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A randomized trial of upper limb botulimun toxin versus placebo injection, combined with physiotherapy, in children with hemiplegia

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ABSTRACT

The main goal of this study was to investigate the efficacy of Botulinum Toxin A (BoNT-A), combined with an individualized intensive physiotherapy/orthoses treatment, in improving upper limb activity and competence in daily activity in children with hemiplegia, and to compare its effectiveness with that of non-pharmacological instruments. It was a Randomized Clinical Trial of 27 children with spastic hemiplegic cerebral palsy, outpatients of two high speciality Centres for child rehabilitation. Each child was assigned by simple randomization to experimental group (BoNT-A) or control group (placebo). Assisting Hand Assessment (AHA) was chosen as primary outcome measure; other measures were selected according to ICF dimensions. Participants were assessed at baseline (T0), at T1, T2, T3 (1–3–6 months after injection, respectively). Every patient was given a specific physiotherapeutic treatment, consisting of individualized goal directed exercises, task oriented activities, daily stretching manoeuvres, functional and/or static orthoses. BoNT-A group showed a significant increase of AHA raw scores at T2, compared to control group (T2–T0: $p = .025$) and functional goals achievement (GAS) was also slightly better in the same group ($p = .033$). Other measures indicated some improvement in both groups, without significant intergroup differences. Children with intermediate severity of hand function at House scale for upper limb impairment seem to have a better benefit from BoNT-A protocol. BoNT-A was effective in improving manipulation in the activity domain, in association with individualized goal-directed physiotherapy and orthoses; the combined treatment is recommended. The study brings more evidence for the efficacy of a combined treatment botulinum toxin injection-physiotherapy-orthoses, and it gives some suggestions for candidate selection and individualized treatment.

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1. Introduction

From the rehabilitation point of view, the most important problem for the functional recovery of children with hemiplegia consists on the treatment of the paretic hand, since standing and walking are spontaneously acquired. Upper limb (UL) spasticity and/or weakness, muscle shortening due contracture and/or retraction, limitation of joint range of motion, bone rotational deformation particularly in forearm and wrist (Boyd & Graham, 1997), reduced unimanual dexterity, poor motor control and especially sensory impairment (Fehlings, Rang, Glazier, & Steele, 2001) hamper the functional development of the affected hand. Learned non-use, development of auxiliary pinches (coping solutions) and especially hyper-specialization of unaffected UL can further worsen affected hand utilization.

In a recent systematic review of therapeutic management of UL dysfunction, Sakzewski, Ziviani, and Boyd (2014) have performed a meta-analysis of all nonsurgical UL therapies for children and youth (aged 0–18 years) with unilateral CP on UL outcomes, achievement of individualized goals and self-care skills. The authors identified thirteen types of UL interventions: BoNT-A treatment and Occupational Therapy (OT), constraint-induced-movement-therapy (CIMT) [classic CIMT, modified CIMT, modified CIMT and bimanual training], forced-use therapy, hand-arm bimanual intensive training (HABIT), neuro-developmental therapy, OT home programmes, UL lycra splints, context-focused therapy, mirror box therapy, acupuncture combined with OT and action observation training. They concluded that there are moderate to strong effects favouring injections of BoNT-A as an adjunct to OT to improve UL and individualized outcomes compared with OT alone, confirming findings of the previous meta-analysis (Sakzewski, Ziviani, & Boyd, 2009) and of the large Cochrane systematic review (Hoare et al., 2010) that BoNT-A provides a supplementary benefit to many UL training approaches. The Cochrane review recommended more precise criteria in case classification and less ambiguousness in defining physiotherapy or occupational treatment.

Some authors (Lukban & Rosales, 2009; Reeuwijk, van Schei, Becher, & Kwakkei, 2006) underlined that, besides differences in treatment goals, the remaining uncertainty of BoTN-A efficacy was mainly due to the use of unsuitable assessment instruments and/or insufficient statistical basis. In addition, the specificity in physiotherapeutic associated treatment was often quite inconsistent (i.e. traditional treatment, standard handling, routine physiotherapy, etc.).

