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Unimanual and Bimanual Intensive Training in Children With Hemiplegic Cerebral Palsy and Persistence in Time of Hand Function Improvement: 6-Month Follow-Up Results of a Multisite Clinical Trial

Ermellina Fedrizzi, MD[1], Melissa Rosa-Rizzotto, MD, PhD[2], Anna Carla Turconi, MD[3], Emanuela Pagliano, MD[1], Elisa Fazzi, MD, PhD[4], Laura Visonà Dalla Pozza, PhD[2], Paola Facchin, MD, PhD[2], and GIPCI Study Group[4]

Abstract

This study aims to compare in hemiplegic children the effectiveness of intensive training (unimanual and bimanual) versus standard treatment in improving hand function, assessing the persistence after 6 months. A multicenter, prospective, cluster-randomized controlled clinical trial was designed comparing 2 groups of children with hemiplegic cerebral palsy, treated for 10 weeks (3 h/d 7 d/wk; first with unimanual constraint-induced movement therapy, second with intensive bimanual training) with a standard treatment group. Children were assessed before and after treatment and at 3 and 6 months postintervention using Quality of Upper Extremity Skills Test (QUEST) and Besta Scales. One hundred five children were recruited (39 constraint-induced movement therapy, 33 intensive bimanual training, 33 standard treatment). Constraint-induced movement therapy and intensive bimanual training groups had significantly improved hand function, showing constant increase in time. Grasp improved immediately and significantly with constraint-induced movement therapy, and with bimanual training grasp improved gradually, reaching the same result. In both, spontaneous hand use increased in long-term assessment.

Keywords

hemiplegic cerebral palsy, modified constraint-induced movement therapy, intensive bimanual training

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Constraint-induced movement therapy has highly diffused in the field of rehabilitation. This growing interest is demonstrated by the relatively high number of clinical trials currently ongoing both in adult and pediatric populations.[1-4] Although in poststroke adults this new therapeutic approach has led to an improvement of upper limb function,[5] its application in children with hemiplegic cerebral palsy is still debated in the international literature and needs further exploration. According to a Cochrane review on constraint-induced movement therapy in children with hemiplegic cerebral palsy,[6] the evidence of success with it is limited, since currently available trials were underpowered, with methodological limitations and differences in the method of restraint, length of restraint, type and duration of therapy, intervention environment and provider, and measurement tools. However, a recent systematic review of constraint-induced movement therapy in children with cerebral palsy[7] concludes that the most rigorous studies demonstrated evidence of improved arm and hand use following constraint-induced movement therapy. Notwithstanding the growing awareness of the role of constraint-induced movement therapy in the rehabilitation of upper limb function, there are still many open questions.

[1] Division of Developmental Neurology, National Neurological Institute C. Besta, Milan, Italy
[2] Department of Pediatrics, Epidemiology and Community Medicine Unit, University of Padua, Padua, Italy
[3] Scientific Research Institute Eugenio Medea, Bosisio Parini, Lecco, Italy
[4] Department of Child Neurology and Psychiatry, IRCCS C. Mondino Institute of Neurology, University of Pavia, Pavia, Italy

Corresponding Author:
Melissa Rosa-Rizzotto, Department of Pediatrics, Epidemiology and Community Medicine Unit, University of Padua, Via Giustiniani, 3, 35128, Padova, Italy.
Email: melissa.rosarizzotto@unipd.it

First of all, is the efficacy of constraint-induced movement therapy due to the restriction of the nonaffected arm or due to the intensity of treatment? Although varying in its implementation, this treatment is characterized by 2 elements: a method of restraint in use of the unimpaired limb combined with an intensive practice of unimanual activities of the affected hand. Taub and Wolf[8] suggested that the impact on constraint-induced movement therapy outcome could be related more to the intensity of the treatment than to the constraint principle itself. This hypothesis was supported by Gordon et al,[9] who published in 2007 a randomized controlled trial demonstrating that hand-arm bimanual intensive therapy (HABIT) improves the quality and quantity of bimanual hand use in children with hemiplegic cerebral palsy. Thereafter, using a quasi-randomized trial, Gordon et al[10] reported that both unilateral and bilateral intensive training lead to improved performance of upper extremity function in children with hemiplegia. Similar results have been demonstrated by a recently published large trial,[11] comparing constraint-induced movement therapy and bimanual training. This study showed only small differences on activity outcome between the 2 training approaches. These data would support the suggestion that the improvement in children treated with constraint-induced movement therapy is not dependent on use of a restraint itself but should be attributed mainly to the intensity of treatment. This hypothesis was confirmed also by the postintervention results of a multisite clinical trial published by Facchin et al.[12]

The second question regards the gain persistence in time. How long will the improvement of hand function obtained by intensive treatment, both with and without restraint, last? As Eliasson[13] suggested, although programs with a short period of specific and intensive training for hand function have been successful, the demonstration that pediatric interventions have an impact in the long term is complex.

Despite its complexity, evaluation of the persistence of the effect of intensive treatment both with and without restraint is very important, particularly for those in the developmental age. In fact, the short-term effect could be attributed to an improvement in performance related to the intensity of treatment, not to a real learning of spontaneous use of the affected hand in activities of daily living, which means automaticity in motor planning.

The third issue regards the learned nonuse or developmental disregard phenomenon. Which is the best approach for overcoming the learned nonuse? According to Taub,[14] in adults the overcoming of the learned nonuse is obtained more efficiently by unimanual training with the application of constraint-induced movement therapy, because both intensive training and restraint of the nonaffected arm induce increased purposive movement of the affected hand. The result consists in an increased size of the cortical representation zone of the treated arm and establishes the basis for further movement and reward for using the affected hand. In this way, the learned nonuse that is normally permanent is reversed.[15,16] In children with hemiplegic cerebral palsy, the learned nonuse was named as developmental disregard because children who suffer from early brain injury did not acquire a motor memory before the lesion has occurred and so they learn asymmetric motor sequences using the most efficient nonaffected hand, tending to limit the use of their affected hand.[17] From a clinical point of view, a key question is whether the overcoming of developmental disregard can be achieved more easily by bimanual training or by constraint-induced movement therapy unimanual training. In the second case, the learning of bimanual motor sequences to be utilized in activities of daily living may be limited.

According to Gordon, ''two hands are better than one''[18] and bimanual training is the best approach to make the children not disregard the affected limb. However, in a small sample study, Sutcliffe reported that all children presenting developmental disregard showed increased hand use after constraint-induced movement therapy treatment, documented using the Pediatric Motor Activity Log (P-MAL) and Assisting Hand Assessment (AHA).[19]

In light of these questions, the present study pursues the following aims:

1. To compare constraint-induced movement therapy and intensive bimanual training with standard treatment in order to assess the role of the intensity of treatment in improving hand function and to measure the persistence of the effect of intensive treatments with and without restraint on patients with hemiplegic cerebral palsy, 3 and 6 months after the end of treatment, and
2. To evaluate the role of bimanual versus unimanual activities in improving the spontaneous use of the affected hand in play and activities of daily living.

Methods

Participants

All the children enrolled in this study were recruited from 20 rehabilitation centers in Italy. Patient inclusion criteria were age range between 2 and 8 years and a diagnosis of hemiplegic cerebral palsy (personal history, clinical and neuroimaging documentation to be collected) according to the Hagberg classification.[20] Exclusion criteria were to have previously undergone restraint therapy or to have received injections of antispasticity drugs into an upper extremity in the previous 6 months. Differing clinical severity and/or comorbidity with other diseases (eg, epilepsy, mental retardation) did not constitute exclusion criteria but have been used to describe clinical variability.

Based on and modified from criteria set by Beckung et al[21] and Eliasson et al,[22] participants were divided into 3 groups according to hand function:

1. Mild: the paretic hand manipulates without restrictions but with limitations in more advanced fine motor skills;
2. Moderate: the paretic hand has only holding function during manipulation;
3. Severe motor impairment: the paretic hand has no functional ability.

