For analysis, the

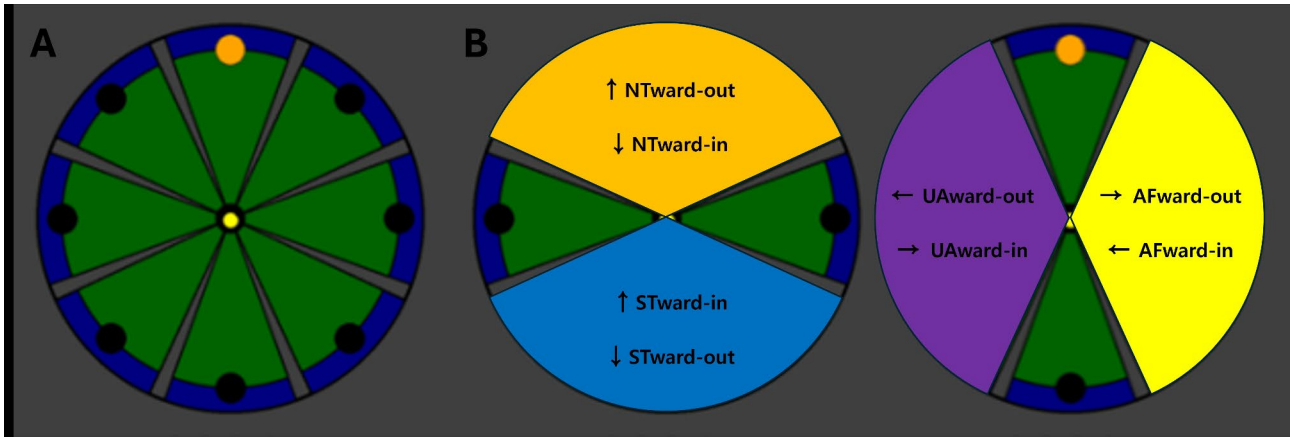

Fig. 1 (**a**) Illustration of central target and eight peripheral targets arranged in a circle for robotic upper limb training. (**b**) Eight individual movements examined in this study

Table 2 Description of robotic kinematic features

Kinematic features	Unit	Description	Characteristic
Spectral arc length (SPARC)	dimensionless	The amplitude and Fourier magnitude spectrum from the hand's velocity profile [18]; lower values indicate a higher number of sub-movements within the motion	Movement smoothness
Mean speed (MeanSp)	m/s	The average speed of the motion for each speed profile during each movement; higher values indicate faster movement	Movement speed
Hand path ratio (HPRatio)	dimensionless	The ratio of the actual distance traveled to the intended distance in a single movement from the start to the target point [19, 20]; higher values indicate longer hand trajectory during the movement	Movement efficiency
Movement deviation (MovDev)	m	The average absolute vertical distance from the ideal path to each point on the actual path [21]; lower values indicate that the actual path closely resembles the intended path	Movement accuracy

average values across the five trials were used to ensure the reliability and consistency of the kinematic measures. In terms of kinematic variables, higher scores for SPARC and MeanSp or lower scores for HPRatio and MovDev indicate better motor function.

Peripheral targets were named based on their location and the side of each participant affected. Specifically, targets located in the east or west were designated as affected (AF) or unaffected (UN) depending on the side of the upper limb affected to ensure consistent analysis across participants. The targets were thus classified as north (NT), south (ST), affected (AF), and unaffected (UN). Subsequently, the three targets in the north direction were combined and labeled as NTward, whereas the three targets in the south direction were grouped and designated as STward. The three targets on the affected side were termed AFward, and those on the unaffected side were denoted as UNward. We then designated the movement from the center to a peripheral target as "out" and the movement from the peripheral target to the center as "in".

We examined eight individual movements (IND): NTward-out, NTward-in, STward-out, STward-in, AFward-out, AFward-in, UNward-out, and UNward-in (Fig. 1). We also analyzed the aggregate movements between the eight peripheral targets and the center (Whole). Finally, the kinematic variables were denoted as "kinematic feature-target location-movement". For example, "SPARC-NTward-out" indicated SPARC (representing smoothness) during movement from the center to northward targets (the two targets adjacent to NT and NT itself), whereas "MovDev-ST-in" indicated movement deviation (representing movement accuracy) during movement from the two targets adjacent to ST and ST itself to the center. Therefore, the kinematic data in this study encompassed kinematic variables for each of the IND (kinematics-IND) and the aggregate movement (kinematics-whole).

For kinematics-IND, we primarily focused on the variables for NTward-out and STward-in movements, as they most effectively reflect the impact of our interventions. Specifically, our intervention targeted elbow flexor spasticity, whereas the other movements were more influenced by shoulder spasticity, which was not the focus of our intervention. Furthermore, we hypothesized that NTward-out movement is the most representative and challenging task because it simulates forward reaching, which necessitates reduced elbow flexor spasticity and sufficient elbow extensor strength to counteract the elbow flexor spasticity. Similarly, we proposed that the STward-in movement also reflects the effects of our intervention, albeit to a lesser extent than NTward-out, because STward-in involves slightly less reaching effort compared to NTward-out.

Statistical analysis

An intention-to-treat analysis was planned to include all participants enrolled in the study, regardless of whether they completed the intervention. Notably, no participants dropped out during the study. Data normality and variance equality were assessed by visually inspecting skewness and kurtosis, which were further confirmed using Levene's test for equality of variances. To examine baseline differences between the four groups, the chi-square test was employed for categorical variables, whereas the Kruskal–Wallis test was used for continuous variables.

A linear mixed-effects regression (LMM) model was used to compare the changes in outcome measures over time (from W0 to W8) between groups. This model was designed to observe the changes depending on each intervention. Additionally, to evaluate the impact of timing on the intervention, the same LMM was applied to the data from W0, W4, and W8. For MAS-EF and MAS-EE, which are ordinal variables, ordinal logistic regression was performed. The models included Group, Time, and the interaction between Group and Time as fixed effects, with values at W0 included as a covariate. Participants were included as a random effect. Group B4R4 served as the reference group, meaning that the effects

observed in the other groups were analyzed relative to Group B4R4. Therefore, if a specific variable showed a significant Time × Group interaction, this indicated that the change in that variable for the specific group was significantly different from that of Group B4R4. Furthermore, the number of significant Time × Group interactions for each kinematic-IND was counted to provide additional insights into the differences in trajectories among the four groups. All statistical analyses were performed using R version 4.2.4 and the R packages lme4 and clmm for repeated measures of numeric and ordinal data, respectively [22, 23]. The statistical significance level (α) was set at 0.05.