The aim of this current study was to show if a combination of BoNT-A, intensive individualized physiotherapy and orthoses in children with unilateral cerebral palsy and spastic UL, can improve activity, compared to a control group having an analogous tailored rehabilitation programme, but placebo injection.

We also aimed to better define approach and proposals of individualized physiotherapy treatment and to identify the possible features of paretic hand most appropriate to respond to BoNT-A treatment.

2. Methods

2.1. Study design

This was a prospective double-blind parallel arm simple randomized controlled trial comparing the effects of BoNT-A, combined with an individualized intensive physiotherapy/orthoses treatment, with placebo, conducted in two Italian centres. It was built following CONSORT guidelines (Weller & McNeil, 2010). The approval of the competent Committee on research ethics of the involved clinical centres was obtained.

2.2. Participants

Only children with hemiplegic cerebral palsy (HCP) were examined. The eligibility criteria were: (i) documented brain lesions at magnetic resonance imaging; (ii) age between 3 and 12 years; (iii) pure spastic UL paralysis; (iv) spastic hyperactivity in affected UL muscles interfering with manipulation capabilities and (v) regular attendance of a rehabilitation centre.

The exclusion criteria were: UL structured deformity, dystonia, recent surgery (within the last year) or BoNT-A treatment for upper/lower limb (six months), major sensorial or cognitive deficits and untreatable epilepsy.

As indicated in Fig. 1, in the interval 2007–2009 247 children with HCP were assessed for eligibility in the two recruitment centres. 202 were excluded because they did not meet the inclusion criteria and in 18 cases parents declined participation, mainly for the randomization procedure. 27 were enrolled, 13 females and 14 males, 17 right, 10 left, mean age 6.27 years (SD 3.22). Once entered the study, none was lost or discontinued the intervention.

Enrolled children were diagnosed according to the child hemiplegia taxonomy of Cioni et al. (1999), based on the lesion type and timing, functionally classified in conformity with the House scale for UL (House, Gwathmey, & Fidler, 1981; Koman et al., 2008). The original House scale considers eight hand classes, starting from the most damaged to the most preserved one. For the trial, children with HCP with paretic hand of House 2–7 grade interval, were enrolled.

Table 1 summarizes the sample characteristics. Despite some differences in distribution of the two groups according to lesion and hand type, no significant statistical discrepancy was detected. The randomization of demographic variables was correct. No statistical significant differences in baseline scores on all measured features were found (Table 2), except for grip strength (Median, BoNT-A group: 12.00 Newtons; Placebo group: 4.30 Newtons; $p = .037$).