We calculated the parameters of an a priori sample of 111 participants to be enrolled, 37 patients for each group, considering a delta value of

the primary outcome measure (affected limb function measured with Besta and Quality of Upper Extremity Skills Test [QUEST] scales) set at 30% ($1 - \beta = 0.80$; $\alpha = 0.05$; $\pi_i = 0.15$).

Study Design

The study was designed as a multicenter, prospective, cluster-randomized controlled clinical trial. The effect of constraint-induced movement therapy (intended as the restraint of the unaffected limb combined with a unimanual intensive rehabilitation program, named from now on as the *modified constraint-induced movement therapy*, because of the adaptation of the method of restraint of the unaffected arm, specific for children needs)[23] was compared with a group undergoing intensive bimanual training, and a group receiving standard treatment. The comprehensive description of the trial's study design and methodology was previously published.[24] The comparisons between modified constraint-induced movement therapy and intensive bimanual training may highlight the effect of restraint and the comparisons between the modified constraint-induced movement therapy and standard treatment group and between the intensive bimanual training and standard treatment group may show the effect of the intensive practice of movements and exercises. The standard treatment was considered as the baseline treatment.

Owing to possible organizational difficulties within the rehabilitation services making the subsequent randomization of patients by treatment group for 3 different treatment approaches in every single clinical center impossible, the authors chose a cluster randomization design.[25,26] Each clinical center was randomized to a treatment option; that is, modified constraint-induced movement therapy was randomly assigned to center 1, intensive bimanual training to center 2, and standard treatment to center 3. In this way, all children enrolled in center 1 were not randomized to treatment allocation but underwent the treatment selected for that center (modified constraint-induced movement therapy in the example). This randomization is called cluster randomization: To each cluster (the clinical center), a treatment group was randomly assigned and the cluster developed only that treatment.

Twenty-one clinical sites took part in the research project (7 for each treatment group). At least 2 clinicians per center were involved in the research project, a physician (neuropediatrician or physiatrist), a physiotherapist, and a pediatric neuropsychomotoricist. All the professionals involved in the research study belong to the Italian Group of Cerebral Palsy (GIPCI Study Group), which was founded in 1994 and is composed of physiotherapists, physicians, psychologists, and epidemiologists. The group has worked together for 15 years to define the decision-making process and clinical management of children with cerebral palsy. Two supervisors of outcome measures examined videotapes of all evaluations of patients from each treatment group and they were blinded to treatment allocation.

Interventions

Modified constraint-induced movement therapy. Children wore a restraining, but fairly comfortable, fabric glove with a built-in volar stiff plastic splint on the dominant hand (which prevents them from flexing their fingers so that they are unable to grasp) and they underwent a unimanual intensive training.

The intervention lasted 10 weeks, 7 days a week. Children were expected to wear the glove for 3 hours a day consecutively. During this interval, the child performed the therapeutic training under the supervision of the therapist and/or parents, without removing the glove. During the treatment period, children underwent an intensive rehabilitation program based on unimanual activities. Sessions were held 3 times weekly (lasting 3 hours divided into 1.5 hours with the therapist and 1.5 hours with parents) at the rehabilitation center: an individual therapist (always the same person throughout the whole period) encouraged the child to solve tasks requiring the unilateral use of the paretic hand. Activities included a perceptual motor task (eg, manipulate plasticine), holding and manipulative tasks (eg, finger paints), posture and balance (eg, playing ball), and self-care and activities of daily living (eg, drink from the glass or smear face with soap).

Parents were trained to carry out similar 3-hour sessions at home on the remaining 4 days, as shown at the rehabilitation center (specific unilateral tasks during play and daily living activities).

Intensive bimanual training. Children were treated for hand impairment following the same approach described earlier, and with the same schedule (3 hours a day 3 times a week, half sessions with the therapist and half with the parents) at the rehabilitation center: the only differences were that children did not wear the glove and were encouraged to solve tasks requiring the use of both hands. Activities included a perceptual motor task (eg, smear both upper limbs with color), holding and manipulative tasks (eg, make pizza), posture and balance (eg, pull a cart), and self-care and activities of daily living (eg, break bread or cakes).

Parents were trained to carry out in the remaining 4 days similar 3-hour sessions at home as shown at the rehabilitation center (specific bimanual tasks during play and daily living activities).

Standard treatment. Children underwent 1-hour standard rehabilitation sessions once or twice a week, and the session frequency differed in relation to the child's age. Infants received physiotherapy twice a week, whereas preschool- and school-age children attend occupational therapy once a week (40-60 minutes).

Outcome Measures

Upper limb function (primary outcome measures). To date, the scales designed for the assessment of upper extremity function in children are very few. Most of them aim to assess hand function on request and only 2 are designed to directly assess spontaneous hand use in play and activities of daily living (AHA, Besta Scale). This represents a strong limitation for assessors because, in children, performance on request is different from spontaneous use in a natural context.

Primary outcome measures refer specifically to upper extremity function and they were assessed in 2 major domains: upper-extremity motor ability (through the administration of the assessment tool Quality of Upper Extremity Skills Test)[27] and hand function assessment evaluating both grasp function and the spontaneous use of the affected side (Besta Scale).[28-30]

Quality of Upper Extremity Skills Test explores 4 main domains of upper extremity function: dissociated movements, grasp,[1] protective extension, and weight bearing. All items are scored separately for both arms and use a dichotomous scale (does the task, doesn't do the task, not tested), and percentage scores are calculated according to a given formula.[31] Such a scoring system allowed us to assess the function of each hand (affected and unaffected) separately, by calculating the subscale percentage for the left and right arm separately.

The Besta Scale was developed in 1985 to assess the quality of grasp (hand function on request) and spontaneous hand use (bilateral manipulation), and their changes in relation to age and degree of impairment. The complete form and the scoring system are shown

in the appendix. Several studies have been performed to test validity, reliability, and interobserver agreement.[28-30]

In the Scale, grasp assessment is performed in a standardized setting, by asking the child to pick up different-sized cubes on request (a quantitative measure of hand capacity) using the affected hand only. The quality of grasp is videotaped and scored in a hierarchical way (from 0 to 3). Spontaneous use is assessed during structured activities and activities of daily living requiring both hands and being standardized according to age in a child-friendly and natural environment (a quantitative measure of hand performance). The scoring system for the quality of manipulation is based on the variability and stereotypy of movement pattern according to Touwen.[32]

During the evaluation sessions, both tests were administered, video-recorded, and scored on subsequent viewing; furthermore, the videotapes were examined for quality evaluation control.

For each scale, the interrater reliability was calculated using the intraclass correlation coefficient (ICC) for all participating professionals. The ICC value was 0.71 for the Quality of Upper Extremity Skills Test, whereas it was 0.86 for the Besta Scale.

Global and developmental assessment (secondary outcome measures). Besides the assessment of the hand function described in the previous paragraph, the evaluation session included the child's general assessment (patient's medical history, physical examination), the patients' cognitive level (Wechsler/Griffiths scales, according to patient age), the child's gross motor development (Gross Motor Function Measure), the level of familial stress (Parenting Stress Index),[33] the parents' evaluation of the child's autonomy in daily living activities (Parents Besta Scale), the child behavioral changes (Child Behavior Checklist),[34] and the treatment satisfaction and compliance perceived by parents (ad hoc questionnaire).

These assessment instruments have been chosen in order to evaluate the role of the child's motor and cognitive development on the treatment effect—changes in hand function—and the eventual occurrence of adverse effects on the child behavior and on the family compliance. The secondary outcome measures will be utilized as covariates in the analysis of the primary outcome—specific modification of upper extremity function—in the follow-up phases (3, 6, and 12 months). These findings will not be presented in the current paper.

