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Il trattamento delle paralisi cerebrali infantili: sperimentazioni cliniche e ricadute assistenziali di nuovi approcci terapeutici e riabilitativi

The treatment of infant cerebral palsy: clinical experimental trials of new therapeutic approaches and outcomes on health care

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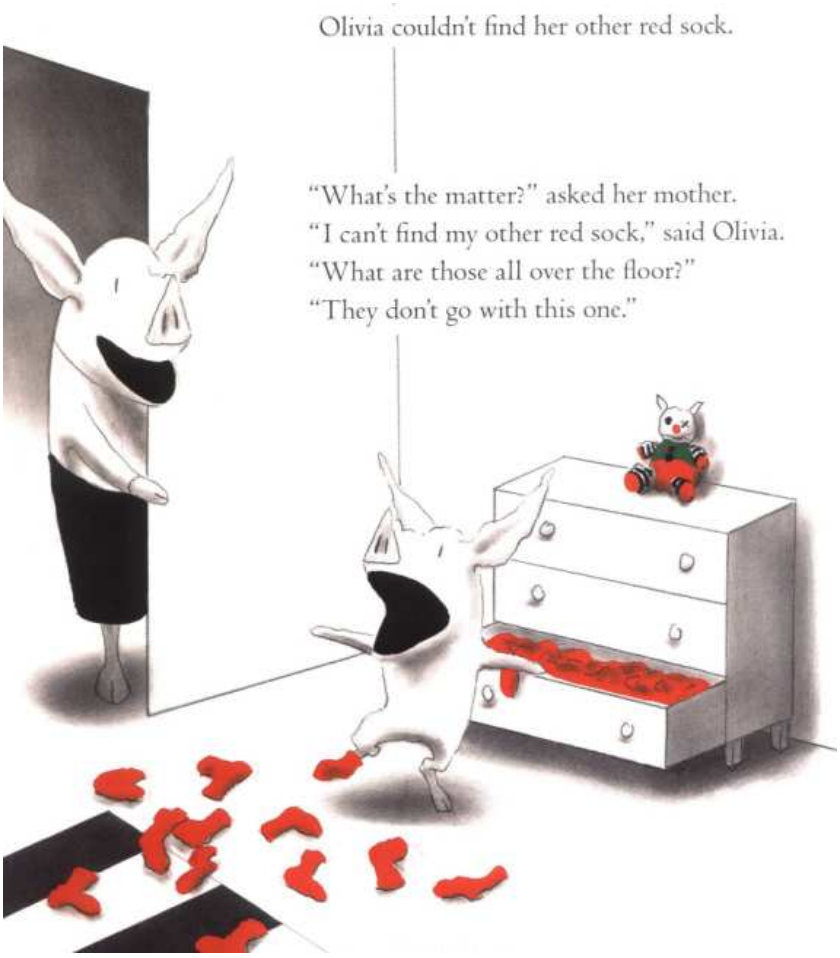
Ai bambini

A mia nonna Isolina



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ABSTRACT

Background

In the last decades, several treatment approaches have been used to improve upper limb function in hemiplegic CP. Only recently has Constraint Induced Movement Therapy (CIMT) emerged as a treatment approach for children with hemiplegic CP with the aim of reversing the behavioral suppression of movement in the affected upper limb. To date, evidence on this treatment has been very poor and limited, since all currently available trials reveal methodological limitations and a need for additional research to support the application of this treatment technique.

Aim

The thesis aims at exploring the safety and efficacy of a new treatment approach, Constraint Induced Movement Therapy has been studied and compared to a bimanual intensive rehabilitation approach and to traditional rehabilitation program.

Methods

This thesis presents the planning and development of a national mustisite clinical trial started in 2006 and carried out in collaboration with 21 Italian rehabilitations centers belonging to the Italian Group for Cerebral Palsy (GIPCI).