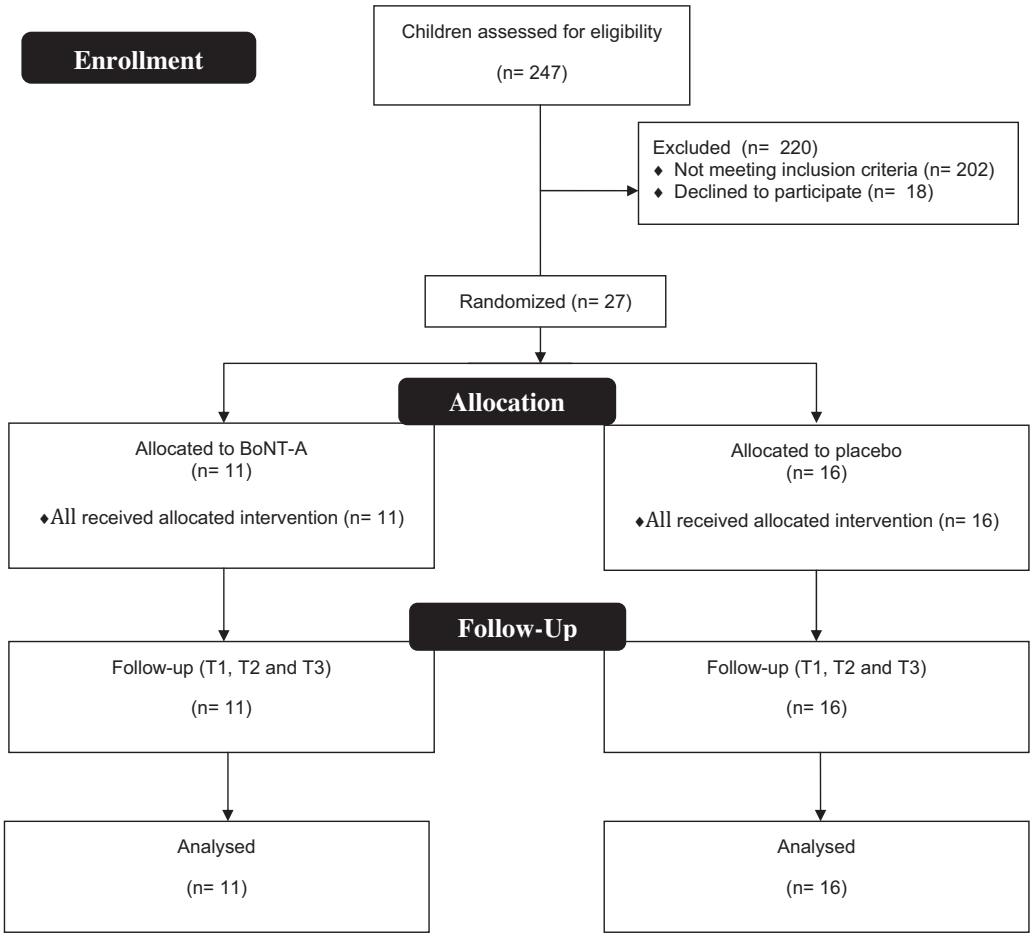

Fig. 1. CONSORT 2010 flow diagram of the present study.

The study took place in two Hospitals (Children Rehabilitation Unit, IRCCS S. Maria Nuova Hospital, Reggio Emilia and Stella Maris Scientific Institute, Pisa, Italy) with children coming from different Italian Rehabilitation centres.

While assessment and injections took place at one of the two hospitals, physiotherapy was delivered at the rehabilitation centres, where the children came from. In order to guarantee a complete agreement between research and case physiotherapists, two specific training courses for case therapists were organized.

Table 1
Sample characteristics.

		BoNT-A group		Placebo group			
		Mean	SD	Mean	SD	T	*p*
Age (years)		7.36	3.18	5.51	3.12	−1.505	.145
Weight (kg)		25.77	1.01	21.43	9.35	−1.150	.260
		N	*p*	*N*	*p*	Chi^2	*p*
Gender	F	6	.55	7	.44	.304	.58
	M	5	.45	9	.56		
Hemi side	L	7	.64	10	.63	.04	.95
	R	4	.36	6	.38		
Lesion type class	I	2	.18	2	.13	.836	.84
	II	5	.45	7	.44		
	III	4	.36	6	.38		
	IV	0	.00	1	.06		
House class		Median		Median		*U*-Score	*p*
		5		4		71.00	.40

SD: Standard Deviation; N: Number; F: Female; M: Male; L: Left; R: Right.

Table 2
Results of primary and secondary outcome measures in the two groups of children.

	Sample Median	BoNT-A group Median	Placebo group Median	*U*-Mann W	*p*
AHA (raw score)					
T0	55.00	57.00	49.50		
T2	60.00	62.00	52.50		
T3	61.00	66.00	57.50		
T2–T0	4.44	7.00	1.50	42.50	.025
T3–T0	5.19	7.00	3.50	56.50	.119
PEDI FS (scaled score)					
T0	66.00	71.70	61.55		
T2	67.60	74.70	61.15		
T3	69.10	75.90	66.80		
T2–T0	2.80	4.70	1.25	46.00	.038
T3–T0	6.10	7.30	4.85	64.50	.246
PEDI CA (scaled score)					
T0	65.70	76.70	62.80		
T2	68.10	76.70	64.50		
T3	72.70	83.20	69.60		
T2–T0	.00	.00	1.75	42.50	.020
T3–T0	3.00	.00	5.40	55.00	.100
ABILHAND-Kids (logits)					
T0	1.20	1.37	1.10		
T2	1.25	1.32	1.20		
T3	1.50	1.51	1.30		
T2–T0	.14	.10	.20	55.00	.102
T3–T0	.25	.19	.30	77.00	.586

AHA: Assisting Hand Assessment; PEDI: Paediatric Evaluation of Disability Inventory; FS: Functional Skills; CA: Caregiver Assistance.