Training of Professionals and Parents

Before starting the controlled trial, a specific training program was provided in order to familiarize professionals (both principal investigator and therapist). The training program consisted of 5 meetings lasting 1 or 2 days, including both training and testing procedures in order to develop a uniform administration of the treatment and also of the evaluation scales and the videotaping of the Quality of Upper Extremity Skills Test and Besta Scale, as extensively explained in a previous paper on the trial's methodological main issues.[24] A 1-day training module was organized every 6 months after the beginning of the trial in order to verify the correct implementation of rehabilitation and assessment sessions, compare practices, and share doubts and questions.

A specific training package was provided at the Rehabilitation Center and a training booklet with a DVD was given to the parents of recruited children in order to standardize the activities at home during play and daily living.

Statistical Analysis

Baseline analysis. Baseline information on each recruited patient was collected before starting the trial: clinical history and main clinical data, personal information, severity level of upper extremity motor impairment, and the presence of other diseases and/or disabilities. The data collected from patients recruited so far are summarized in Table 1. Categorical data are expressed as "number with percentage," whereas continuous data are reported as "mean with standard deviation (SD)."

To verify whether the individuals were randomly distributed within the clusters according to the main covariates (ie, age, severity of impairment, cognitive disturbances), 3 variance analyses (1-way analysis of variance [ANOVA]) have been conducted considering each participating center as a single cluster (because every center carries out only 1 type of treatment). No significant differences among intercluster and intracluster variability were observed in children enrolled in the trial: for this reason, the statistical power needed to randomize the clusters is considered equal to the one obtained by randomizing individuals.[24]

Primary outcomes analysis. The analysis regarding the primary outcome measures was carried out considering the differences on the global and partial scores of both the Besta Scale and the Quality of Upper Extremity Skills Test before (t_0) and after treatment (t_1), and for the 3-month (t_2) and 6-month (t_3) assessment for each treatment group (modified constraint-induced movement therapy, intensive bimanual training, and standard treatment). Moreover, the subscales have been studied separately in order to verify the effect on specific skills and patterns of movement.

Besta Scale (appendix). The analysis based on this scale was conducted by calculating 4 mean scores of 23 items (range, 0-3): 1 global score calculated as the mean of all 23 items, and 3 subscale mean scores (Grasp, Bimanual Use, Activities of Daily Living).

Quality of Upper Extremity Skills Test. The analysis of this scale consisted in calculating 5 scores according to the algorithms given in the scale manual (range, 0-100). The scores are Dissociated movements, Grasps, Weight bearing, Protective extension, and Total score. Furthermore, adjunctive scores were calculated for each subject by summing up similar items, and a value of 1 was assigned to the score every time the answer was "yes." The 4 homogenous groups of items were as follows:

- dissociated movements (shoulder, elbow, wrist, fingers): 32 items;
- grasp (cube of 2.5 cm, cereal, pencil or pen): 12 items;
- weight bearing (prone, quadruped): 25 items;
- protective extension (front, lateral, back): 18 items.

The scores were calculated separately for the left and right hand (in order to separate the evaluation of the affected and the unaffected hand) for each subject.

For each scale and subscale, mean scores were calculated before and after treatment and for the 3- and 6-month assessment for each treatment group. These scores (before and after treatment, 3 and 6 months) were compared by the Wilcoxon signed rank test (nonparametric paired sample t test).

For the comparison among treatment groups, the mean differences (expressed as percentage) on the global and subscale scores have been calculated as indicated: $\Delta\% = (t_n \text{ score} - t_{n-1} \text{ score})/t_{n-1} \text{ score}$.

Table 1. Descriptive Characteristics of Participants.

Characteristics	mCIMT (n = 39) n (%)	IBT (n = 33) n (%)	ST (n = 33) n (%)	*P* Value
Age, y				.242
<3	10 (26)	13 (40)	9 (27)	–
3-5	18 (46)	15 (45)	15 (46)	–
6-8	11 (28)	5 (15)	9 (27)	–
Sex: female	20 (51)	16 (48)	16 (48)	–
Hemiplegia: side, right	24 (62)	15 (45)	17 (52)	–
Hemiplegia: level of severity				.601
1	9 (24)	10 (30)	7 (22)	–
2	15 (38)	12 (36)	18 (54)	–
3	15 (38)	11 (34)	8 (24)	–
Gestational age, No. of months (SD)	36.3 (5.2)	35.4 (8.5)	36.9 (4.5)	–
Age of onset, No. of months (SD)	2.7 (5.9)	3.4 (4.2)	7.5 (11.5)	–
Cognitive disturbances				.074
Normal	24 (67)	27 (93)	22 (73)	
Clinical	12 (33)	2 (7)	8 (27)	
Stereognosis alterations	3 (8)	4 (14)	3 (15)	–
Speech/language delay	9 (24)	6 (21)	7 (29)	–
Mood disturbances	5 (13)	6 (21)	5 (23)	–
Visual impairment	10 (26)	0 (0)	2 (10)	–
Visual attention disorders	5 (13)	1 (4)	2 (10)	–
Hearing impairment	1 (3)	0 (0)	0 (0)	–
Associated malformations	6 (16)	1 (4)	0 (0)	–
Epilepsy	5 (13)	3 (10)	3 (13)	–
Other comorbidities	4 (11)	0 (0)	0 (0)	–
Besta Scale–global score, mean (SD) baseline	2.41 (0.80)	2.54 (0.88)	2.63 (0.84)	
QUEST–global score, mean (SD) baseline	69.4 (15.8)	66.3 (20.3)	72.2 (17.2)	

Abbreviations: IBT, intensive bimanual training; mCIMT, modified constraint-induced movement therapy; ST, standard treatment.
$^{*}P < .05$; $^{**}P < .01$; $^{\dagger}P < .001$ (1-way ANOVA).

The Kruskal-Wallis test (nonparametric ANOVA) was used to test statistical significance for the 3-group comparison (modified constraint-induced movement therapy vs intensive bimanual training vs standard treatment) and the Mann-Whitney test (nonparametric independent samples *t* test) for paired group comparisons (modified constraint-induced movement therapy vs intensive bimanual training; intensive bimanual training vs standard treatment; modified constraint-induced movement therapy vs standard treatment).

To calculate the percentualized differences, all scores have been increased by 1 unit, to avoid the case where before treatment score = 0: the $\Delta\%$ could not be calculated in this case.

Statistical analysis was performed with the SAS package, rel. 9.1 (SAS Institute Inc., Cary, North Carolina). A *P* value less than .05 was considered statistically significant.

Results

Between March 2006 and December 2008, 105 patients were recruited and assigned to the treatment groups modified constraint-induced movement therapy (mCIMT; n = 39), intensive bimanual training (IBT; n = 33), and standard treatment (ST; n = 33).

In accordance with the cluster randomization design, the clinical centers were asked to deliver the assigned treatment to all eligible patients. One of the centers of the modified constraint-induced movement therapy group asked to add 2 extra patients to the experimental group because of organizational reasons (2 patients were enrolled contemporarily in the final recruitment phase), so that the expected total of 37 was exceeded. No dropout for this group was observed. Standard treatment and intensive bimanual training groups had a 10% dropout rate before the trial started because of minor reasons. These dropout patients were not significantly statistically different from the enrolled ones.

For enrolled patients (105 patients), at baseline, there were no significant differences between the study groups on demographic (age; $P = .2420$), severity of impairment ($P = .6009$), or cognitive-level characteristics ($P = .0738$) (Table 1). One patient recruited in the intensive bimanual training group withdrew from the study because the family moved and did not undergo the posttreatment assessment.