The effectiveness and safety of CIMT combined with an intensive rehabilitation program was compared to 2 comparison groups: one treated with an intensive rehabilitation program and the other with standard treatment. Patients with

hemiplegic cerebral palsy, aged between 2 and 8 years, who have never undergone constraint therapy have been recruited. Primary outcome measures include 2 major domains: UE motor ability (QUEST) and hand function assessment evaluating both grip function and spontaneous use of the affected side (Besta Scale). Secondary outcome measures concern overall function, behavior, compliance and satisfaction with treatment program of both child and family. Patients' follow-up assessment was performed at 3, 6 and 12 months after the end of treatment.

Collected data have been analyzed through univariate and multivariate statistical analysis.

The experimental phase was preceded by a standardized analysis or primary outcome measures (QUEST and Besta Scale) in order to evaluate the agreement among the assessors of all participating centers. All evaluators scored the same 84 video-recorded tests each (42 QUEST and 42 Besta Scales administered to 42 children, 2 per each participating center). The analysis evaluated the inter-rater agreement and the reliability of primary outcome measures.

During the clinical trial all the professionals involved in the project have been interviewed to explore their opinion on conducting clinical research in the field of rehabilitation and in their daily practice.

Results

105 children have been recruited (39 undergoing CIMT, 33 undergoing bimanual intensive rehabilitation program and 33 undergoing traditional rehabilitation program). The main results demonstrate a significant effect of both intensive

programs on the upper limb function. CIMT results particularly effective in ameliorating the grasp function, while bimanual intensive rehabilitation program results particularly efficacious in activity of daily living tasks. The traditional treatment does not show a significant modification of upper limb function. The patterns of brain plasticity and the process cortical reorganization following injury seem to play a crucial role in upper limb function modifications after intense treatment.

Secondary outcome measures show the importance of the intensity of treatment and follow-up to reduce family stress and behavioral disturbances in children.

The agreement analysis demonstrated an overall good inter-rater agreement and the reliability of both scales in assessing hand and upper limb function.

68 professionals have been involved in the survey regarding research in rehabilitation. The main results show the importance of conducting research in rehabilitation not only to obtain evidence for new therapeutic approaches, but also to standardize the practices and to share and improve the ability to use new and standardized assessment tools.

Conclusions

The researches conducted and the results obtained seem particularly important for the current rehabilitation practice and for the organization of rehabilitation programs in the dedicated health care service. Further research is needed on these issues, since, if these results will be confirmed they could dramatically change the approach to children with hemiplegic cerebral palsy and modify sensitively their disease's natural history.

CHAPTER 1. INTRODUCTION

Cerebral palsy in children

Cerebral palsy (CP) describes a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non progressive disturbances that occurred in the developing fetal or infant brain[1 2]. It is characterized by sensorimotor dysfunction as manifested by atypical muscle tone, posture and movement. Severity of impairment varies widely, depending on the site and severity of brain damage[3].

Hemiplegia is a unilateral physical impairment[4], is a common type of CP accounting for 36-40% of all CP. Typically, the upper limb is more involved than the lower, with impairments of spasticity, sensation and reduced strength[5].

One of the most disabling symptoms of hemiplegia is unilaterally impaired hand and arm function, which affects self-care activities such as feeding, dressing, and grooming[6]. The impairment of the hand is often the result of damage to the motor cortex and corticospinal pathways responsible for the fine motor control of the fingers and hand[7]. Thus, skilled independent finger movements do not develop typically in children with hemiplegia. During tasks that require fine manipulation, such children often use several fingers, and often show abnormal hand posturing as well as reduction in distal strength and dexterity[7 8].

Sensory disturbances can occur as well, further complicating any motor impairment[9]. Furthermore, children with hemiplegia due to cerebral palsy (CP, the most motorically studied subtype of hemiplegia) have difficulty with the timing

and coordination of reaching movements, grasping, movement planning, and a deficient capacity to modulate postural adjustments during reaching[10].

The resulting sensory and motor impairments in children with hemiplegia compromise movement efficiency. Such children often tend not to use the affected extremity, resulting in a developmentally learned non-use of the involved upper extremity that can be termed 'developmental disuse'[5 10 11].

