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ORIGINAL REPORT

ROBOT-MEDIATED AND CLINICAL SCALES EVALUATION AFTER UPPER LIMB BOTULINUM TOXIN TYPE A INJECTION IN CHILDREN WITH HEMIPLEGIA

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Objective: **The aim of this pilot study was to examine changes in different aspects of impairment, including spasticity in the upper limbs, of hemiplegic children following botulinum toxin type A intervention. Progress was assessed using standard clinical measurements and a robotic device.**
Design: **Pre-post multiple baseline.**
Subjects: **Six children with hemiplegia.**
Methods: **Botulinium toxin type A injections were administered into the affected upper limb muscles. Outcomes were evaluated before and one month after the injection. Outcome assessments included: Melbourne Scale, Modified Ashworth Scale (MAS) and Passive Range of Motion. Furthermore, a robotic device was employed as an evaluation tool.**
Results: **Patients treated with botulinum toxin type A had significantly greater reduction in spasticity (MAS, $p < 0.01$), which explains an improvement in upper limb function and quality movement measured with the Melbourne Scale ($p < 0.01$). These improvements are consistent with robot-based evaluation results that showed statistically significant changes ($p < 0.01$) following botulinum toxin type A injections.**
Conclusion: **The upper limb performs a wide variety of movements. The multi-joint nature of the task during the robot-mediated evaluation required active control of joint interaction forces. There was good correlation between clinical scales and robotic evaluation. Hence the robot-mediated assessment may be used as an additional tool to quantify the degree of motor improvement after botulinum toxin type A injections.**

Key words: robotics, botulinum toxin, child, muscle spasticity, upper extremity.

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INTRODUCTION

Muscle spasticity of the limbs is a common clinical sign in children with acquired or congenital neurological disorders (ND). Lance's (1) definition of spasticity is: "a motor disorder characterized by a velocity- dependent increase in tonic stretch reflexes with exaggerated tendon jerk, resulting from hyper-excitability of the stretch reflex, as one component of the upper motor neuron syndrome". Spasticity is characterized by a number of motor disorders that include positive and negative symptoms and that characterize children affected by ND. Positive symptoms include spasticity, hypertonia, increased muscle stiffness and excessive co-contraction between agonist and antagonist muscles. Negative symptoms include muscle weakness, abnormal postural adjustments, abnormal motor synergies and inter-joint incoordination (2–5). Children affected by hemiparesis during reaching movements showed an unstructured inter-joint coordination between elbow and shoulder from the middle to the end of the reaching act. In particular, in mid-reach, they had difficulties in coordinating elbow flexion with shoulder horizontal adduction, in going from flexion to extension of the elbow and in coordinating these with shoulder movement (6, 7).

Goal-directed movement in hemiparetic children is characterized by decreased movement speed, smoothness and coordination, and abnormal muscle synergy. Deficits in voluntary control of movement, together with presence of spasticity, have been associated with disorders in the organization of segmental reflex activity (7).

In the last few years botulinum toxin type A (BoNT-A) has been widely used in the management of spasticity in children with acquired or congenital brain injury in order to reduce hypertonicity and improve functional outcomes (8, 9) enhancing motor skill development. The reduction in spasticity after BoNT-A injection seems to be useful in the management of muscle contracture and bone deformity (10, 11), improving the joint range of motion, muscle coordination, and motor function with long-lasting effectiveness from 2 to 4 months (12–14). Several studies (15, 16) assess these changes by using conventional clinical scales that may, however, be insufficient to quantify the functional improvement in the limb after the injection (17). Quantitative and qualitative descriptions of motor synergy changes after a brain injury are poor overall and this hampers understanding of the process underlying the recovery of motor function (18–20). Robotic devices provide

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force feedback for sensory-motor-type rehabilitative training, assist patient's movement and allow us objectively to measure and quantify the improvement, measuring speed, direction and strength of residual activity (21–23). They can also be used to measure displacement and force by obtaining speed, acceleration and jerk of the upper limb, which are important parameters to assess the repeatability of movement and which are strictly related to the capability of coordination of adjacent arm joints (24, 25). Flash & Hogan (26, 27) found that, for unimpaired subjects, the movements tend to be characterized by a low level of jerk, which implies a jerk minimization strategy adopted by the central nervous system in planning control movements. This is quite clear because a minimization of the jerk (reducing acceleration variation) involves a further strategy of energy saving during movement in terms of muscle activities. Jerk analysis may therefore be used as an indicator of the "smoothness" of a trajectory, or of its level of segmentation.