Upper Limb Function: Global Score

Raw mean scores. Upper limb function was assessed by calculating raw mean scores for each scale, for each assessment session (t_0, t_1, t_2, and t_3), and for each treatment group (Table 2). Raw mean scores were calculated for the global score and for each subscale score.

Table 2. Mean Global and Subscores per Treatment Group on the Besta and Quality of Upper Extremity Skills Test Scales Before (t_0) and After (t_1) Treatment and in the 2 Follow-up Sessions (t_2 and t_3).[a]

		Besta Scale												Quality of Upper Extremity Skills Test									
		Global Score			Grasp, Affected Side			Bimanual Use			ADL Use			Global Score			Grasp[b]			Grasp, Affected Side			Grasp, Unaffected Side		
	Time	Mean	SD	*P*	Mean	SD	*P*	Mean	SD	*P*	Mean	SD	*P*	Mean	SD	*P*	Mean	SD	*P*	Mean	SD	*P*	Mean	SD	*P*
mCIMT	t_0	2.41	0.80		2.85	0.77		2.54	0.88		2.14	0.92		69.4	15.8		65.1	16.8		5.2	3.8		11.5	1.9	
	t_1 (p t_1-t_0)[c]	2.62	0.75	<.001	3.15	0.66	.002	2.76	0.80	.010	2.28	0.86	.208	76.3	14.9	<.001	72.1	18.8	<.001	6.9	3.9	<.001	11.1	1.8	.157
	t_2 (p t_2-t_1)[c]	2.66	0.84	.099	3.13	0.70	.938	2.74	0.86	.851	2.40	0.95	.015	73.8	16.7	.111	70.8	18.7	.761	6.5	3.8	.208	11.6	1.8	.042
	t_3 (p t_3-t_2)[c]	2.66	0.83	.912	3.12	0.71	.496	2.77	0.84	.688	2.39	0.93	.809	76.1	15.2	.229	69.2	18.7	.358	6.3	3.9	.221	11.9	1.6	.042
IBT	t_0	2.54	0.88		2.80	0.91		2.67	0.87		2.40	1.00		66.3	20.3		64.2	21.3		5.7	4.0		11.2	2.2	
	t_1 (p t_1-t_0)[c]	2.74	0.87	<.001	2.88	0.86	.263	2.94	0.81	.001	2.59	0.99	.001	70.0	20.3	.002	66.9	22.1	.040	5.9	3.7	.107	11.4	2.2	.044
	t_2 (p t_2-t_1)[c]	2.80	0.92	.278	2.95	0.91	.200	2.93	0.86	.915	2.70	1.03	.122	71.4	19.1	.123	67.6	20.7	.427	6.0	3.6	.377	11.0	2.2	.985
	t_3 (p t_3-t_2)[c]	2.86	0.90	.883	3.01	0.91	.672	3.05	0.86	.560	2.73	0.97	.910	74.6	18.3	.294	68.9	24.0	.742	7.3	4.1	.023	11.7	2.3	.109
ST	t_0	2.63	0.84		2.96	0.87		2.89	0.85		2.35	0.91		72.2	17.2		64.9	21.5		6.1	3.9		11.8	1.3	
	t_1 (p t_1-t_0)[c]	2.71	0.79	.127	3.01	0.78	.650	3.02	0.68	.107	2.43	0.93	.098	72.6	17.7	.601	66.1	20.8	.474	6.1	3.8	1.000	11.6	1.7	.332
	t_2 (p t_2-t_1)[c]	2.68	0.71	.212	3.05	0.73	.383	2.97	0.68	.502	2.38	0.83	.378	68.0	15.9	.776	62.4	16.5	.738	5.3	3.5	.522	11.3	1.6	.945
	t_3 (p t_3-t_2)[c]	2.70	0.67	.615	3.05	0.73	1.000	2.93	0.69	.554	2.44	0.78	.636	71.3	15.7	.681	66.5	19.9	.820	6.0	3.6	.408	11.9	1.1	.328

Abbreviations: ADL, activities of daily living; IBT, intensive bimanual training; mCIMT, modified constraint-induced movement therapy; ST, standard treatment.

[a] *P* values were calculated comparing each time with the previous, eg, p t_1-t_0, p t_2-t_1, p t_3-t_2, for each treatment group.

[b] Quality of Upper Extremity Skills Test Grasp score results from the combination of performance on request of both arms (affected and nonaffected).

[c] Wilcoxon signed rank test—nonparametric paired samples *t* test.

Modified constraint-induced movement therapy and intensive bimanual training showed a similar and constant increase in time on both scales, whereas standard treatment showed no substantial increases (Table 2).

Statistically significant differences were observed in the modified constraint-induced movement therapy and intensive bimanual training groups mostly before and after treatment (t_0 and t_1). Modified constraint-induced movement therapy resulted in statistically significant t_1 for global scores of each scale (Besta: $P = .0004$; Quality of Upper Extremity Skills Test: $P < .0001$). Similarly, intensive bimanual training resulted in statistically significant t_1 (Besta: $P < .001$; Quality of Upper Extremity Skills Test: $P = .0015$). The standard treatment group showed no significant differences and a constant trend with only slight improvements.

Mean percentualized differences. The mean percentualized differences on the global and subscale scores were calculated [$\Delta\% = (t_n \text{ score} - t_{n-1} \text{ score})/t_{n-1} \text{ score})$]. Modified constraint-induced movement therapy and intensive bimanual training showed a similar constant improvement, much higher than the standard treatment group (Table 3).

Group comparison. In the paired comparison at the end of treatment, the statistically significant differences proved to be modified constraint-induced movement therapy versus standard treatment (on Quality of Upper Extremity Skills Test, $P = .0001$) and intensive bimanual training versus standard treatment (on Besta: $P = .0502$, and at Quality of Upper Extremity Skills Test, $P = .0124$) (Table 4). No statistically significant difference was observed in the comparison of the 2 intensive treatments.

In the follow-up evaluation, no significant differences were found, except from the comparison of intensive bimanual training with modified constraint-induced movement therapy, in favor of the first ($\Delta\%_{mCIMT} = -2.60\%$, $\Delta\%_{IBT} = 6.53\%$; $P = .0139$) at 3-month assessment.

Subscores: Grasp on Request

Affected hand raw mean. In mean scores, modified constraint-induced movement therapy showed a significant improvement in t_1 in grasp (Besta: $P = .0019$; Quality of Upper Extremity Skills Test: $P = .0004$; Quality of Upper Extremity Skills Test, affected hand: $P < .0001$). For the intensive bimanual training group, the improvement observed is statistically significant only for the Quality of Upper Extremity Skills Test (QUEST: $P = .0395$). Standard treatment showed no improvement. In the follow-up assessment, no significant differences were observed.

Affected hand mean percentualized differences. In $\Delta\%$ analysis, at t_1, modified constraint-induced movement therapy showed a relevant improvement in comparison to the other treatment groups ($\Delta\%_{mCIMT} = 80.9$; $\Delta\%_{IBT} = 35.8$; $\Delta\%_{ST} = 4.2$; $P = .0006$). In t_2 and t_3, modified constraint-induced movement therapy showed no further significant improvement, whereas intensive bimanual training demonstrated a constant increase, achieving scores similar to modified constraint-induced movement therapy in t_3 ($P = .0270$) (Table 3, Figure 1A).

Affected hand groups comparison. In the paired comparison, these results were confirmed. On the Besta Scale, modified constraint-induced movement therapy showed a significant improvement in grasp compared with standard treatment. On Quality of Upper Extremity Skills Test, modified constraint-induced movement therapy proved to be better than standard treatment at the end of treatment and then intensive bimanual training at the end of treatment. After 3 and 6 months, intensive bimanual training compared to modified constraint-induced movement therapy improved significantly, reaching the same result at the last follow-up assessment (Table 4).