Results

A total of 42 participants were initially enrolled in the study, with two participants (one from Group B4R4 and one from Group B0R0) dropping out before the intervention began. No participants discontinued the intervention once it commenced. Thus, statistical analysis was performed on the remaining 40 participants (Fig. 2). There were no significant differences in baseline clinical characteristics between the four groups (Table 3). For robotic kinematic data, there were no group differences in SPARC-Whole ($p=0.319$) and MovDev-Whole ($p=0.408$) (Supplementary Table 1). However, significant group differences were observed in MeanSp-Whole ($p<0.001$) and HPRatio-Whole ($p=0.004$). No adverse events occurred during the study.

The estimates of model intercepts and slopes (i.e., changes in variables per week) and corresponding p-values are provided in the Supplementary tables, with Group B4R4 serving as the reference group. Tables 3 and 4 display the significance of Time × Group interactions. These significant Time × Group interactions indicate that the changes in variables for each group were greater than those for Group B4R4.

Changes from W0 to W4

Clinical assessments from W0 to W4 (Supplementary table 2)

From W0 to W4, no significant Time × Group interactions were observed for FMA-total and FMA-proximal (Fig. 3). The effect of time in Group B4R4 was not significantly different from zero for FMA-total (mean difference: 1.20, 95% CI: −0.60–3.00; $p=0.188$) and FMA-proximal (mean difference: 0.70, 95% CI: −1.10–2.50; $p=0.438$). For elbow spasticity from W0 to W4, significant Time × Group interactions were observed in Group B0R0 ($p<0.001$) and Group B0R4 ($p<0.001$) for MAS-EF (Fig. 4). No Time effect was observed in Group B4R4 ($p=0.608$). For the SIS variables, no significant Time × Group interactions or Time effects were observed in Group B4R4 from W0 to W4.

Robotic kinematic assessments from W0 and W4 (Table 4, supplementary table 3)

Figure 5 displays the kinematic data trajectories for each group at each time point. For SPARC-Whole, significant Time × Group interactions were observed in Groups B0R0 ($p<0.001$) and B0R4 ($p=0.012$), along with a significant Time effect in Group B4R4 ($p=0.024$). Significant Time × Group interactions for SPARC-IND were observed only in Group B0R0, with three significant interactions. For MeanSp, MeanSp-Whole showed a significant Time × Group interaction in Group B0R0 and a significant Time effect in Group B4R4. Significant Time × Group interactions for MeanSp-IND were found in Group B0R0 (one interaction), Group B0R4 (one interaction), and Group B4R0 (two interactions). Time effects were significant in three MeanSp-IND variables in Group B4R4. For HPRatio-Whole, significant Time × Group interactions were observed in Groups B0R0 and B0R4. The number of significant Time × Group interactions for HPRatio-IND was four in Group B0R0. For MovDev-Whole, significant Time × Group interactions were seen in Groups B0R0, B0R4, and B4R0, with a significant Time effect in Group B4R4. The number of significant Time × Group interactions for MovDev-IND was two in Group B0R0.

For NTward-out, no Time × Group interaction was observed in any kinematic variables (Fig. 6; Table 4). For STward-in, Group B0R0 exhibited Time × Group interactions in SPARC and HPRatio, whereas Group B4R0 showed a Time × Group interaction in MeanSp.

Changes across W0, W4, and W8

Clinical assessments across W0, W4, and W8 (Supplementary table 4)

Figure 3 displays the trajectories for FMA-total and FMA-proximal across W0, W4, and W8. The LMM analysis revealed a significant Group-by-Time interaction effect in FMA-total for Group B0R4, indicating that Group B0R4 showed greater improvement in FMA-total compared to Group B4R4 (mean difference: 1.40, 95% CI: 0.05–2.75; $p=0.042$). The Time effect in Group B4R4 was significantly different from zero for FMA-total (mean difference: 1.10, 95% CI: 0.13–2.07; $p=0.027$). For FMA-proximal, no Time × Group interaction was observed, but the Time effect in Group B4R4 was significantly different from zero (mean difference: 1.05, 95% CI: 0.13–1.97; $p=0.025$). In terms of spasticity, no significant Time × Group interactions were found, but Time effects were significantly different from zero for both MAS-EF and MAS-EE ($p<0.001$) (Fig. 4). For the SIS variables, no significant Time × Group interactions or Time effects were observed in Group B4R4.