2.3. Interventions

2.3.1. BoNT-A and placebo injection

Patients were randomly assigned to BoNT-A or placebo group. The treated group received BoNT-A injections in spastic muscles of the affected UL. The control group received placebo (saline) injections following the same procedure. Due to ethic reasons, patients of the control group received the same BoNT-A injections 6 months after the conclusion of the research trial.

We used Botox from Allergan, dilution 100 U per 1 ml, average dosage 2 U/kg body weight/muscle above the elbow, 1–2 U/kg/muscle in the forearm, 0.5–1 U/kg/muscle in the hand. Total individual dose $<$300 U, more than one injection site per muscle in the arm-forearm. Echo guided multiple injections were performed under sedation. Table 3 lists the muscles chosen for injection. Note that in most cases the selected muscles were more or less the same for both groups.

In BoNT-A group, side effects were not observed. In the placebo one, bicep muscle pain was accused in one case, with spontaneous remission after a few days. Injected muscle weakness, reported by some authors as an adverse effect, is part of the desired result.

2.3.2. Physiotherapy programme and splinting

A great effort was made in instructing case physiotherapist to standardized treatment. Physiotherapeutic treatment (identical for both groups) was based on daily specifically individualized unimanual and bimanual goal directed exercises,

Table 3
Injected muscles in the BoNT-A and Placebo groups.

	Sample	BoNT-A group	Placebo group
Injected muscles	%	%	%
PT	78	73	81
FCU	67	73	63
AP	59	55	63
OP	37	36	38
FCR	30	36	25
B	26	18	31
PM	19	9	25
FDS	7	9	6
FPB	7	18	0
SS	4	0	6

Pt: pronator theres; FCU: flexor carpis ulnaris; AP: adductor pollicis; OP: opponens pollicis; FCR: flexor carpis radialis; B: biceps; PM: pectoralis major; FDS: flexor digitorum superficialis; FPB: flexor pollicis brevis; SS: sub scapularis.

task oriented activities and stretching manoeuvres, organized in three 45-min weekly sessions, for 24 weeks, according to an agreed-upon protocol carried out both by case physiotherapist and family. Exercises and activities were planned for each child by an experienced paediatric research physiotherapist and carefully delivered to case therapist with video supports and instructions regarding setting, materials and, if necessary, special aids. The stretching, consisting of slow, gradual, progressive and persistent manoeuvres, was performed daily for the first two months. Parents were also instructed to guarantee continuity during the week. Abandoning the pursuit of restoring normal patterns, the therapeutic activities consisted of a series of goal directed actions, voluntarily executed by the child, under the direct guidance of the therapist. The degree of exercise difficulty took into account manipulation strategy, age, gender, maturation of competence, degree of visual-perceptive integration, child interest, previous experiences and learning ability. Particular attention was paid to functional activities able to emphasize the recruitment of the antagonist muscles to those injected. Each exercise was slightly modified after a few repetitions, in order to maintain high intentional interest, limit child frustration and improve learning. This required the preparation of a vast number of exercises, specifically tailored for each child. Motor and perception oriented exercises were set up separately or in completely integrated activities. Therapeutic intervention was usually perceived as play activities by children and their families. From T0 to T1, the exercises were principally unimanual, with both transitive and intransitive actions, successively becoming bimanual from T1 to T2 and finally bimanual with high complexity from T2 to T3. The required unimanual action was first executed (with motor, perceptual or cognitive facilitation) by the unaffected hand, in order to make the following performance of the plegic one easier. Common toys, ordinary objects and specifically constructed items were used. The case therapist and parents were periodically updated on the up-coming aspects of the therapeutic programme by the research therapist. This therapeutic model is coherent with recent statements by Charles and Gordon (2006).