Unaffected hand raw mean score. Children undergoing modified constraint-induced movement therapy showed a mild worsening in hand grasp of the unaffected side in t_1, although this worsening was not statistically significant ($P = .1572$); however, this worsening was completely recovered in t_2 and t_3 (Table 2).

Unaffected hand mean percentualized difference. In the analysis utilizing the $\Delta\%$, the modified constraint-induced movement therapy initial worsening was confirmed in grasp on request and showed a recovery in subsequent assessments, with small improvements similar to those obtained with standard treatment (Figure 1B).

Intensive bimanual training showed a significant improvement in hand performance in t_1 greater than the 2 other treatment groups ($P = .0280$), and a growing trend over time, always more than modified constraint-induced movement therapy and standard treatment (Figure 1B).

Unaffected hand groups comparison. In the paired comparison, intensive bimanual training proved to be significantly better than both standard treatment and modified constraint-induced movement therapy ($P = .0098$ and $P = .0090$, respectively) in improving unaffected hand grasp (Table 4).

Subscores: Spontaneous Use in Bimanual Activities

Raw mean scores. The spontaneous use of the affected hand in bimanual activities in play improved in children treated with both intensive approaches, and the differences proved to be statistically significant between t_0 and t_1 ($P = .0005$ and $P = .0101$, respectively). Standard treatment showed no significant changes (Table 2).

Mean percentualized differences. The intensive treatment groups did not lose the acquired gain in time and this was demonstrated by further analysis ($\Delta\%$). In the follow-up, modified constraint-induced movement therapy and intensive bimanual training showed a super-imposable trend that was far better than standard treatment (Table 3, Figure 1C).

Table 3. Δ% Global and Subscores per Treatment Group on the Besta and Quality of Upper Extremity Skills Test Scales Before (t_0) and After (t_1) Treatment and in the 2 Follow-up Sessions (t_2 and t_3)[a] Time.

		BESTA Scale								Quality of Upper Extremity Skills Test							
	Treatment Groups	Global Score	P[b]	Grasp, Affected Side	P[b]	Bimanual Use	P[b]	ADL Use	P[b]	Global Score	P[b]	Grasp[c]	P[b]	Grasp, Affected Side	P[b]	Grasp, Unaffected Side	P[b]
t_1-t_0	mCIMT	11.83%		17.43%		13.94%		11.55%		11.31%		12.70%		80.93%		–2.17%	
	IBT	9.85%	.215	5.66%	.137	13.78%	.549	10.71%	.427	10.88%	.001	6.89%	.357	35.79%	.001	5.65%	.028
	ST	5.12%		4.06%		8.97%		5.11%		0.86%		4.84%		4.18%		–2.13%	
t_2-t_1	mCIMT	1.11%		–0.56%		–0.02%		5.05%		–2.60%		0.93%		0.20%		6.31%	
	IBT	3.08%	.967	4.10%	.339	0.31%	.785	5.38%	.701	6.53%	.088	–6.63%	.741	25.17%	.145	3.17%	.418
	ST	2.49%		2.96%		1.61%		3.55%		2.60%		8.69%		8.12%		4.25%	
t_3-t_2	mCIMT	0.68%		0.09%		2.40%		1.50%		4.00%		–2.11%		–0.32%		3.21%	
	IBT	0.10%	.655	0.70%	.950	0.85%	.437	0.79%	.894	3.89%	.960	10.33%	.397	20.92%	.027	6.09%	.801
	ST	0.23%		–0.39%		–1.33%		2.28%		2.35%		1.62%		7.30%		8.27%	

Abbreviations: ADL, activities of daily living; mCIMT, modified constraint-induced movement therapy; IBT, intensive bimanual training; ST, standard treatment.

[a] P values were calculated comparing the 3 treatment groups using the Kruskal-Wallis test—nonparametric version of ANOVA for each time interval p t_1-t_0, p t_2-t_1, p t_3-t_2.

[b] Kruskal-Wallis test.

[c] Quality of Upper Extremity Skills Test Grasp score results from the combination of performance on request of both arms (affected and nonaffected).

Table 4. *P* Values (Mann-Whitney Test—Nonparametric Independent Samples *t*-Test) for Δ% per Treatment Group Before (t_0) and After (t_1) Treatment and at Follow-up (t_2 and t_3).

Time	Besta	mCIMT vs ST	IBT vs ST	IBT vs mCIMT	Quality of Upper Extremity Skills Test	mCIMT vs ST	IBT vs ST	IBT vs mCIMT
t_1-t_0	Global score	.094	.050	.316	Global score	<.001	.012	.155
	Grasp affected	.034	.375	.065	Grasp[a]	.073	.245	.285
	Bimanual use	.323	.116	.311	Grasp affected	<.001	.125	.011
	ADL use	.377	.067	.245	Grasp unaffected	.467	.010	.009
t_2-t_1	Global score	.492	.415	.411	Global score	.156	.168	.014
	Grasp affected	.287	.245	.062	Grasp[a]	.477	.289	.230
	Bimanual use	.279	.265	.485	Grasp affected	.100	.285	.032
	ADL use	.214	.500	.270	Grasp unaffected	.100	.297	.231
t_3-t_2	Global score	.207	.212	.463	Global score	.490	.402	.406
	Grasp affected	.417	.485	.380	Grasp[a]	.199	.356	.101
	Bimanual use	.122	.166	.328	Grasp affected	.083	.118	.005
	ADL use	.452	.353	.341	Grasp unaffected	.294	.268	.455

Abbreviations: ADL, activities of daily living; mCIMT, modified constraint-induced movement therapy; IBT, intensive bimanual training; ST, standard treatment.
[a] Quality of Upper Extremity Skills Test Grasp score results from the combination of performance on request of both arms (affected and nonaffected).

Group comparison. In the paired comparison, no significant differences were found.

Subscores: Spontaneous Use in Activities of Daily Living

Raw mean scores. In the activities of daily living measured by the Besta Scale, the spontaneous use of the affected hand was improved by intensive bimanual training, with an immediate effect measured at t_1 ($P = .0005$) and subsequent maintenance with progressive improvement (Table 2). Modified constraint-induced movement therapy produced an improvement that proved to be statistically significant at the t_2-t_1 comparison ($P = .0154$) and the improvement was persistent (Table 2). Standard treatment demonstrated no significant improvement.

Mean percentualized differences. Modified constraint-induced movement therapy and intensive bimanual training showed a superimposable trend that was far better than standard treatment (Table 3, Figure 1D).

Group comparison. In the paired comparison, no significant differences were found.

Discussion

This multisite clinical trial has compared 1 control group of children, considered as a baseline standard treatment, with 2 experimental groups of children with hemiplegia treated with intensive rehabilitation practices. The first experimental group utilized restraint of the affected hand and a unimanual intensive rehabilitation treatment (modified constraint-induced movement therapy group) whereas the second underwent a bimanual intensive rehabilitation treatment without restraint (intensive bimanual training group). The total recruitment consisted of 105 children and it constitutes an adequate sample size of patients in order to evaluate the existence of a difference in the efficacy of tested treatments of 30% and a power of 80%.

The comparison of 3 groups of patients allowed us to analyze both the efficacy of the intensive uni- or bimanual practice in comparison with the standard treatment (comparison of modified constraint-induced movement therapy with standard treatment and intensive bimanual training vs standard treatment) and the eventual adjunctive advantages given by the constraint or by the bimanual intensive practice (intensive bimanual training vs modified constraint-induced movement therapy).

First, our results demonstrate a substantial improvement of paretic upper limb function in children treated both with restraint of the unaffected hand and intensive unilateral practice and in those treated with intensive bilateral practice without restriction, while the children of the standard treatment group showed minimal or no changes of hand function. These results are in accordance with those reported by Gordon et al, which emphasize the importance of the intensity of treatment in improving motor performance.[9] Similar findings have been recently reported by Sakzewsky et al.[11] In our children, the improvement of paretic hand function was demonstrated after the training period[12] and persisted at the follow-up evaluation up to 6 months after the end of treatment in both groups of children treated with an intensive practice: these data are clinically very important and should deeply influence the approach to rehabilitation in children, currently generally based on once- or twice-a-week training sessions.