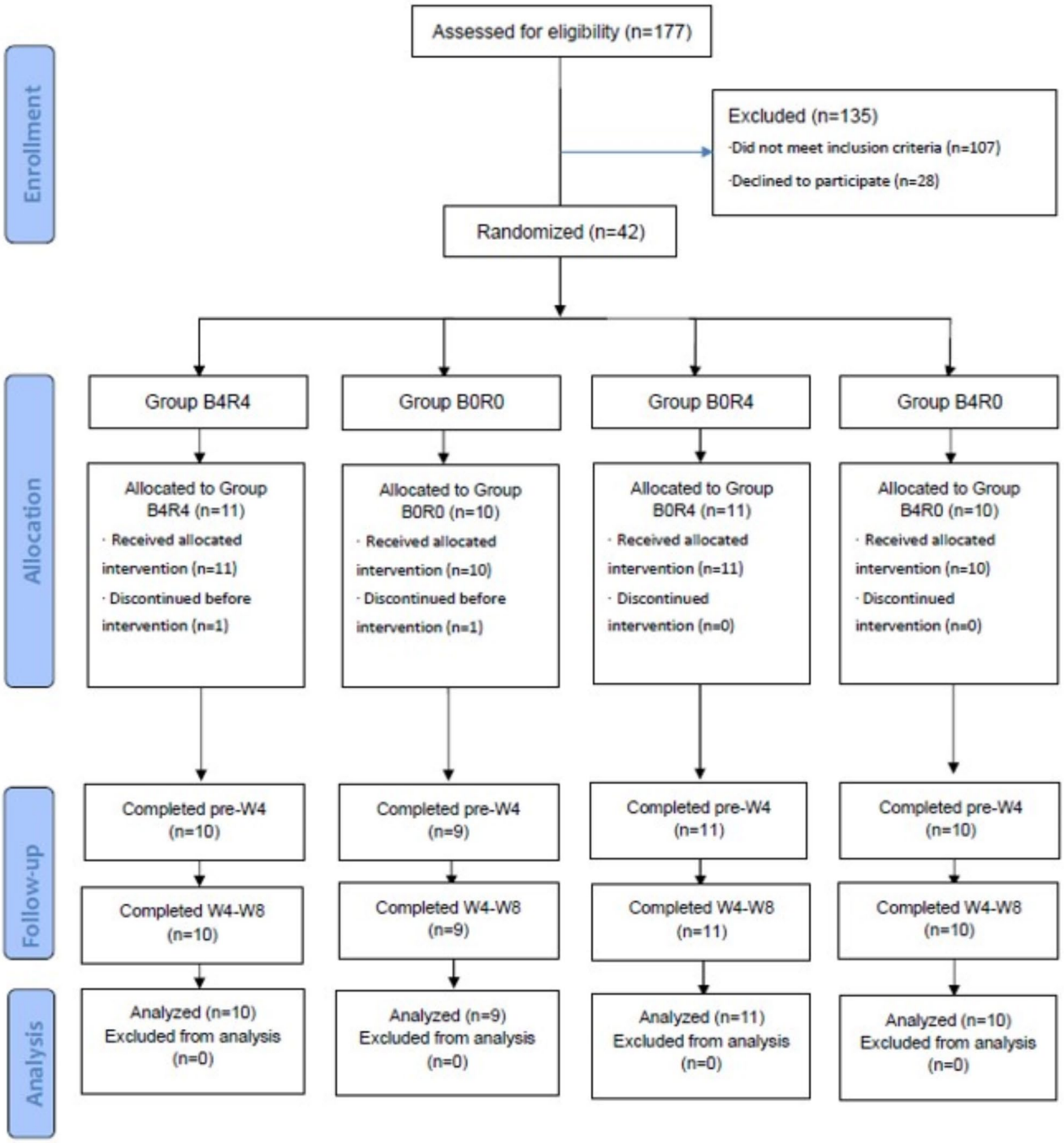

Fig. 2 CONSORT flow diagram throughout the study

Robotic kinematic assessments across W0, W4, and W8 (Table 5, supplementary table 5)

Figure 5 displays the kinematic data trajectories for each group at each time point. For SPARC-Whole, significant Time × Group interactions were observed in Groups B0R0, B0R4, and B4R0 compared to Group B4R4, along with a significant Time effect in Group B4R4. The number of significant Time × Group interactions for SPARC-IND was two in Group B0R0, four in Group B0R4, and zero in Group B4R0. For MeanSp-Whole, a significant Time × Group interaction was observed only in Group B0R4, with a significant Time effect in Group B4R4. The number of significant Time × Group interactions for MeanSp-IND was four in Group B0R4, with no significant interactions in Groups B0R0 and B4R0. HPRatio-Whole showed significant Time × Group interactions in Groups B0R0 and B0R4, with significant

Table 3 Demographic and baseline clinical characteristics

	Group B4R4 (*n* = 10)	Group B0R0 (*n* = 9)	Group B0R4 (*n* = 11)	Group B4R0 (*n* = 10)	*P*-value
Age, years	45.8 ± 11.2	51.8 ± 8.0	48.7 ± 9.9	50.5 ± 9.9	0.631
Sex, male	8 (80)	5 (55.6)	8 (72.7)	6 (60)	0.639
Time after onset, months	22.8 ± 10.2	22.2 ± 10.2	18.0 ± 5.6	17.3 ± 17.0	0.3
Affected arm, right	6 (60)	6 (66.7)	7 (27.2)	6 (30)	0.988

Time effects in Group B4R4. For HPRatio-IND, significant Time × Group interactions were observed in Groups B0R0 (three interactions) and B0R4 (five interactions). MovDev-Whole showed significant Time × Group interactions in Groups B0R0, B0R4, and B4R0, with significant Time effects in Group B4R4. The number of significant Time × Group interactions for MovDev-IND was two in Group B0R0 and five in Group B0R4.

In NTward-out movements, only Group B0R4 exhibited significant Time × Group interactions in MeanSp, HPRatio, and MovDev, with no significant Time effects in Group B4R4 for any kinematic variables (Fig. 6; Table 5). For STward-in movements, Group B0R4 demonstrated

Table 4 Significance of time X group interactions of kinematics across W0 and W4

SPARC	NTward-out	STward-in	NTward-in	STward-out	UNward-out	UNward-in	AFward-out	AFward-in	Whole
Time (Group B4R4)	0.211	0.343	0.144	0.361	0.305	0.147	0.153	0.854	**0.024**
Time x Group B0R0	0.310	**0.043**	0.059	0.206	**0.018**	**0.014**	0.911	0.108	**< 0.001**
Time x Group B0R4	0.132	0.100	0.465	0.820	0.178	0.534	0.843	0.243	**0.012**
Time x Group B4R0	0.108	0.840	0.820	0.804	0.268	0.943	0.580	0.393	0.063
MeanSp	NTward-out	STward-in	NTward-in	STward-out	UNward-out	UNward-in	AFward-out	AFward-in	Whole
Time (Group B4R4)	0.138	**0.050**	0.118	0.327	0.588	0.135	**0.047**	**0.049**	**< 0.001**
Time x Group B0R0	0.849	0.858	0.308	**0.004**	0.084	0.089	0.707	0.946	**0.005**
Time x Group B0R4	0.118	0.630	0.322	0.712	**0.033**	0.926	0.372	0.292	0.183
Time x Group B4R0	0.903	**0.021**	0.416	**0.044**	0.606	0.328	0.626	0.091	0.050
HPRatio	NTward-out	STward-in	NTward-in	STward-out	UNward-out	UNward-in	AFward-out	AFward-in	Whole
Time (Group B4R4)	0.363	0.213	0.244	0.481	0.320	0.075	0.188	0.991	0.051
Time x Group B0R0	0.146	**0.040**	0.054	0.402	**0.015**	**0.044**	0.778	**0.036**	**< 0.001**
Time x Group B0R4	0.075	0.142	0.646	0.323	0.109	0.624	0.706	0.170	**0.003**
Time x Group B4R0	0.099	0.971	0.999	0.592	0.297	0.665	0.618	0.323	0.054
MovDev	NTward-out	STward-in	NTward-in	STward-out	UNward-out	UNward-in	AFward-out	AFward-in	Whole
Time (Group B4R4)	0.348	0.334	0.129	0.376	0.246	0.064	0.190	0.967	**0.049**
Time x Group B0R0	0.115	0.053	0.075	0.416	**0.014**	**0.049**	0.862	0.063	**< 0.001**
Time x Group B0R4	0.070	0.111	0.507	0.398	0.137	0.595	0.613	0.137	**0.003**
Time x Group B4R0	0.080	0.814	0.863	0.597	0.249	0.644	0.648	0.268	**0.033**