The aims of this pilot study were to evaluate the effects of botulinum toxin interventions on different aspects of impairment including spasticity of the upper limb in children with acquired or congenital hemiparesis, and to investigate the kinematics of elbow and shoulder intrinsic movements utilizing a robotic device.

METHODS

Six children, aged from 7 to 14 years, were enrolled in this pilot study: 3 with cerebral palsy (CP), 2 with traumatic brain injuries and one with stroke.

Inclusion criteria were: (*i*) hemiplegia; (*ii*) the presence, without contracture, of 2/3 Modified Ashworth Scale (MAS) stable spasticity of shoulder, elbow, forearm and wrist; (*iii*) an adequate active range of motion (ROM) of elbow and shoulder to perform the robotic evaluation task; (*iv*) onset of brain injury having occurred at least 6 months previously; and (*v*) the ability to attend all testing sessions.

No other medication was prescribed for reducing spasticity during the period of study, and children who received BoNT-A injection within 6 months of study enrolment were excluded. Children were recruited from a pool of patients from the Rehabilitation Department of the Children's Hospital "Bambino Gesù" (Rome, Italy). Informed parental consent and children's assent to BoNT-A injection were obtained and the study protocol was signed before enrolment. The research conforms to the ethical standards laid down in the 1964 Declaration of Helsinki. The experimental protocol was approved by the ethics committee at Children's Hospital "Bambino Gesù", where the study was conducted.

Apparatus

We used the InMotion2 robot (Interactive Motion Technologies, Inc., Cambridge, MA, USA) (Fig. 1A). MIT-Manus is a planar 2 degrees-of-freedom (DOF) highly back-drivable (i.e. low inertia and friction). This robot was developed specifically for upper limb neurorehabilitation (28). No modifications were required to allow its use in children because this is an end-effector-based robot. We only modified the chair size and the hand-holder to fit smaller patients. Subjects were seated with the trunk strapped by a 5-point seatbelt to limit forward trunk compensation, and their paretic arm was placed in a hand-holder attached to the robot end-effector.

The robot allows gravity compensation by means of arm sustainers and it moves on a horizontal plan involving the shoulder and the elbow. The subject's wrist was strapped to a moulded support in order to avoid any other joint rotation apart from the shoulder and elbow.

The robot sensors allow for accurate and continuous measurement of relevant key variables including position and velocity (sampled at 200 Hz, with accuracies of 0.1 mm and 1.5 mm/sec, respectively). A computer screen located in front of the child provides online visual feedback of the target location and of the handle's movement.

A physical therapist was present during the trials to ensure proper positioning of the child and to provide verbal instructions and incentive.

Procedures

All children were injected with BoNT-A in the muscles of the forearm and upper arm by the same physician, who was experienced in botulinum toxin injection technique. The dosage and locations of the intramuscular BoNT-A injection were defined specifically for each child based on the severity and distribution of the spastic muscles involved and on the weight of the child. The recommended 1–2 units/kg body weight of BoNT-A for each muscle over the upper limb was administered. Among the injected muscles, the targeted biceps brachii muscle (one of the main elbow flexors) was always included for injection. Other muscles that were injected with intramuscular BoNT-A included the flexor carpi radialis, the flexor carpi ulnaris, and the pronator teres. Table I shows the subjects' clinical data and injection sites. A topical anaesthetic spray was applied locally before the injection.