Second, at the end of treatment, the modified constraint-induced movement therapy group (unimanual intensive training) showed a significant improvement in the grasp abilities of the affected hand, greater than the one achieved by the intensive bimanual training group (intensive bimanual training). This advantage was confirmed both with the Quality of Upper Extremity Skills Test and the Besta Scale (grasp on request). Our data are in agreement with many other studies that reported

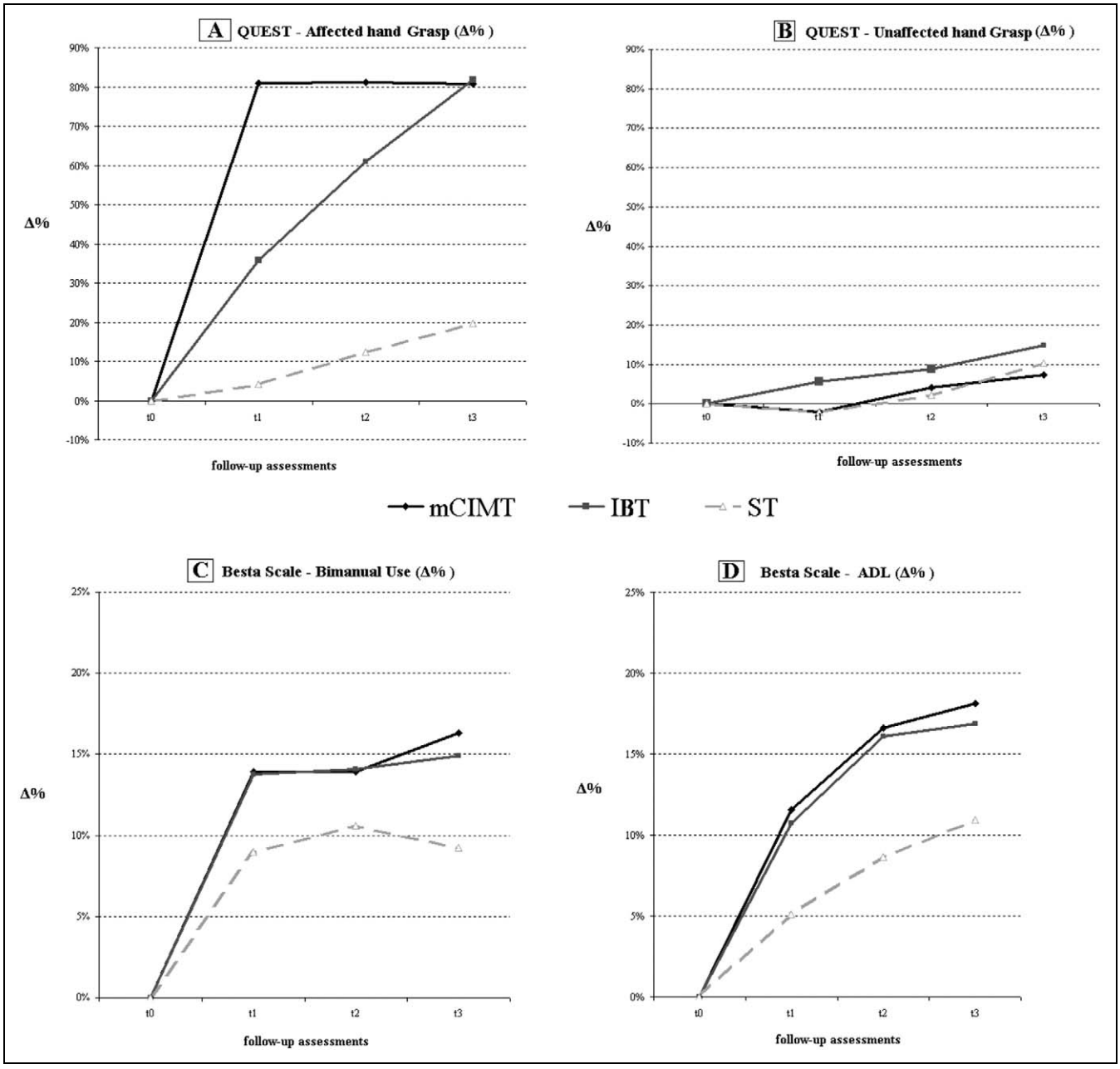

Figure 1. Trends in time (t_0, t_1, t_2, and t_3) for each treatment group (modified constraint-induced movement therapy, intensive bimanual training, and standard treatment) at Quality of Upper Extremity Skills Test for the Δ% of the affected (A) and unaffected hand (B), and at Besta Scale for the Δ% of bimanual use (C) and of activities of daily living subscores (D). Abbreviations: ADL, activities of daily living; IBT, intensive bimanual training; mCIMT, modified constraint-induced movement therapy; ST, standard treatment.

the positive effects of modified constraint-induced movement therapy on the affected hand grasp at the postintervention assessment.[2,3]

The mechanism of action of constraint therapy has been recently explored in different models (animal model, adult and pediatric patients). Using transcranial magnetic stimulation in adult stroke patients, some studies[14] showed an expansion of the motor map in the ipsilesional hemisphere and a reduction in the contralesional motor map after constraint-induced movement therapy.

In pediatric cerebral palsy, the modified constraint-induced movement therapy effect has been studied recently by Sutcliffe,[19] who used functional MRI to demonstrate functional cortical changes during pediatric constraint therapy and an increased contralateral cortical activation for the affected hand in a group of hemiplegic children. Friel and Martin[35] are suggesting another mechanism for understanding the efficacy of constraint-induced movement therapy: on the basis of their study of the bilateral activity-dependent interactions in the developing corticospinal system, they hypothesized that

driving down the activity of the undamaged corticospinal system by restraining the nonaffected hand may enable the damaged corticospinal system to reconnect more effectively with the spinal motor circuit. This hypothesis could be supported by the trend of a slight reduction in the functional gain in grasp observed only in children of the modified constraint-induced movement therapy group at the 3- and 6-month assessments after the end of treatment, both in the Quality of Upper Extremity Skills Test and the Besta Scale examination. These data could be attributed to the reintroduction of the inhibition of the undamaged hemisphere on the damaged one after the end of the restraint of the nonaffected hand.

More difficult to explain is the progressive and constant improvement of the grasp function in the group of children treated with intensive bimanual training without restraint (intensive bimanual training) at the follow-up assessment: this improvement is slight after the end of treatment (t_1) compared to the great improvement of the children of the modified constraint-induced movement therapy group, but in the following months it increased gradually both at the Quality of Upper Extremity Skills Test and the Besta scale. At the 6-month (t_3) assessment using the Quality of Upper Extremity Skills Test, the grasp value of children of the intensive bimanual training group reaches the values of grasp function of the modified constraint-induced movement therapy group. It is possible that the intensity of the bimanual training and the parents' instruction and training to continue the practice at home after the end of treatment promoted not only the learning of bilateral sequences in play and activities of daily living but also a persistent improvement of the quality of pinch on request.

Another interesting aspect concerns the grasp function as regards the grasp Quality of Upper Extremity Skills Test subscore of the nonaffected upper limb in children treated with intensive bimanual training, which increases significantly more at the end of treatment (t_1) than in the children treated with modified constraint-induced movement therapy intensive training, who showed a mild reduction in grasp function. The restraint of the nonaffected hand for a long period in the modified constraint-induced movement therapy group of children may imply a transient reduction of grasp ability, which is immediately restored at the 3- and 6-month follow-up assessment. The reversibility of this finding seems to exclude the possibility of permanent damage to the healthy hemisphere because of a forced and long restraint of the nonaffected hand, as hypothesized by some authors,[36] and confirms the safety of the modified constraint-induced movement therapy.