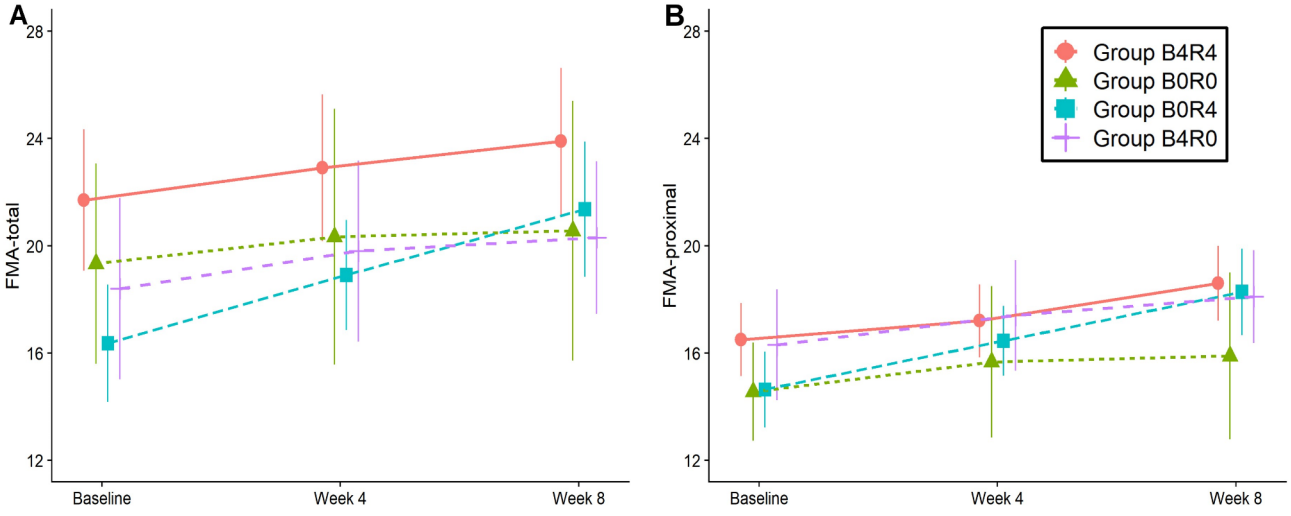

Fig. 3 Predicted values of FMA across four groups, derived from a linear mixed-effects model. (**a**) FMA-total, (**b**) FMA-proximal. Values are presented as mean ± standard error

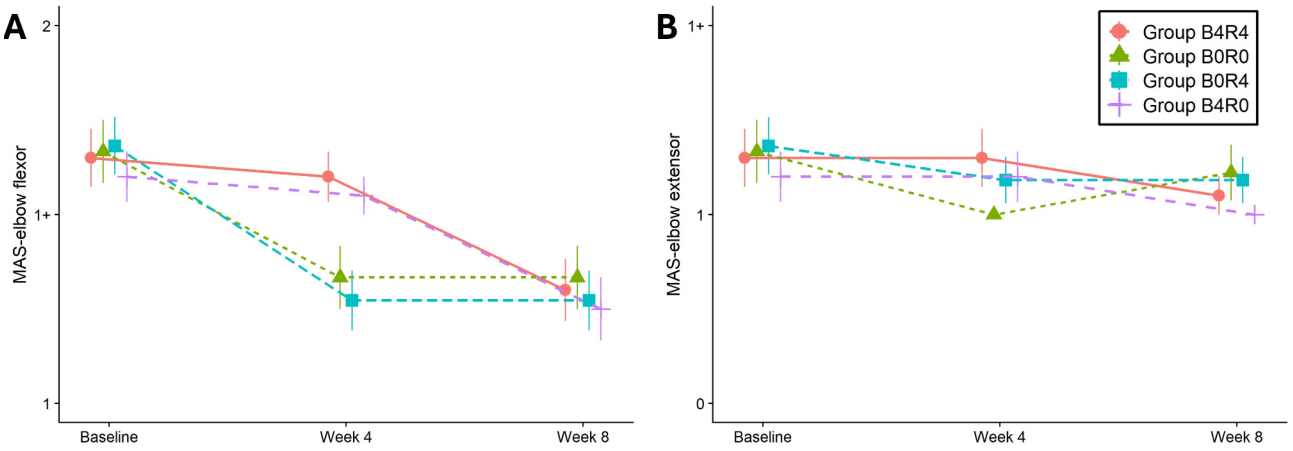

Fig. 4 Predicted spasticity values across four groups based on results from an ordinal logistic regression model. (**a**) MAS-elbow flexor, (**b**) MAS-elbow extensor. Values are presented as mean ± standard error