The rehabilitation programme remained unchanged during the month of observation and consisted of passive and dynamic stretching of the injected muscles and of the use of positioning splints to be used at night only.

The evaluation protocol consisted of a clinical evaluation by means of videorecording and 2 robot-mediated assessments (before/after BoNT-A injection). Children were required to perform 2 baseline evaluations over a 3-month period before the BoNT-A injection to measure upper limb motor performance. The same evaluation was performed 4 weeks after the injection at the peak effect of botulinum toxin (29, 30). Clinical evaluation provided information on the degree of upper limb spasticity, passive ROM and function, to be compared with robotic evaluation findings. The clinical evaluations included the MAS (31), the Passive Range of Motion (PROM) (32, 33) measurement of elbow, forearm and wrist and the Melbourne Assessment of Unilateral Upper Limb (34, 35).

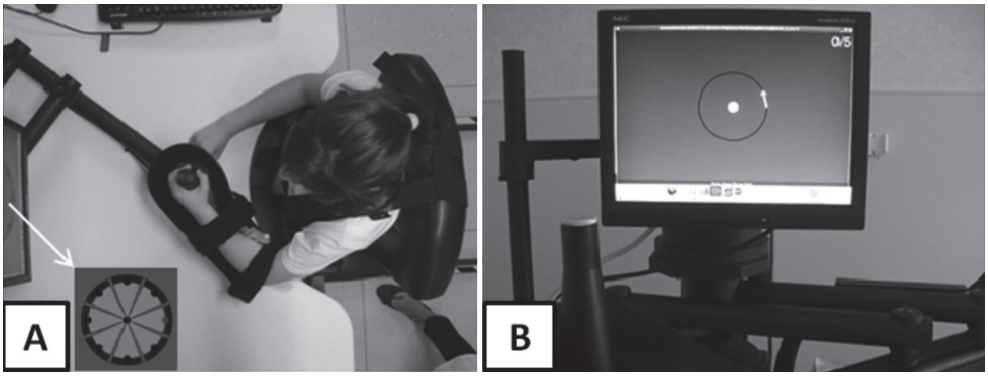

Fig. 1. (A) Centre out target set: each subject was asked to move their arm towards 8 different peripheral targets then return to the centre. (B) Drawing circle task: starting from 3 o'clock and moving counter-clockwise (CCW).

Table I. *Summary of the subjects' clinical data and botulinum toxin type A injection sites*

Gender/ age, years	Diagnosis	Injection site (U)
F/14	Right hemiplegia, stroke (at age 5 years)	Biceps brachii (25 U), pronator teres (15 U), FCR (15 U), FCU (15 U)
M/7	Right hemiplegia, CP	Biceps brachii (20 U), pronator teres (15 U), FCR (10 U), FCU (15 U)
M/8	Left hemiplegia, TBI (at age 6 years)	Biceps brachii (20 U), pronator teres (10 U)
F/8	Right hemiplegia, TBI (6 months previously)	Biceps brachii (20 U), pronator teres (15 U), FCR (10), FCU (10 U)
M/14	Right hemiplegia, CP	Biceps brachii (25 U), pronator teres (15 U), FCR (10 U), FCU (15 U)
M/12	Left hemiplegia, CP	Biceps brachii (25 U), pronator teres (15 U)

CP: cerebral palsy; F: female; FCR: flexor carpi radialis; FCU: flexor carpi ulnaris; M: male; TBI: traumatic brain injury: U: units.

Robot-mediated evaluation consisted of 2 different tasks. First, visually-evoked, goal-directed planar reaching movements used as a familiarization phase to allow subjects to practice with the manipulandum; 8 targets were equally spaced on a circumference and visual feedback of both target and robot handle location were provided on a computer screen in front of the child. The task required each subject to attempt to move their arm from the centre position to a target and then return to the centre (36), for a total of 80 reaching movements. The second task involved drawing circular shapes clockwise and counter-clockwise (see Fig. 1B). The experiment consisted of drawing 20 circular shapes of 16 cm radius by moving the end-effector of the robot on a horizontal plane in both directions (clockwise and counter-clockwise) (28, 37). During this task, no control was applied by the robot to the patient's hand, and the elbow was supported by a low friction pad. Robotic evaluation sessions lasted between 40 min and 1 h.