Will the advantage obtained in grasping with the restraint and the unimanual training of the affected hand in the modified constraint-induced movement therapy group of children be directly transferred to daily activities and in independent achievement? Shifting from the hand function to the hand use in activities of daily living, the bimanual spontaneous use of the affected hand in play and in self-care activities at the end of treatment is improved in the modified constraint-induced movement therapy group ($P = .02$), but the significance is stronger for the intensive bimanual training group ($P = .0005$ and .001). These data are in accordance with a recent randomized controlled trial carried out by Aarts et al,[3] who reported that modified constraint-induced movement therapy followed by bimanual training is effective to improve spontaneous use of the affected limb during play and self-care activities, assessed with the Assisting Hand Assessment in children with unilateral spastic cerebral palsy.

In our study, the improvement of paretic hand spontaneous bimanual use in play and Activities of Daily Living was maintained at the following 3- and 6-month assessment with the Besta Scale after the end of treatment in both groups of children treated with intensive unimanual and bimanual practice. In fact they continue to improve with a similar trend from the end of treatment to the 6-month evaluation. This progressive improvement in spontaneous hand use of treated children could be referred either to the intensity or to the duration of the training. However, in our opinion, one of the factors that could have played a role in promoting the continuity of the subsequent improvement in hand use in both groups of intensively treated children could have been the training and the involvement of parents during the treatment period, and providing the family a booklet and DVD with examples of play and daily life situations to practice at home.

The parents were encouraged to continue to follow the suggestions learned during treatment at home after the end of the trial and so the effect of treatment could have been transferred and prolonged in the life situation. This is in accordance with recent observations by Taub,[14] who reported that the ''transfer package,'' focused on the use of the affected arm in a life situation, made a much more important contribution to modified constraint-induced movement therapy outcome than the type of training, and that the restraint component was relatively unimportant.

The persistence of the long-term effect in the spontaneous use of the hand in play and life activities in our treated children indicates therefore that the intensity of treatment and the transfer of suggestions to the parents are the most important factors for learning new strategies to improve the quality and the frequency of hand use. This should lead to the remodeling of neural circuitry and to a refining of motor planning.

The intriguing question concerning which is the best approach, the unimanual or the bimanual training, for overcoming the developmental disregard has to be further studied. In fact, the improvement of the spontaneous use in life situations found in both groups of our children do not express per se the overcoming of developmental disregard. According to Taub,[14] this is the difference between a measure of what a person can do when asked to do the best and a measure of what a person actually does spontaneously in a real-world situation. The problem to be solved is how to quantify the developmental disregard: in children with unilateral cerebral palsy, Sutcliffe introduced a quantification of developmental disregard by calculating the differences between the baseline scare of Quality of Upper Extremity Skills Test and the Pediatric Motor Activity Log score, which represents the amount of typical use of the hemiplegic hand. Aarts et al[3] assessed developmental disregard

with the video observations of the duration and frequency of the spontaneous use of the affected hand during 2 selected activities, 1 demanding the use of both hands and the other stimulating, but not demanding, the use of both hands. In our study, the developmental disregard could be measured on the Besta Scale by the difference between the grasp on request score, which express the capacity (grasp subscale) and the spontaneous use score in play and activities of daily living (bimanual and ADL subscales), which express the real performance. However, the problem of quantifying the developmental disregard is very complex and in our opinion requires further investigation.

Finally, the assessment tools chosen for this trial to measure the primary outcome before and after treatment proved to be very useful and appropriate to the aim of the study. In fact, the Besta Scale, whose interobserver agreement was defined before the beginning of the trial, enabled us to assess the differences between the grasp function on request (Capacity) and the spontaneous use in life situation (Performance). The Assisting Hand Assessment, which was published and distributed after the beginning of our study, is a useful tool for the assessment of spontaneous bimanual use, but it is unable to evaluate the use of the hands in self-care activities.

In conclusion, deriving from a clinical trial with an adequate sample size, the findings of this study indicate that the intensity of treatment improves the hand function in both groups of children treated either with unimanual or with bimanual training with respect to the control group. Furthermore, the grasp is shown to improve significantly in the modified constraint-induced movement therapy group of children at the end of treatment, then remaining stable, while in the intensive bimanual training group the grasp improvement continues until the assessment at 6 months. Finally, in both groups of intensively treated children, the spontaneous use of hand in play and life situations increases at the long-term assessment at 6 months, indicating that children have learned new strategies for bimanual coordination in accomplishing the tasks related to their developmental age. The most relevant clinical implication of these findings for the rehabilitation of children with hemiplegic cerebral palsy, besides the positive role of treatment intensity, concerns the great value of the parents' training, which enables the suggestions for practicing at home in the real world what children have learned during the treatment sessions.

Appendix

Besta Scale

Patient ID_____ Date of birth _____ Sex m f Assessor_____

A) Assessment on the **grasp function** of the paretic hand on request

Grasp a cube 1.5 cm	0	1	2	3
Grasp a cube 2.5 cm	0	1	2	3
Grasp a cube 4 cm	0	1	2	3
Grasp a marble	0	1	2	3
Total		**/12**		

B) Qualitative assessment of the spontaneous use of the paretic hand in **bimanual manipulatory activities** (objects are standardized by age classes)

6-12 months

Hold a big ball (Ø 40 cm)	0	1	2	3
Tear tissue paper	0	1	2	3
Grasp a baby's bottle	0	1	2	3
Grasp a doll	0	1	2	3
Total		**/12**		

13-24 months

Throw a big ball (Ø 40 cm)	0	1	2	3
Tear tissue paper	0	1	2	3
Drink from a bottle or a baby's bottle	0	1	2	3
Unwrap a packet (transparent paper)	0	1	2	3
Total		**/12**		

25-36 months

Throw a big ball (Ø 40 cm)	0	1	2	3
Tear tissue paper	0	1	2	3
Uncork a bottle (popup plug)	0	1	2	3
Unwrap a packet (rubber band)	0	1	2	3
Total		**/12**		

37-48 months

Throw a big ball (Ø 40 cm)	0	1	2	3
Tear tissue paper	0	1	2	3
Uncork a bottle (popup plug) and fill it (water)	0	1	2	3
Unwrap a packet (ribbon)	0	1	2	3
Total		**/12**		

5-6 years

Throw a small ball (Ø 20 cm)	0	1	2	3
Tear paper into small pieces	0	1	2	3
Uncork a bottle (screw plug) and fill it (water)	0	1	2	3
Unwrap a packet (knotted ribbon)	0	1	2	3
Total		**/12**		

>7 years

Unwrap a packet (knotted ribbon)	0	1	2	3
Wrap a packet (knotted ribbon)	0	1	2	3
Fold a sheet and put it into an envelope	0	1	2	3
Paste paper shapes on the corresponding outlines	0	1	2	3
Total		**/12**		

C) Qualitative assessment of the use of the paretic hand in feeding and clothing **Activities of Daily Living** (tasks are standardized by age classes)

18 months-7 years

Drink from a cup (>18 m)	0	1	2	3
Drink from a big glass (>18 m)	0	1	2	3
Slice bread (>18 m)	0	1	2	3
Fold a napkin (> 3 y)	0	1	2	3
Cut using knife and fork (> 6 y)	0	1	2	3
Wash hands (> 2 y)	0	1	2	3
Wash face (> 2 y)	0	1	2	3
Take off shoes (> 2 y)	0	1	2	3
Take off socks (>18 m)	0	1	2	3
Take off sweater (> 3 y)	0	1	2	3
Take off trousers (> 2 y)	0	1	2	3
Total		**/33**		