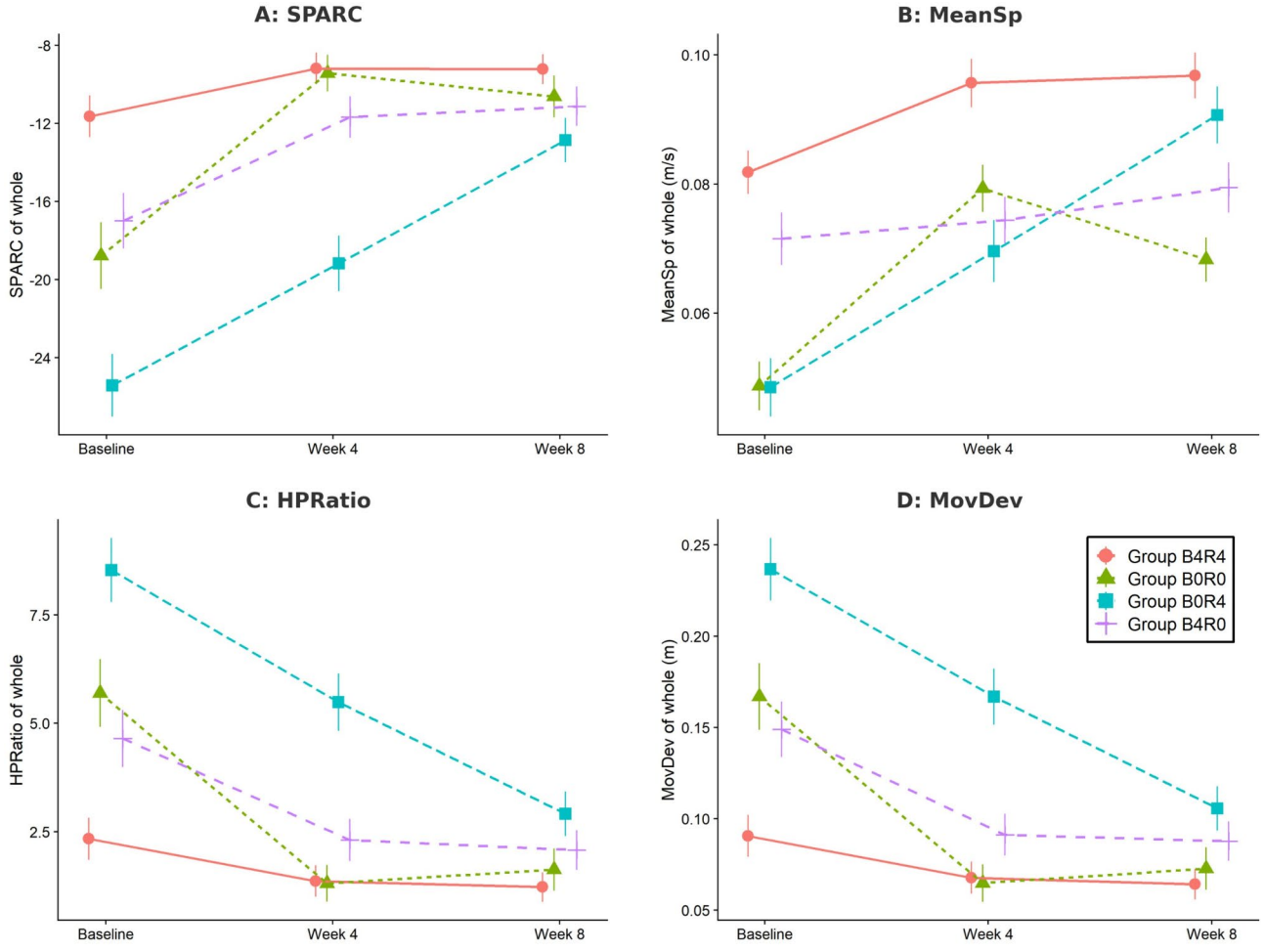

Fig. 5 Predicted values of robotic kinematic assessments across four groups, derived from a linear mixed-effects model. (**a**) SPARC-Whole (movement smoothness); (**b**) MeanSp-Whole (movement speed); (**c**) HPRatio-Whole (movement efficiency); (**d**) MovDev-Whole (movement accuracy). Values are presented as mean ± standard error