Typically, rehabilitation techniques have focused on teaching and reinforcing compensatory strategies that encourage use of the non-involved upper extremity to decrease functional limitations. Strong evidence for the successful application of any therapeutic approach is lacking[11]. Recent evidence suggests that children with hemiplegic CP can improve motor performance if provided sufficient practice. This finding indicates that intensive practice may improve function in the involved upper extremity that could lead to increased use in daily life[11 12].

Epidemiology

Cerebral palsy is the most common physical disability of childhood with a prevalence of approximately 2 per 1000 newborns, in most developed countries[13 14 15].

In 1998, fourteen centres in eight European countries started a network called Surveillance of Cerebral Palsy in Europe (SCPE)[16]. After reaching consensus about the criteria to classify CP, they presented the prevalence rates in six countries, and more detailed prevalence estimates of 13 areas[17]. In Table 1.1 a summary of the prevalence estimates of CP of the SCPE, as well as from some other north-western Europe countries, is given. As can be concluded from this

table the prevalence and the trends in time of CP are comparable in these countries[18 19].

Table 1.1. Prevalence of cerebral palsy in Northwest Europe

	Birthyear	Prevalence per 1000 lifebirths
Northeast England	1964 – 1968	1.68
	1969 – 1973	1.39
	1974 – 1978	1.71
	1979 – 1983	2.00
	1984 – 1988	2.27
	1989 – 1993	2.45
Scotland, England	1984 – 1989	2.10
Northern Ireland	1981 – 1993	2.24
Norway	1977 – 1981	1.91
	1982 – 1986	1.98
	1987 – 1991	2.05
Denmark	1979 – 1986	2.80
	1987 – 1990	2.40
Sweden	1979 – 1982	2.17
	1990 – 1993	2.20
	1991 – 1994	2.12
The Netherlands	1977 – 1979	0.77
	1980 – 1982	1.00
	1983 – 1985	1.84
	1986 – 1988	2.44

The prevalence of CP rises in time from well below 2.0 per 1000 life births in the 1970s to well above 2.0 in the 1990s. Boys form a small majority (58%). It seems fair to assume that these European data are not very different from findings in other parts of the world[13]. For example the prevalence of CP in China is reported to be 1.6 per 1000 children under age 7[20 21]. In Mississippi (USA) 2.12 per 1000 inhabitants were diagnosed with CP with a higher prevalence for males, and a, non-significant, higher prevalence in black people[22]. The prevalence of CP in

Australia is 2.0 to 2.5 per 1000 live births[23]. The prevalence of CP among low-birthweight children is higher than among normal birthweight children[24].

Clinical main characteristics and classification

Table 1.2 gives a summary of the data about the most common impairments associated with CP, crude prevalences are given.

Table 1.2. Prevalence of impairments among children with cerebral palsy

Impairment	%
Motor	100
Cognitive (*)	23–44
Sensibility	44–51
Speach	42–81
Visual (**)	62–71
Hearing (#)	25
Epilepsy	22–40
Feeding	
Gastrointestinal	
Growth	23
Weight	52
Urinary incontinence	23.5

*Cognitive impairment: IQ<70.
**Visual impairment: moderate = 6/18–6/60 D, severe = <6/60 D.
#Hearing impairment: moderate = 45–70 dB loss, severe = 70 dB loss.

Motor impairment is obligatory for the diagnosis CP. In people with hemiplegic CP the prevalence of additional impairments is 42%. Common additional impairments are cognitive impairments, epilepsy, sensory, endocrine and urogenital impairments[3 25].

As can be seen in Table 1.2, a large proportion of people with CP have some kind of cognitive impairment[26]. The prevalence varies with the type of CP and especially increases when epilepsy is present. In severely disabled CP children, 97.7% are profoundly mentally impaired. But, since 1976 the prevalence of severe mental retardation has decreased significantly. About 40% of children with hemiplegic CP have normal cognitive abilities, while children and adolescents with tetraplegic CP are generally severely intellectually impaired[3 25].