7-8 years

Wear a sweater	0	1	2	3
Wear trousers	0	1	2	3
Wear socks	0	1	2	3
Wear shoes	0	1	2	3
Total		**/12**		

GLOBAL SCORE

A = ___/12
B = ___/12
C = ___/12 or ___/24 or ___/33

Scoring system

Grasp Assessment (Section A)

0 Grasp absent
1 Reaching (get by and move)
2 Palmar, radial palmar, radial digital, inferior pincer
3 Pincer/finer pincer

Spontaneous Use in Play and Activities of Daily Living (Sections B and C)

(the scoring system was based on variability and stereotypy of movement patterns)

0 no use of the impaired limb
1 use of the impaired limb in a stereotyped pattern for holding (wrist support)
2 cooperation of the impaired hand with holding functions with a restricted number of stereotyped patterns
3 cooperation of the impaired hand with holding and manipulative functions, using a varied repertoire of patterns

Authors' Note

GIPCI Study Group: Dr Valentina Aguggiaro, Physical Therapist, Rehabilitation Center, La Nostra Famiglia, Padua, Italy**;** Dr Vera Ancona, Medical Doctor, Rehabilitation Center, La Nostra Famiglia, Treviso, Italy; Dr Elena Andreucci, Medical Doctor, National Neurological Institute C Besta, Milan, Italy; Dr Maria Banditori, Physical Therapist, Rehabilitation Center, La Nostra Famiglia, Treviso, Italy; Dr Francesco Bon, Medical Doctor, Child and Adolescent Psychiatry Unit, Local Health Unit No. 12, Venice, Italy; Dr Martina Bua, Psychologist, Epidemiology and Community Medicine Unit, Pediatrics Department, University of Padua, Padova, Italy; Dr MariaVittoria Castelli, Physical Therapist, Child and Adolescent Psychiatry Unit, Lecco Hospital, Lecco, Italy; Dr Monica Cazzagon, Medical Doctor, Rehabilitation Center, La Nostra Famiglia, Pasian di Prato, Udine, Italy; Dr Carlo Di Brina, Medical Doctor, Viterbo Rehabilitation Center, Viterbo, Italy; Dr Cristiana Dornini, Physical Therapist, AIAS Milano, Milan, Italy; Dr Donatella Fusari, Physical Therapist, Child and Adolescent Psychiatry Unit, Bergamo Hospital, Bergamo, Italy; Dr Tony Genovese, Physical Therapist, Rehabilitation Department, Local Health Unit No. 5, Messina, Italy; Dr Chiara Germinasi, Medical Doctor, Scientific Research Institute Eugenio Medea, Bosisio Parini, Lecco, Italy; Dr Paola Giannarelli, Physical Therapist, Pediatric Rehabilitation Dept, Children's Hospital Bambino Gesù, Rome, Italy; Dr Michelina Inverno, Medical Doctor, Child and Adolescent Psychiatry Unit, Lecco Hospital, Lecco, Italy; Dr Annalisa La Gamba, Medical Doctor, Rehabilitation Center, La Nostra Famiglia, Padua, Italy; Dr Vera Loreti, Physical Therapist, Viterbo Rehabilitation Center, Viterbo, Italy; Dr Giuseppina Luati, Physical Therapist, Child Neurology Rehabilitation Center, Hospital Macchi, Velate, Varese, Italy; Dr Giovanna Lucco, Physical Therapist, Department of Neonatology, IRCCS Mangiagalli Hospital, Milan, Italy; Dr Antonella Luparia, Physical Therapist, Department of Child Neurology and

Psychiatry, IRCCS C. Mondino Institute of Neurology, University of Pavia, Pavia, Italy; Dr Priscilla Maddalena, Physical Therapist, Rehabilitation Center, La Nostra Famiglia, Vicenza, Italy; Dr Antonia Madella Noja, TdR AIAS Milano, Milan, Italy; Dr Bertilla Magagnin, Physical Therapist, Scientific Research Institute Eugenio Medea, Conegliano V.To, Treviso, Italy; Dr Pasquale Mandalari, Medical Doctor, Rehabilitation Department, Local Health Unit No. 5, Messina, Italy; Dr Alessia Marchi, Physical Therapist, Developmental Neurology Unit, National Neurological Institute C Besta, Milan, Italy; Dr Andrea Martinuzzi, Medical Doctor, Scientific Research Institute Eugenio Medea, Conegliano V.To, Treviso, Italy; Dr Michela Marzaroli, Medical Doctor, Child and Adolescent Psychiatry Unit, Bergamo Hospital, Bergamo, Italy; Dr Chiara Megliani, Medical Doctor, Scientific Research Institute Eugenio Medea, Bosisio Parini, Lecco, Italy; Dr Francesca Molteni, Physical Therapist, Scientific Research Institute Eugenio Medea, Bosisio Parini, Lecco, Italy; Dr Marco Pezzani, Medical Doctor, Child and Adolescent Psychiatry Unit, Bergamo Hospital, Bergamo, Italy; Dr Odoardo Picciolini, Medical Doctor, Department of Neonatology, IRCCS Mangiagalli Hospital, Milan, Italy; Dr Cristina Ranzato, Biologist, PhD, Epidemiology and Community Medicine Unit, Pediatrics Department, University of Padua, Padua, Italy; Dr Silvana Sartor, Physical Therapist, Child and Adolescent Psychiatry Unit, Local Health Unit No. 12, Venice, Italy; Dr Angela Setaro, Physical Therapist, S. Stefano Rehabilitation Centre, Fabriano, Italy; Dr Sabrina Signorini, Medical Doctor, Department of Child Neurology and Psychiatry, IRCCS C. Mondino Institute of Neurology, University of Pavia, Pavia, Italy; Dr Giuseppe Stefanoni, Physical Therapist, Scientific Research Institute Eugenio Medea, Bosisio Parini, Lecco, Italy; Dr Massimo Stortini, Medical Doctor, Pediatric Rehabilitation Department, Children's Hospital Bambino Gesù, Rome, Italy; Dr Michela Tentori, Physical Therapist, Rehabilitation Center, La Nostra Famiglia, Pasian di Prato, Udine, Italy; Dr Lorella Tornetta, Medical Doctor, Child and Adolescent Psichiatry Department, Sant'Anna Hospital OIRM, Turin, Italy; Dr Antonio Trabacca, Medical Doctor, Scientific Research Institute Eugenio Medea, Ostuni, Italy; Dr Teresa Vespino, Physical Therapist, Scientific Research Institute Eugenio Medea, Ostuni, Italy; Dr Ambra Villani, Physical Therapist, Rehabilitation Department, Local Health Unit No. 3, Genoa, Italy; Dr Fabio Zambonin, Medical Doctor, Child Neurology Rehabilitation Center, Hospital Macchi, Velate, Varese, Italy; Dr Ursula Zumaglini, Medical Doctor, Rehabilitation Department, Local Health Unit No. 3, Genoa, Italy.

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Author Contributions

EF contributed to the writing of the background, the discussion, and in the quality evaluation of the videos of the scale administration. MR-R wrote the first draft of the manuscript and contributed to the management of trial development. ACT, EP, and EF were the local coordinators of the centers with the highest number of patients enrolled; they contributed to the definition of treatment options. LVDP carried out the statistical analysis and has written the Methods section. PF has written the trial study design and the research project and has contributed in writing results and to discussions in defining future perspectives. Professionals included in the GIPCI study group contributed to patient enrollment, treatment administration, and assessment of patients. Cristina Ranzato (GIPCI study group) contributed to the manuscript draft editing and review.

Declaration of Conflicting Interests

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Ethical Approval

This study was approved by the institutional review board and by the ethical committee. Before starting the research program, all enrolled patients and their families were fully informed about the trial and treatments and expressed a formal written consent.

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