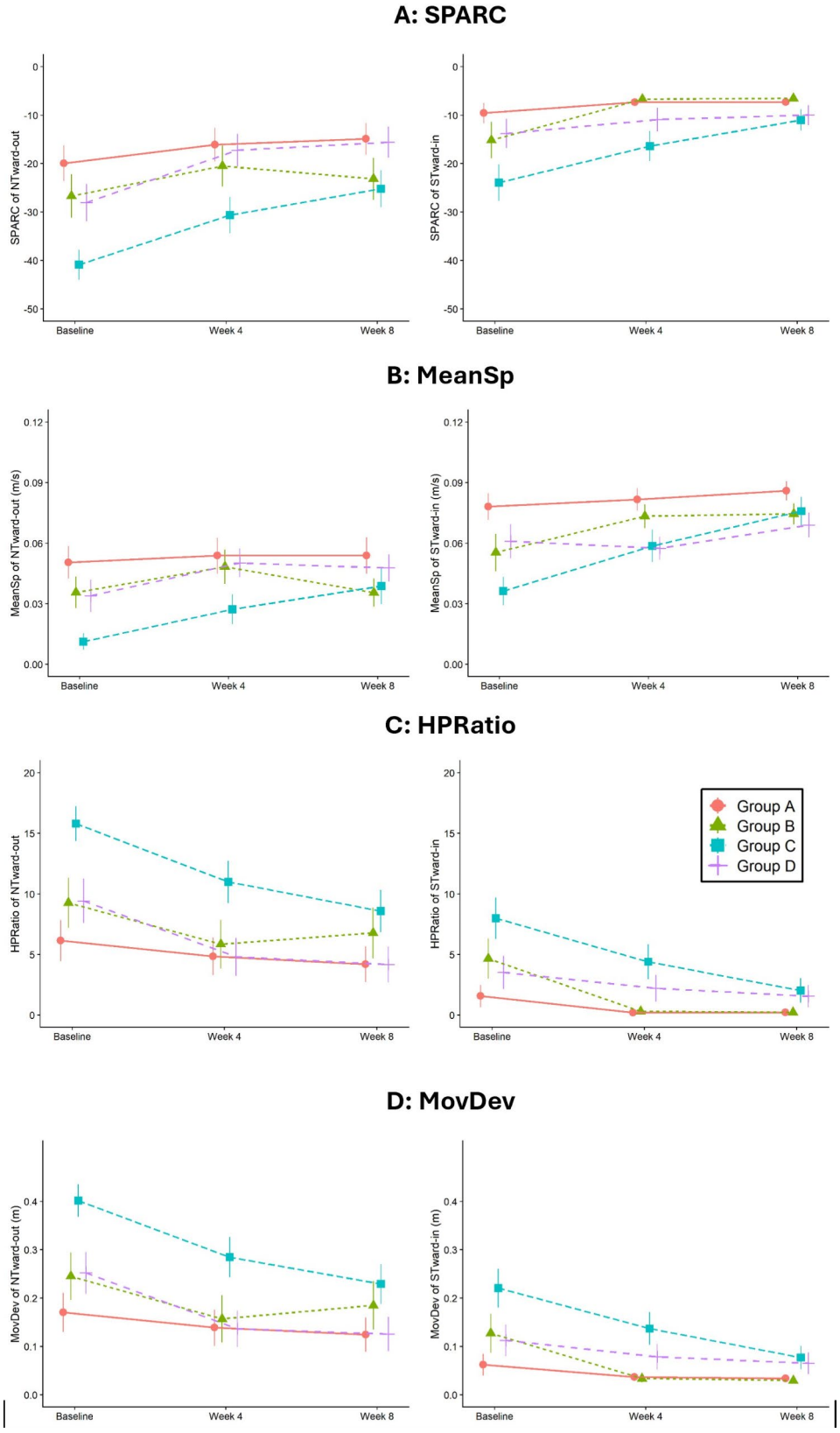

Fig. 6 Predicted values of robotic kinematic assessments for NTward-out and STward-in movements across four groups. Left: NTward-out; Right: STward-in. (**a**) SPARC (movement smoothness); (**b**) MeanSp (movement speed); (**c**) HPRatio (movement efficiency); (**d**) MovDev (movement accuracy). Values are presented as mean ± standard error

Table 5 Significance of time X group interactions of kinematics across W0, W4 and W8

SPARC	NTward-out	STward-in	NTward-in	STward-out	UNward-out	UNward-in	AFward-out	AFward-in	Whole
Time (Group B4R4)	0.103	0.314	0.320	0.934	0.115	0.288	0.189	0.720	**0.036**
Time x Group B0R0	0.830	**0.033**	0.008	0.099	0.163	**0.019**	0.308	0.092	**<0.001**
Time x Group B0R4	**0.014**	**0.001**	0.069	**0.005**	**0.042**	0.140	0.129	**0.002**	**<0.001**
Time x Group B4R0	0.092	0.633	0.315	0.561	0.999	0.180	0.267	0.423	**0.035**
MeanSp	NTward-out	STward-in	NTward-in	STward-out	UNward-out	UNward-in	AFward-out	AFward-in	Whole
Time (Group B4R4)	0.052	0.054	0.150	0.455	0.117	0.199	**0.029**	0.101	**<0.001**
Time x Group B0R0	0.244	0.748	0.902	0.067	0.874	0.411	0.299	0.604	0.415
Time x Group B0R4	**0.013**	**0.034**	0.353	**0.009**	**0.018**	0.093	0.496	0.339	**<0.001**
Time x Group B4R0	0.781	0.172	0.516	0.987	0.478	0.713	0.886	0.242	0.241
HPRatio	NTward-out	STward-in	NTward-in	STward-out	UNward-out	UNward-in	AFward-out	AFward-in	Whole
Time (Group B4R4)	0.180	0.200	0.223	0.995	0.150	0.073	0.208	0.976	**0.036**
Time x Group B0R0	0.461	**0.026**	0.054	0.198	0.103	**0.045**	0.416	**0.017**	**<0.001**
Time x Group B0R4	**0.009**	**0.002**	0.132	**0.001**	**0.034**	0.293	0.111	**0.002**	**<0.001**
Time x Group B4R0	0.109	0.682	0.420	0.618	0.980	0.422	0.363	0.271	0.052
MovDev	NTward-out	STward-in	NTward-in	STward-out	UNward-out	UNward-in	AFward-out	AFward-in	Whole
Time (Group B4R4)	0.182	0.258	0.145	0.895	0.128	0.054	0.218	0.991	**0.032**
Time x Group B0R0	0.442	**0.039**	0.053	0.249	0.088	0.050	0.413	**0.044**	**<0.001**
Time x Group B0R4	**0.009**	**0.001**	0.147	**0.001**	**0.031**	0.297	0.078	**0.001**	**<0.001**
Time x Group B4R0	0.101	0.599	0.455	0.677	0.853	0.586	0.386	0.252	**0.045**

significant Time × Group interactions in all kinematic variables, whereas Group B0R0 showed Time × Group interactions in SPARC, HPRatio, and MovDev, with no significant Time effects in Group B4R4 for any kinematic variables.

Discussion

As outlined in the introduction, this study explores two primary themes. First, the results from W0 to W4 reflect the effects of each intervention—RT, BTX, or RT + BTX. Second, the results from W0 to W8 examine the effects based on the timing of each intervention.

Effects of each RT or BTX: results from W0 to W4

From W0 to W4, no significant Time × Group interactions were observed in the FMA across any of the groups. Regarding kinematic-whole measures, Group B0R0 demonstrated significant Time × Group interactions in all kinematic-whole measures, Group B0R4 showed significant interactions in three kinematic-whole measures, and Group B4R0 showed significant interactions in just one kinematic-whole measure compared to Group B4R4. Furthermore, Group B0R0 exhibited the greatest number (9) of significant Time × Group interactions in kinematic-IND measures.

In terms of spasticity, significant Time × Group interactions in MAS-EF were observed in Groups B0R0 and B0R4, whereas Groups B4R4 and B4R0 did not show any significant Time × Group interactions. This suggests that significant spasticity reduction occurred only in the groups receiving BTX, indicating that RT alone was insufficient to reduce spasticity. Although the W4 to W8 data are not included here, significant changes in MAS-EF were also observed in Groups B4R4 and B4R0 from W4 to W8. These results demonstrate that spasticity improvements were primarily achieved through BTX rather than RT. Similar findings were reported by Pennati et al., who found that spasticity reduction was significantly greater with BTX compared to RT [9].

The effects of RT may vary depending on the type of rehabilitation robot or the training method used. A previous study comparing two training methods with the same robot used in our study—one similar to ours (upper limb movement regardless of flexion or extension) and the other focusing on extensor training—found no change in elbow spasticity in either group [24]. However, non-specific RT improved passive elbow ROM, while extensor-focused RT enhanced active elbow extension. These findings suggest that if RT had focused more on extensor movements alongside BTX injections, the synergistic effects might have been more pronounced. This is because the relaxed extensors, following BTX administration, could benefit more from robotic facilitation of extensor movement. As robotic rehabilitation continues to advance, more personalized training tailored to individual user characteristics and the specific mechanisms of the rehabilitation robot is likely to be more effective [25, 26].