Measurements

All data were acquired at 200 Hz and smoothed by using a 6th order Butterworth filter, with a 170 ms window (cut-off frequency 11 Hz). A set of derived kinematic indices were extracted from raw data, which enabled the comparison of the children's motor skill before and after BoNT-A injection. These indices are:

- *Point Into Area (PIA):* PIA was measured using data from the drawing circle task. This is the number of points of the trajectory inside a region limited by an inner and outer circle (Fig. 2A). The higher the number of points of the traced trajectory inside the region, the better the execution of the task.
- *Average speed:* this is the mean value of the end-point velocity from movement onset to termination.
- *Average jerk:* was measured as the average of the jerk over the duration of the movement.
- *Shoulder-elbow angular error:* for each subject the arm and forearm lengths were measured and an inverse kinematic algorithm applied to measure the instantaneous shoulder and elbow angle while performing the drawing task. The data was evaluated using the angle convention (18) of Fig. 2B, as described by Dipietro et al. (18).

In order to evaluate the elbow and shoulder angular error while tracing the circle, a desired trajectory has been defined. Previous research (38) has shown that humans tend to perform planar trajectories with the goal of making the smoothest movements; this outcome led to a formalization of a dynamic optimization model in order to minimize the accelerative transient; smoothness appears to be a relevant feature of an unimpaired subject's movement. In addition, there is an old conjecture in movement neuroscience that continuous arm movement appears to be composed of discrete sub-movements. Krebs et al. (39) showed how smoothness and number of sub-movements change with recovery and can be used as an indicator of the level of the pathology.

Hence, we decided to use a minimum jerk model to define a desired path to be compared with the patient's ones; a 30 control-points circular path at minimum jerk profile was generated with the same duration as the real trajectory. The control points were used to evaluate the ideal shoulder-elbow angles and compare them with the actual angles of the patient's joints during movement.

This pilot study used a multiple baseline design to assess the stability of the lesion before BoNT-A injection and the changes induced in the upper limb by the same injection.

Descriptive summary statistics for differences between the mean scores and the mean changes from baseline for main measures are presented.

Paired and independent *t*-tests were used to compare change scores from enrolment to protocol completion. Statistical significance was set at $p \leq 0.05$.

RESULTS

MAS measurements confirm a significant reduction in muscle spasticity for BoNT-A treated children. In addition, this effect on muscle tone is in agreement with the functional scale changes. Mean score (standard deviation (SD)) paired sample *t*-tests for MAS across all joints, Melbourne scale and PROM of elbow, forearm and wrist results are shown in Table II.

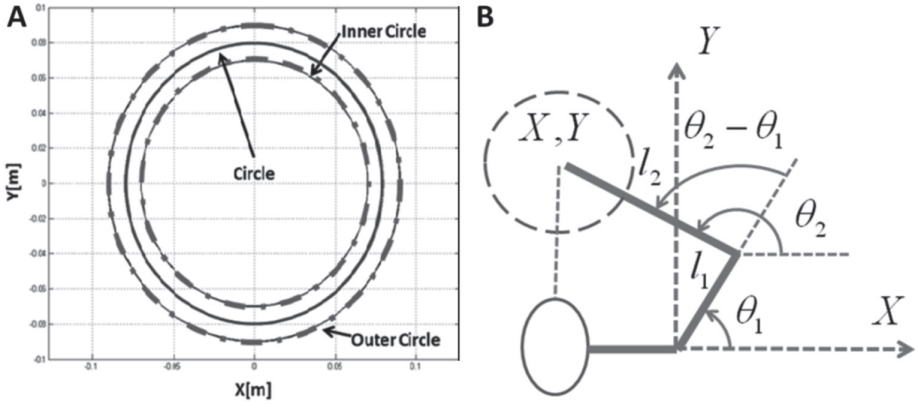

Fig. 2. (A) Visualization of the sensitive area around the circle used for the evaluation of the Point Into Area (PIA) index; the radii of the inner and the outer circle are 7 mm and 9 mm, respectively. (B) Angle convention used to operate the kinematic inversion in order to obtain the shoulder and elbow angles form the Cartesian trajectory of the robot handle.