Positional splints were recommended only for night use (Kanellopoulos et al., 2009), while functional orthoses were worn during the day for at least 6 h, during play, daily activities and certain exercises. Every child was given a customized positional splint after injection. Those with adducted thumb or thumb in palm were also fitted with functional dynamic orthoses in order to facilitate grasping and holding. Tolerability, consistency and effectiveness of orthoses were noted. Moreover, any difficulty in child collaboration or family compliance was registered in a logbook for each case on use in the two centres, where any comments around compliance, parent and child satisfaction for the treatment project, criticisms were noticed. Specific family meetings, aimed at transferring abilities acquired during therapeutic sessions to everyday life, were also carried out at the planned check-up sessions, i.e. 1, 3 and 6 months after injection.

2.4. Outcome measures

The assessment process was coherent with Gilmore, Boyd, and Sakzewski (2008) recommendations for test selection. Evaluation was scheduled for T0 (baseline), T1, T2, T3. Assessment instruments were distributed according the ICF dimensions: 1 – Body functions and structures: grip strength dynamometric measure, Modified Ashworth Scale (MAS) (Bohannon & Smith, 1987), Physician Rating Scale for UL (PRS – UL active ROM measure) (Koman, Mooney, Smith, Goodman, & Mulvaney, 1994; Slawek, Bogucki, & Reclawowicz, 2005); 2 – Activity and daily life: Assisting Hand Assessment (AHA) (Krumlinde-Sundholm & Eliasson, 2003), Paediatric Evaluation of Disability Inventory (PEDI) (Haley, Ludlow, & Coster, 1993), ABILHAND-Kids (Arnould, Penta, Renders, & Thonnard, 2004). The AHA scale, a standardized procedure to measure the use of affected UL in bimanual semi structured play activities, was selected as primary outcome measure. Among the secondary outcome measures PEDI is a questionnaire around daily life autonomy in the domains of Self Care, Mobility and Social Function, distributed for the Scales of Functional Skills (FS) and Caregiver Assistance (CA). GAS (Goal Attainment Scaling) (Steenbeek, Ketelaar, Galama, & Gorter, 2007; Turner-Stokes, 2009) was used to explore personal goal achievement. GAS consists of a 5-point scale, where 0 corresponds to goal achievement, +1 and +2 if the patient exceeds expected results, −1 and −2 if the patient does not reach expected results, on the basis of pre-established criteria.

2.5. Sample size

According to CONSORT guidelines (Weller et al., 2010), the sample size estimate was based on projected treatment effect on the primary outcome measure. The AHA scale responsiveness to change has been shown in a study in which Eliasson, Krumlinde-Sundholm, Shaw, and Wang (2005) used this scale as the outcome measure in evaluating the effects of a modified model of CIMT. The authors reported a significant effect size of 1.16. The statistical analysis indicated that, in order to detect a 1.16 effect size at a significant level of .05 and 80% power, a minimum sample size of 24 subjects distributed in two groups was required.

2.6. Randomization

An independent statistic centre assigned BoNT-A or placebo administration according to a computer generated simple randomization (Suresh, 2011). The allocation sequence was concealed from the researchers enrolling participants in sequentially numbered, opaque, sealed envelopes. The appropriate numbered envelope was opened at the hospital by the nurse; the card inside indicated if the patient was to be inoculated with BoNT-A or placebo.

2.7. Blinding

Objectivity was based on "blindness" of all partners: child, family, physician executing BoNT-A or placebo (normal saline solution) injections and physiotherapists (researcher and case PT). Only the nurse who prepared the injection containing BoNT-A or saline solution knew the destination. Test scoring and clinical result evaluation of therapeutic treatments were also blindly measured by physiotherapists other than those who had made the assessment at baseline.

2.8. Statistical analysis

Clinical data were analyzed by means of the Statistical Package for Social Sciences (SPSS, version 20.0). The statistical quantitative or semi-quantitative analysis used in this trial were: (i) two-sample Student's *t*-test, used to detect the differences between BoNT-A and placebo groups, relatively to the following parameters: age, weight, injected botulinum toxin quantity, expressed as mean ± standard deviation (SD); (ii) Mann–Whitney test, used to assess the differences between the groups regarding delta changes of all selected outcome measures at T2 (primary end point) and T3, compared to T0; (iii) for each test, significance level was set at $p < .05$; Bonferroni correction for the two comparisons (alpha error limit .025).