Effects of timing of RT and BTX injection: results across W0, W4, and W8

Throughout the entire intervention phase (across W0, W4, and W8), only Group B0R4 demonstrated a significant Time × Group interaction in the FMA compared to Group B4R4. For kinematic-whole measures, Group

B0R4 showed significant Time × Group interactions in all kinematic-whole measures. Group B0R0 exhibited significant interactions in two measures and Group B4R0 in one. Additionally, Group B0R4 had the highest number of significant Time × Group interactions in kinematics-IND, followed by Group B0R0, whereas Group B4R0 did not show any significant interactions in kinematics-IND. Elbow spasticity, however, did not show any significant Time × Group interactions, suggesting no difference in spasticity across the groups. In summary, Group B0R4 achieved the most effective motor function recovery, followed by Group B0R0, Group B4R0, and finally Group B4R4, with no differences in spasticity observed.

Given that the total amount of RT was identical for all participants, the timing of RT relative to the BTX injection was crucial. BTX typically reaches peak efficacy in reducing muscle spasticity approximately two weeks post-injection, and Group B0R4 received RT when BTX effects were at their peak. Thus, at the time of RT, Group B0R4 likely experienced the greatest reduction in spasticity attributable to BTX, followed by Group B0R0 with a moderate reduction. Group B4R0 may not have experienced any spasticity reduction from BTX. Consequently, the effectiveness of RT was influenced by the degree of spasticity present during RT sessions. RT yielded the most effective results on motor function when the effects of BTX were maximized.

The link between spasticity reduction and motor function recovery can be understood as follows: Participants who experienced greater spasticity alleviation from BTX were likely to have more opportunities for motor learning, as spasticity affects motor learning capability [27]. Additionally, resistance from spastic muscles can hinder robotic-assisted movements during RT. Therefore, spasticity reduction allows for more harmonious movement, as intended by RT, with fewer conflicts between the participants and the robot. A usability test from an upper limb robotic rehabilitation study found that the assistive force from the robot caused conflicts with participants' spasticity, providing resistance against intended voluntary movements. Thus, more coordinated movements were possible with decreased spasticity [12]. In our study, the intervention dose (number of repetitions) of RT was identical for every participant, and this more coordinated interaction between the human and robot might have influenced the results. Optimal timing of RT during peak BTX effect could enhance neuroplasticity and lead to better integration of new motor skills.

Notably, Group B0R4 demonstrated improvements in SPARC, HPRatio, and MovDev, along with improvements in MeanSp, indicating that the improvements in Group B0R4 led to faster, more efficient, and accurate performance without a speed-accuracy trade-off. This suggests that improvements in one aspect (e.g., smoothness, accuracy) were not counterbalanced by deteriorations in another aspect (e.g., speed). Therefore, the optimal application of interventions, considering the mechanisms of each intervention, can promote motor skill learning and maximize functional gain [28, 29].

Kinematic analysis

Our results were robust owing to the incorporation of kinematic analysis, which provides objective and sensitive assessments of movement in individuals with stroke [30–32]. Our study demonstrated that robotic kinematic assessments provided more sensitive and detailed information, including movement smoothness, speed, efficiency, and accuracy, which clinical measurements alone could not offer. Notably, we analyzed not only the overall kinematic data (kinematic-whole measures) but also data segmented by direction, allowing for in-depth information. There were variations in kinematic variables depending on specific movements, aligning with a previous study [12]. This likely reflects that the participants experienced differential difficulty owing to their ULS. Additionally, the differential change depending on the movement showed that the effects of intervention varied across various movements. Therefore, kinematic analysis methods in this study provided a more informative picture reflecting individualized pathophysiology and recovery patterns of participants with stroke.

Particularly, the NTward-out and STward-in movements best reflect the effects of our intervention, as they require both a decrease in elbow flexor spasticity and sufficient voluntary elbow extensor activation to counteract flexor spasticity. For NTward-out, significant Time x Group interactions were not observed from W0 to W4 in any groups but emerged from W0 to W8 only in Group B0R4. Similarly, STward-in, which requires elbow joint movement similar to NTward-out but to a lesser extent, showed comparable trends. From W0 to W4, Group B0R0 showed significant Time x Group interactions in SPARC-STward-in and HPRatio-STward-in. From W0 to W8, significant Time x Group interactions in SPARC-STward-in and HPRatio-STward-in were maintained, and a significant Time x Group interaction in MovDev-STward-in emerged in Group B0R0.

Moreover, the inclusion of multiple kinematic variables provided additional insights. We hypothesized that movement smoothness would be the most representative outcome variable, as it is known to have stronger correlations with motor performance than other kinematic measures and has demonstrated greater sensitivity in detecting motor improvements [12, 13, 25, 33]. Concordantly, smoothness, which was represented by SPARC, demonstrated significant findings in the present study. Significant interactions were observed in Group B0R0 from W0 to W4, as well as in Group B0R0 and primarily

Group B0R4 across W0, W4, and W8. These findings highlight the complementary roles of BTX and RT in rehabilitation, with BTX establishing the physiological foundation by reducing spasticity and RT subsequently enhancing motor control to facilitate smoother movement. The timing of these interventions was critical, as demonstrated by the superior outcomes in Group B0R4. These significant findings in smoothness are especially meaningful because it is known as a key indicator of upper limb impairment and recovery among individuals with stroke [34].

HPRatio, reflecting movement efficiency, showed a similar pattern to SPARC. From W0 to W4, HPRatio-Whole improved in Groups B0R0 and B0R4; however, only Group B0R0 exhibited significant changes in individual movements. This highlights the importance of BTX-driven spasticity reduction in enabling smoother motion and minimizing resistance during movement execution. Across W0, W4, and W8, HPRatio-Whole improved in Groups B0R0, B0R4, and B4R4, with the most frequent individual movement improvements in Group B0R4, followed by Group B0R0, and none in Group B4R4. This suggests that RT is most effective when timed with sufficient spasticity reduction. BTX optimizes the motor learning environment by reducing spasticity, thereby enhancing robotic interaction and improving movement efficiency.