Table II. *Before vs after botulinum toxin type A (BoNT-A) injection: scale scores (n = 6)*

Evaluation	Time of the evaluation	Mean (SD)	*p*-value
Melbourne Scale	Admission*	58.8 (16)	
	Discharge	63.3 (18)	
	Difference	4.5 (1.7)	0.01
MAS across all joints†	Admission*	8.8 (3.7)	
	Discharge	6.7 (3.6)	
	Difference	2.1 (0.1)	< 0.001
PROM elbow‡	Admission*	29.1 (10.2)	
	Discharge	17.5 (12.9)	
	Difference	11.6 (2.7)	0.008
PROM forearm§	Admission*	44.1 (14)	
	Discharge	50 (19)	
	Difference	5.8 (4.2)	0.03
PROM wrist¶	Admission*	35.8 (14.4)	
	Discharge	34.4 (11.7)	
	Difference	4.1 (2.6)	0.09

*Mean of scores from 2 baseline evaluations for each child.
†Mean Modified Ashworth Scale (MAS) of shoulder elbow and wrist.
‡Passive Range of Motion (PROM) of elbow: flex-extension 150–0°.
§PROM of forearm: prono-supination 0–80°.
¶PROM of wrist: flex-extension 0–70°.
SD: standard deviation.

The changes in elbow flexor PROM and prono-supinators of forearm PROM were statistically significant, with *p*-values of 0.008 and 0.03, respectively. PROM at the wrist increased in 3 subjects, with initial range limitations in the wrist, but the changes were not significant ($p = 0.09$).

As regards MAS values, it was observed that in 5 of the 6 subjects spasticity decreased in at least one joint at some time during the 4 weeks following the injection (see Table II). The changes in elbow flexor MAS and prono-supinators of forearm MAS were statistically significant, with *p*-values of 0.01 and 0.02, respectively. Changes in wrist flexor muscles, however, were not statistically significant.

Upper limb function and quality of movement (Melbourne Assessment of Unilateral Upper Limb) increased in 5 of 6 children (Table II). The changes were statistically significant ($p = 0.01$). In particular, improvement was obtained at elbow-level, with an improvement in the ROM and greater accuracy and fluency of reach and placement movements.

Robot-mediated evaluation results

An initial qualitative analysis of the circle task can be performed by tracing the trajectory before and after BoNT-A injection. Fig. 3 shows 5 different circles drawn before and after application of