3. Results

3.1. Activity

AHA values, indicated as raw score, were slightly different in the two groups at baseline, but the difference was not statistically relevant. Both experimental and control group showed a progressive increase of the score. At T2, primary end point, between group difference was significantly higher in the experimental group ($p = .025$). Children injected with BoNT-A further improved at T3, but the control group also increased his raw values, and therefore the difference between the two groups was no longer significant (Table 2).

Moreover, the changes observed in the experimental group were greater than the recommended smallest detectable difference (Smallest Detectable Difference-SDD >4 points) (Holmefur, Aarts, Hoare, & Krumlinde-Sundholm, 2009) (Fig. 2), in contrast with the smaller increase of the control group.

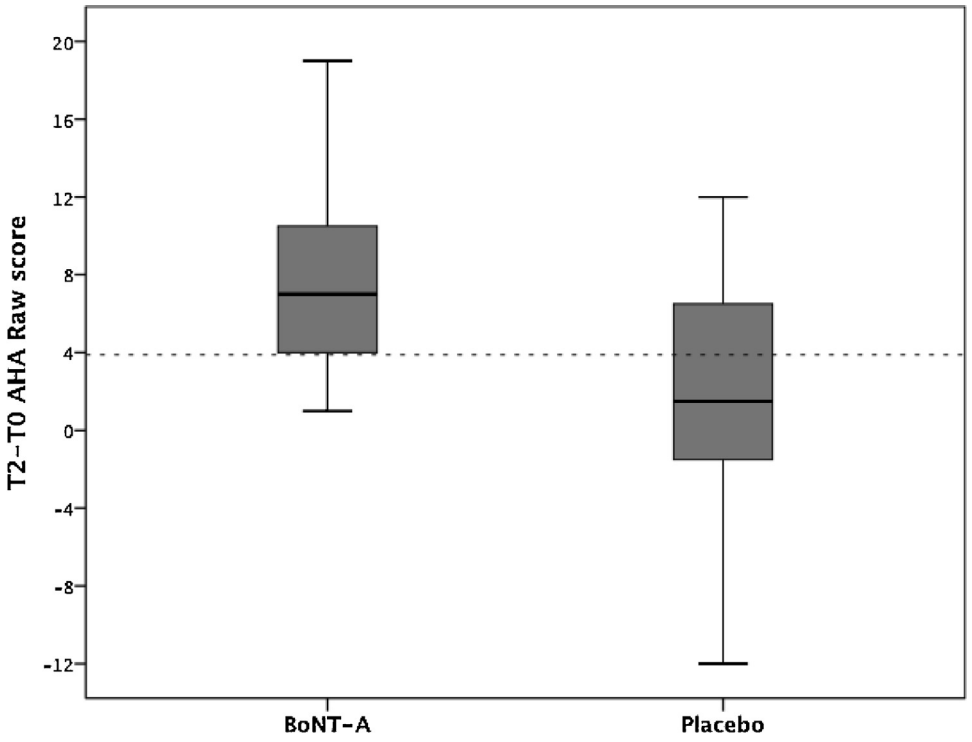

Fig. 2. Changes in AHA raw score: Boxplots of delta scores between T2 and baseline (T0). Dotted line indicates the level of Smallest Detectable Difference (SDD)

3.2. Daily life

Some positive changes were observed in the scaled scores of PEDI FS (functional skill) and CA (caregiver assistance), both in the experimental and control group, but none of these changes reached a statistically significant value for intergroup difference, with the partial exception of PEDI CA at T2, in favour of the control group. However, none of the observed differences reached the SDD value for this scale that is of 11 scaled score points (Iyer, Haley, Watkins, & Dumas, 2003) (Table 2).

Similarly, ABILHAND-Kids results showed some positive changes from T0, to T2 and T3 for both groups, but intergroup differences were not significant (Table 2).

3.3. Body functions and structures

Neither MAS (Modified Ashword Scale for spasticity), nor Physician Rating Scale for UL showed statistical relevant differences between the two groups.