For MeanSp, a significant improvement in MeanSp-Whole from W0 to W4 was observed only in Group B0R0, while a significant improvement in MeanSp-Whole from W0 to W8 was observed in Group B0R4. Thus, the improvements in MeanSp-Whole in Groups B0R0 and B0R4 can be interpreted as meaningful fundamental changes resulting from the synergistic effects of RT and BTX, as well as the specific mechanisms of action of each intervention. Meanwhile, MeanSp exhibited distinct temporal patterns. From W0 to W4, significant Time × Group interactions were observed in MeanSp, differing from other kinematic variables, including smoothness, efficiency, and accuracy. This speed-accuracy trade-off is commonly encountered, and the improvements from W0 to W4 could be understood as not being generalized to the whole aspects of movement [35]. Interestingly, across W0, W4, and W8, significant Time x Group interactions were consistently observed for all kinematic variables, indicating that improvements in speed did not come at the expense of movement smoothness, efficiency, or accuracy.

These results support our previous discussion, highlighting two key findings. First, the combined effects of RT and BTX are superior to either sole intervention, as demonstrated by the results of Group B0R0 from W0 to W4. Group B0R0, which exhibited significant improvements in STward-in but not in NTward-out, suggests that the combination of BTX and RT can enhance upper limb function in individuals with post-stroke upper limb spasticity, albeit with a more limited impact on relatively less challenging tasks. For individuals in the acute or subacute phase of stroke, when neuroplasticity remains highly active, these effects may influence the recovery trajectory, particularly given the established benefits of early BTX injection [36]. Therefore, early interventions, as seen in Group B0R0, may be advantageous during the initial phase after stroke.

Second, the training effects of RT were most pronounced when spasticity was maximally reduced due to BTX injection, as observed in Group B0R4 from W0 to W8. Group B0R4 showed significant improvements in both NTward-out and STward-in, with NTward-out being the more challenging task. The results from W0 to W8 further suggest that more complex tasks require more time to achieve significant improvements than simpler tasks. This can be understood in the context of BTX creating a plastic state, enabling subsequent RT to drive functional improvements through motor learning, a process that requires time. This interpretation is supported by the fact that NTward-out movements demand greater strengthening of agonist muscles and improved coordination, in addition to spasticity reduction, compared to STward-in movements.

These findings suggest that Group B0R4 exhibited more fundamental improvements in motor function, representing the most effective approach. Therefore, for individuals with chronic stroke who have limited access to resources, an approach in which RT begins when BTX effects are maximized, starting RT approximately 2 weeks after BTX injection, would be preferable, considering the mode of action of BTX. Although Group B0R4 was designed to initiate RT 4 weeks post-BTX for study robustness, these findings suggest that earlier RT initiation may optimize rehabilitation outcomes.

Study limitations

There are several limitations to this study. First, we enrolled only individuals with chronic stroke, which limited our ability to observe the effects of BTX and RT in the subacute phase, where natural recovery processes may be more prominent. Given the potential for neuroplasticity and the impact of earlier rehabilitation and BTX administration in the early phase of stroke, results from subacute phase individuals with stroke might be more pronounced than the current findings [36, 37]. The delayed initiation of RT in individuals with chronic stroke may have limited the degree of neuroplastic adaptation, whereas earlier intervention in the subacute phase could potentially enhance synaptic remodeling and motor learning. Future studies should explore whether initiating RT at the peak of BTX efficacy in the subacute phase

produces greater functional gains. Second, the sample size was small. Additionally, a power analysis to determine the required sample size was not performed, as this study was designed as a pilot investigation. However, we used kinematic data, which is more sensitive than clinical scales, allowing us to capture significant findings despite the small sample size. Third, spasticity in muscles other than the elbow flexors was not treated with BTX injection, which may limit the generalizability of the results to all individuals with ULS. Fourth, participants received conventional therapy in addition to the study interventions, which may have influenced the results, particularly the effects of RT. However, given that all participants received the same amount of intervention, we believe our results primarily reflect the effects of RT and BTX.

Therefore, further studies with a larger sample size and sufficient statistical power based on the present study's findings are needed. Additionally, studies that include individuals in the subacute phase of stroke who may have greater potential for neuroplasticity are warranted.

Conclusion

This study highlights the superior efficacy of combining RT with BTX injections in improving motor function in individuals with ULS. The findings suggest that this combination is more effective than either intervention alone or no additional intervention. Moreover, initiating RT 1 month after BTX injection resulted in the most substantial motor function improvements compared to other timing combinations, emphasizing the importance of timing in maximizing therapeutic outcomes. These results underscore the importance of integrating RT and BTX, taking into account the mode of action of each intervention, to optimize therapeutic benefits in individuals with post-stroke ULS.

These findings have important clinical implications for the rehabilitation of individuals with post-stroke ULS, suggesting that combining RT with BTX could be a more effective therapeutic strategy than stand-alone intervention. Furthermore, the results highlight that careful consideration of the timing of RT initiation after BTX injections can enhance therapeutic efficacy. This approach has the potential to advance rehabilitation strategies, improving functional recovery for individuals with ULS in neurorehabilitation settings.

Abbreviations

ADL	Activities of Daily Living
AFward	Affected Side Movements
BTX	Botulinum Toxin
CT	Conventional Therapy
FMA	Fugl-Meyer Assessment
HPRatio	Hand Path Ratio
IND	Individual Movements
LMM	Linear Mixed-Effects Regression
MAS	Modified Ashworth Scale
MeanSp	Mean Speed
MovDev	Movement Deviation
NTward	Northward Movements
RT	Robotic Training
SIS	Stroke Impact Scale
SPARC	Spectral Arc Length Measure
STward	Southward Movements
ULS	Upper Limb Spasticity
UNward	Unaffected Side Movements
W0	Week 0 (Baseline)
W4	Week 4
W8	Week 8

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12984-025-01584-1.

Supplementary Material 1

Author contributions

Joon-Ho Shin: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing-original draft, Writing-review & editing; Gyulee Park: Data acquisition, Data curation, Visualization; Hayeon Kim: Data acquisition, Data curation; Duk Youn Cho: Data acquisition, Data curation; Suncheol Kwon: Data curation, Methodology, Formal Analysis.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Rehabilitation Hospital (NRC-2014-01-005) and registered at clinicaltrials.gov (NCT02228863). All participants provided informed consent before enrollment in the study.

Competing interests

The authors declare no competing interests.

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