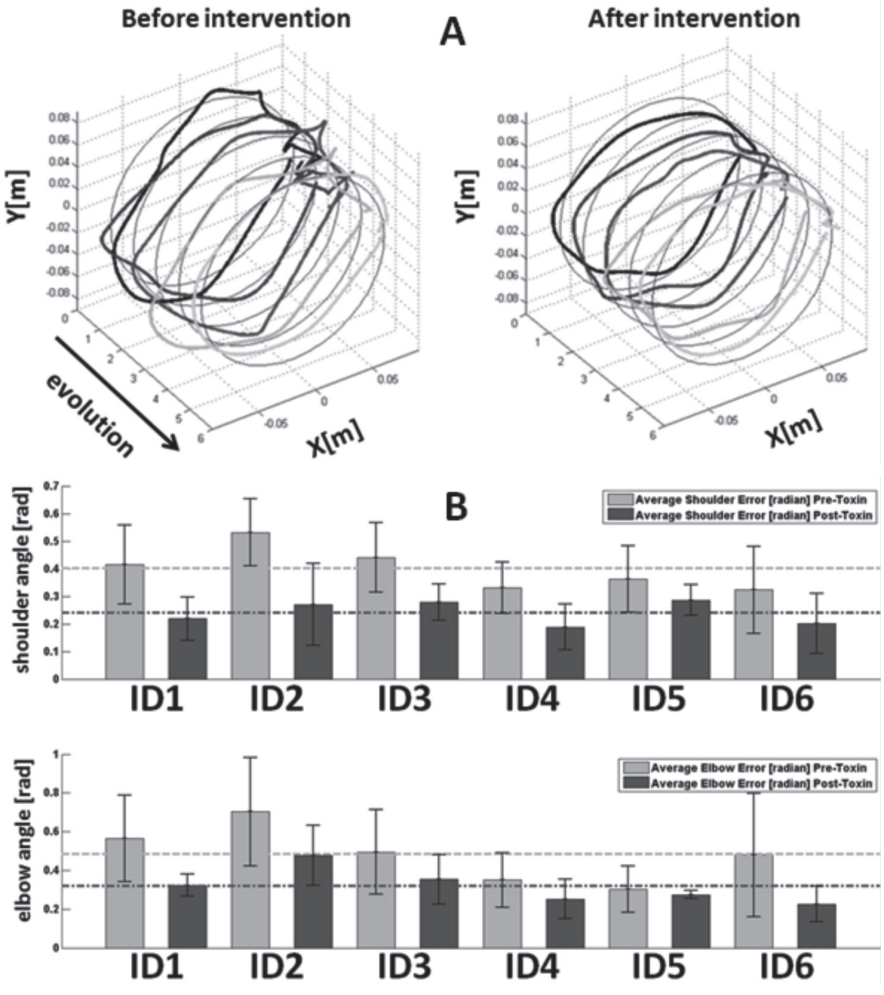

Fig. 3. (A) Plots of the circular shapes drawn by one subject before and after botulinum toxin injection. The black lines are the desired Cartesian trajectories. (B) Mean angular error of the shoulder and elbow correlate to minimum jerk simulation model. In all patients, the angular error of shoulder and elbow decreases over the course of treatment and seems to converge towards the predicted value of the minimum jerk model.

the toxin; the figure clearly shows that the movements appear to be more accurate and smoother after the injection.

After the injection, the angular error between the 2 paths seems to decrease, improving during the execution of the tasks; for instance the 5 trials depicted in Fig. 3A highlight to what extent the subject is able to move the shoulder and elbow in a smoother way, showing trajectories with a lower level of segmentation and lower value of mean jerk. Another important aspect is the high accuracy of the predictive model, in which an improvement in the patient's performance appears to converge towards the minimum jerk model.

Taking into account the results for all subjects, a clear and significant difference was found in the angular error of shoulder ($p = 0.005$) and elbow ($p = 0.001$) before and after the use of botulinum toxin (Fig. 3B); all the subjects appear to use their joints in a more synergistic way. This complementary outcome can be observed by comparing the shoulder elbow angular error with the ideal angular path evaluated by means of the minimum jerk model; as shown in Fig. 4 the joints angle seems to become closer to the ones resulting from the simulation. A complementary outcome is given by the PIA index (Fig. 5), which confirmed the higher accuracy in movements for all the subjects except ID5; significant improvements ($p < 0.01$) were observed in almost all patients in tracing the circular shape after BoNT-A injection.

The average jerk seems to decrease ($p = 0.026$) in all the subjects after the toxin injection, confirming the observation of higher smoothness of the trajectories and improvement in angular shoulder elbow error compared with the minimum jerk model. On the other hand, the average speed does not appear to have a clear trend over the course of the therapy; if some patients performed the task at a significantly higher velocity, in the others the average speed was almost unchanged; the subjects' capability to perform better during the therapy does not seem to be related to velocity but more to fine control of limb position. A further possible explanation could be that during the exercise no time constraints were imposed on the subject for completion of the task.