BoNT-A group showed an evident reduction of grasp strength score median value at T1 and T2 (8.30 and 9.30 Newtons, respectively), with incomplete recovery at T3 (10.65 Newtons), compatible with botulinum toxin action, as already reported by other authors (Fehlings et al., 2001). Conversely, placebo group values after a modest reduction at T1 progressively increased (Median values, T1: 3.50, T2: 5.30 and T3: 5.80 Newtons). However, also in this case intergroup differences were not statistically significant. There was no correlation between BoNT-A quantities and loss of muscle strength in index T1-T0. The grasp strength reduction was therefore independent from the quantity of botulinum toxin injected.

3.4. GAS

Goals were the expression of what both family and team had defined as reasonable expectations. Overall the results were in favour of BoNT-A group, because negative results (missed goals) were present in the placebo group but never in the BoNT-A one. Intergroup differences were quite high in particular at T2, when p value obtained with Mann Whitney test was at the edge of significance for Bonferroni correction ($p = .03$).

In order to investigate which types of ULs had the best results and then which would be the best candidate to benefit from a combined treatment with botulinum toxin, we compared the AHA results of BoNT-A injected subjects at T0–T2–T3, with hand House level and age. At T2 all subjects improved, confirming the correct selection of participants (see inclusion and exclusion criteria), but the biggest change from AHA T0 values was detected in the subjects classified as House 4–5, i.e. with an intermediate severity. More limited response was observed in children whose hands were classified as being functionally better or worse than the previous grades (i.e. House 2–3 or 6–7). Despite the small number of subjects (11) the difference in favour of House 4–5 was significant (U 3, $p = .028$).

No clear effect of the age at injection was found; younger children (3 years) changed more rapidly (from T0 to T2) but they did not maintain their improvement at T3.

4. Discussion

The results of the present study provides further evidence on BoNT-A influence on activity level modification of the UL, measured by AHA in children with HCP. AHA score progression at T2 (3 months after injection) was clearly higher for BoNT-A group. Actually both BoNT-A and placebo showed some improvement even if differing in time and modality, but injected subjects had a greater and more rapid change. At the interval between T2 and T3 (6 months after injection), the improvement of BoNT group apparently stopped, while placebo group continued to show changes, but lower than SDD. At T3 no statistical difference was detectable between the two groups. The widespread functional improvement in both BoNT-A and placebo, and the slower, but more constant change in placebo group, could suggest the significant role of intensive individualized physiotherapy treatment.

The same can be considered for daily life activity modification (PEDI FS – PEDI CA): both groups improved somewhat, even if the degree of change was no clinically relevant in PEDI. Although ABILHAND-Kids values did not reach statistical significance, a positive modification, congruent with PEDI FS data, was also registered.

Interesting information was also obtained from GAS, probably because this measure allows for a real personalization of goals. At T3 the families, whose goals were aimed at daily life, manifested a good satisfaction. The limits of GAS are well known, but this test is an indispensable tool in measuring change linked to individual rehabilitative expectations. On the other hand it is a very good self-measure instrument for clinicians to verify their ability in functional prognosis.

We also investigated the effects of the combined treatment (BoNT-A, physiotherapy and orthoses) on structural parameters (ICF dimension of body functions and structures) because of the possible influence of anatomic modification on activity. Unfortunately, our data cannot reinforce the evidence on the efficacy of Botulinum toxin in modifying segmental parameters for UL. This finding is partly in contrast with Russo et al. (2007) but consistent with Esquenazi, Novak, Sheean, Singer, and Ward (2010), who deemed BoNT-A action on UL spastic muscle only "probably effective" in children according to American Academy of Neurology (AAN) Classification of Evidence.

An important contribution in improving segment alignment came from stretching manoeuvres, combined with night static orthoses in all subjects, even though no statistical evidence was reached by Physician Rating Scale.

