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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; $p = .037$).