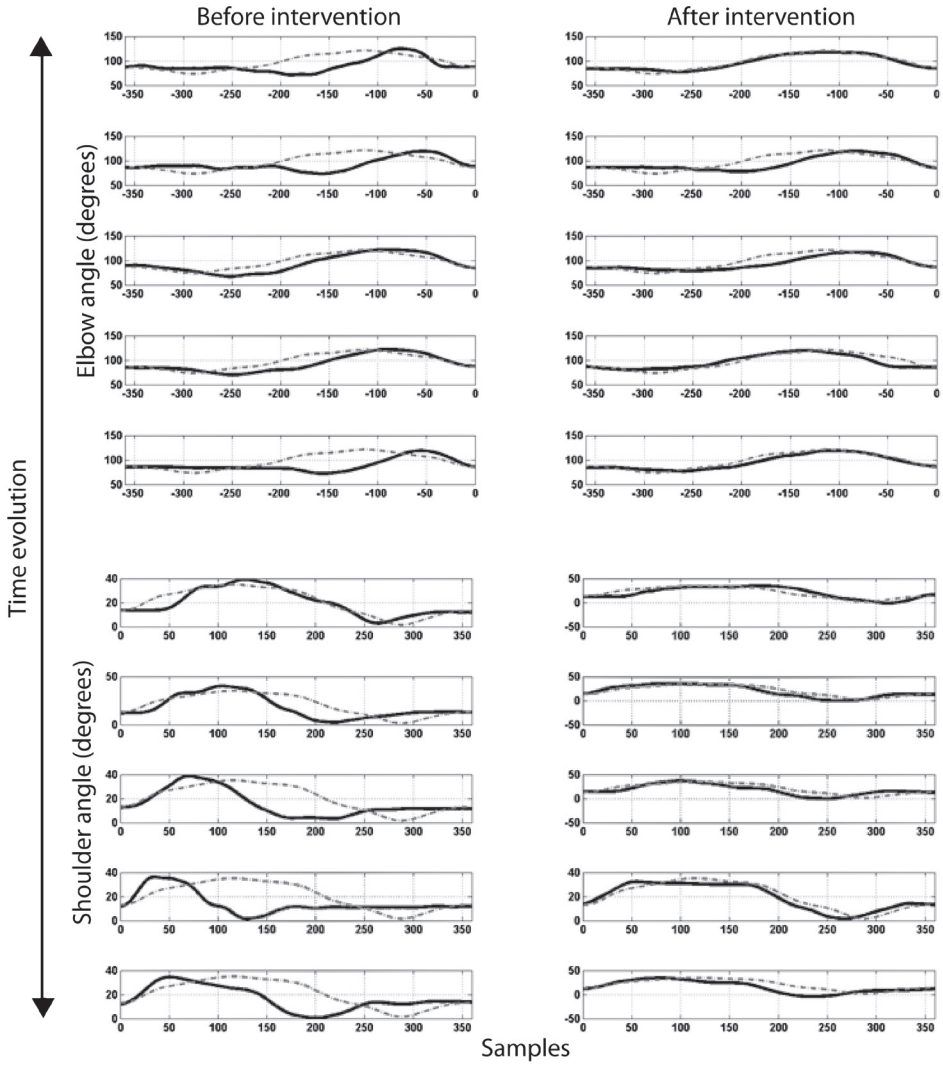

Fig. 4. Elbow and shoulder angular error for one subject. The dotted lines represent the results of the angle generated by the minimum jerk model; a lower angular error between patient's shoulder and elbow and simulated trajectories is clearly visible in the plots performed after the application of botulinum toxin.