Regarding possible emerging features of ULs most appropriate to benefit from a combined treatment, we investigated within the study group, in order to detect advisable criteria for the best selection of candidate hands for BoNT-A therapy. The limited number of subjects included in our sample does not allow any conclusive statement. We can make only few considerations. The degree of impairment could be relevant, since the poorest change has been obtained in the best and worst hands. The most significant change in AHA was detectable in children with House level 4–5. That means that the best advantage was taken by hands with intermediate level of impairment. This is congruent with the modifiability principle: the central nervous system of a child with a good enough functioning affected hand has no reason to change strategies, whereas for extremely impaired hands limited sources make progress very hard to be achieved.

The age at injection, at least for the considered interval selected for this study (3–12 years), did not seem to influence the degree of improvement, but perhaps its modality. Children may have different modalities of learning at various ages and this fact could suggest the opportunity to differentiate treatment approach. The intensive physiotherapy treatment built on task oriented activities and goal-directed exercises, personalized for each child with hemiplegia, combined with BoNT-A and orthoses, can improve manipulation ability also in children older than 6 years, an age in which the regular therapeutic treatment usually ends. The good results obtained in older subjects seem to confirm the good plasticity degree for hand function during the entire growth period. Therefore age could not be so decisive in determining the responsiveness.

The present study brings further evidence around the role of individualized intensive physiotherapy combined with splinting (Hoare et al., 2010), since both groups had a functional improvement, even if lower for placebo.

Much effort and time were spent to guarantee the quality of physiotherapeutic treatment. Training courses for case physiotherapists were crucial. Very precise information on individualized goal-directed exercises (setting, objects, special tools, frequency and duration) was given at T0, T1 and T2. This was very important for treatment success, but it also created a great opportunity for study and discussion. Many different individually tailored play like activities were created. Each activity was video recorded and a kind of exercises inventory was made to guarantee their reproducibility.

Sharing objectives and instruments with families is crucial in transferring treatment principles to daily life. The cooperation of family is an important element able to improve both the quality of results and the perceived satisfaction by all involved actors.

The degree of satisfaction, both for family and children, was kept high from the beginning to the end of our study, as registered in the logbook of each case.

Overall the results of the present study confirm the effectiveness of BoNT injection suggested by previous reports and meta-analysis, providing in addition a detailed description of the combined rehabilitation procedures to be applied in the children, within the framework of a strict collaboration between families, children and clinicians working in hospital or in the local rehabilitation centres.

Despite these strengths, this study and the obtained results have also important limitations, especially the limited number of enrolled subjects, compared to the complexity of clinical features of HCP and the multi-axial ICF outcome measures, in addition to the primary ones. The blindness of the trial severely limited family agreement, so that it was hard to enrol a larger population of children. At the end this negatively influenced the strength of statistical evidence, and it might have hidden potential effects of BoNT treatment on some other measure, in addition to AHA. A block randomization would have avoided the quite different number of subjects we ended up in the two study groups. The small number of participants also reduced the effectiveness of randomization on the degree of impairment of the two groups at baseline. This difference was not statistically significant, but we cannot exclude that this had some influence on final data, since a different starting functional level may imply a different potential modifiability. A higher starting functional level may reduce the possibility for further improvement. This could explain why PEDI CA values remained constant over time and ABILHAND-Kids improvement for the BoNT-A group did not achieve a statistical significance. Conversely, one could argue that a higher starting functional level may enhance learning ability; therefore no certain hypothesis around this aspect can be stated.

5. Conclusions

BoNT-A, combined with physiotherapy and orthoses, was confirmed as effective in improving manipulation in the activity domain, but the role of individualized goal-directed physiotherapy is determinant, as evidenced by placebo group progress. Orthoses are a well accepted support to physiotherapy.

Considering our experience and previous data available in the literature, we may suggest that a more evident result in functional improvement, mainly depends on: (i) correct candidate selection (mild to moderate levels of muscle spasticity, intermediate level of impairment, no behavioural/intellectual disorders); (ii) clear individual goals definition; (iii) BoNT-A as part of a combined treatment (physiotherapy, occupational therapy, splinting); (iv) transfer of exercise principles to daily life activities and (v) family and case team cooperation.

Future studies on larger group of subjects and on a longer time span of follow-up would be desirable to check results stability and their influence on functional development.

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