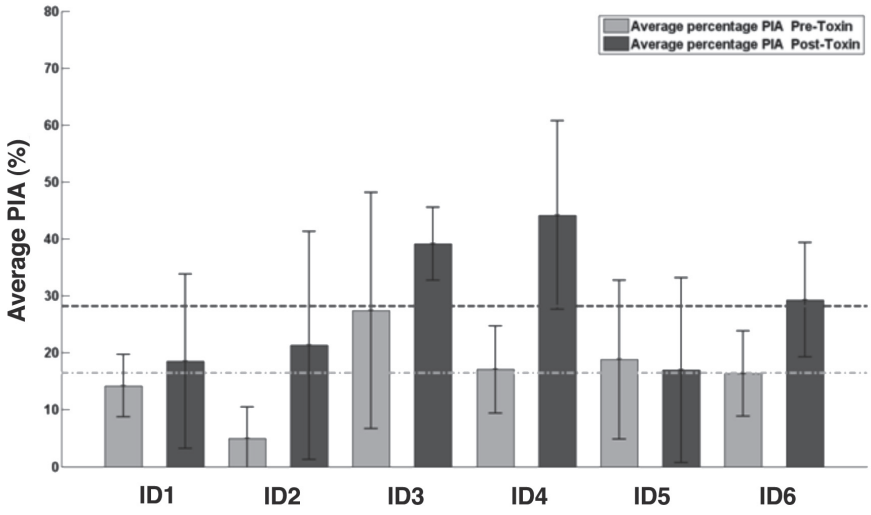

Fig. 5. Point Into Area (PIA) evaluated for all the subjects during the trials; the score represents the percentage of the total points of the real trajectory that are inside the borders of interest.

DISCUSSION

Evaluation of the clinical scales of the upper limb reveals a final score improvement one month after botulinum toxin injection; likewise, robot-mediated evaluation shows an improvement in smoothness and in the circle trajectories' profile. Generally, children with hemiplegia show multi-joint pointing movements characterized by lower speed, increased variability, higher segmentation and spatiotemporal incoordination between adjacent arm joints (7). Arm movement trajectory is more dispersed and spatially segmented (7, 19). Robot evaluation tasks require a multi-joint movement that demands a more complex coordination than single joint movement (37), especially in the case of planar drawing of 2-dimensional shapes. Furthermore, a more accurate circle drawing is the result of a higher synergy in shoulder and elbow coordination (18, 37). After BoNT-A injection, we observed changes in the drawing circle trajectory, with a profile closer to the ideal one, as indicated by the smoothness indices. This improvement is consistent with the results of the clinical scales. In fact MAS, PROM and Melbourne Assessment indicate statistically significant changes; these findings reflect the pharmacological effects of BoNT-A, i.e. a reduction in muscle tone and a significant improvement in PROM during the period of chemodenervation induced by the botulinum toxin. However, the sample is too small to confirm the existence of a link between body structure, function and changes in functional activities.

The shoulder-elbow angular error indicates to what extent the real trajectory drawn by the child is close to the ideal one. In fact the improvement in this parameter could be correlated with a smooth coordination between shoulder and elbow when the end-point effector of the upper limb (the hand) is constrained by the robot handling.

Robotic tasks require eye-hand coordination, i.e. the movements must be actively controlled in terms of end-point accuracy. From this perspective, after BoNT-A injection data show shorter execution time, higher smoothness in drawing circle movement, and greater consistency of jerk profile across trials, indicating a better control strategy and a lower reliance on proprioceptive feedback. In clinical neurorehabilitation, motor synergies are considered as a compensatory strategy developed when the subject tries to move (3) and are characterized by the loss of control between agonist-antagonist reciprocal activation (19). The trajectory recorded by the robotic device appears to be useful to provide a quantitative (smoothness indices changes) and qualitative description of the changes in pathological synergies.

The responsiveness to botulinum toxin injection was found in trajectory profile, shoulder-elbow angular error and average jerk. Few studies have investigated the effects of botulinum toxin through objective measurement (8); furthermore, since no other studies have used a robotic device, such as InMotion2 (Interactive Motion Technologies, Inc., Cambridge, MA, USA), to evaluate the motor function improvement of children's upper limb after BoNT-A injection, these results cannot be compared with any others. Therefore, although the InMotion2 is probably not a suitable device for routine evaluation of the upper limb in children treated with BoNT-A injection, it is a reliable and sensitive tool for controlled trials and to evaluate and study some of the characteristics of motor recovery (40).

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