There is no association between IQ level and memory scores and location of brain damage (left or right). Nonverbal learning impairments, characterized by good language abilities and week visual-spatial abilities with fear of new situations and stepwise development, are common[3 25].

Behavior problems are five times more likely in children with CP (25.5%) compared with children with no known health problem[27]. The odds ratio for behavior problems of children with CP without mental retardation is 4.9. The attention deficit hyperactivity disorder (ADHD) is more common among children with CP. Other specific behavior problems in children with CP are dependency, being headstrong, and hyperactivity in general[28].

A large minority of people with CP has epilepsy, and the prevalence varies with the type of motor impairment. It is most common among the hemi- and tetraplegics[7].

Sensibility and senses may be affected as well[7]. Stereognosis and two-point discrimination of the hands is impaired in 44 – 51% of all children with CP (astereognosia in 20%). Term children tend to be more severely affected. Sensory impairments are most common among hemiplegic CP people. Nine out of 10 hemiplegic children have significant bilateral sensory deficits. Stereognosis and proprioception are the chief modalities affected bilaterally. The extent of sensory loss does not mirror the severity of the motor deficit. Chronic pain is reported by 28% of the adults with CP, versus 15% of the adults in the general population. Impairment of speech is common and strongly associated with the type and severity of the motor impairment. The most common impairment is dysarthria but aphasia occurs also.

Ophthalmic abnormalities are present in 62% of CP children[29]. Low visual acuity is reported in 71% of children with CP. Because ophthalmological examination cannot explain the low visual acuity of the vast majority, there is a high probability of cerebral visual disturbance[30].

Impairments in hearing do occur but less often than the other impairments; however, data are very scarce.

Peculiar radiological features may be observed in children affected by cerebral palsy[8]. MRI brain abnormalities can be classified into four groups: i.e. group 1: brain malformations; group 2: cortical-subcortical lesions; group 3: abnormalities

of the periventricular white matter; and group 4: postnatal brain-injuries. In groups 1 and 2 the severity of hemiplegia is mainly moderate, while it is mild in groups 3 and 4. The third group presents a large involvement of the lower limb, while the upper limb is more affected in the other groups[31].

Mental retardation occurs in one-third of children in groups 1 and 4, less often in the other two. Seizures occur in half of the children in groups 1 or 2, while the incidence was lower in the other two. In very low-birthweight children (500 – 1499 g) periventricular leukomalacia, and secondly, intraventricular hemorrhage are predictive of cerebral palsy and of functional outcome[31]. Among all CP categories, abnormal cranial ultrasound is most strongly associated with hemiplegia, normal cranial ultrasounds with diplegia[31]. In children with bilateral spastic CP hypoperfusion in the thalamus or cerebellar hemispheres is found. Mildly decreased perfusion is associated with mild delays in gross motor development, while almost all children with severe hypoperfusion show severe developmental delay[31].

Possible treatment and rehabilitation approaches

Clinicians dedicate considerable time and resources towards upper limb rehabilitation[32]. The management options are summarized in Table 1.3 and include different types of physiotherapy and occupational therapy such as neurodevelopmental therapy or motor learning; conductive education; peripheral splinting and casting; focal and generalized pharmacotherapy (such as botulinum toxin type A injections or intrathecal baclofen); and surgery aimed at improving upper limb function or reducing deformity[33].

Table 1.3. Treatment options for upper limb dysfunction in children with cerebral palsy

Behavioural and environmental treatments	Physiotherapy Occupational therapy Neurodevelopmental treatment Motor learning Conductive education Strength training Constrain Induced Movement therapy
Peripheral splinting & casting	
Special seating	
Electrophysical agents	Neuromuscular Electrical Stimulation EMG biofeedback
Pharmacological - focal	Phenol Botulinum Toxine A
Pharmacological – generalized spasticity management	Intratecal Baclofen
Surgery	Selective dorsal Rhizotomy

These therapies are based on a variety of theoretical constructs, with different treatment elements, although some overlap may exist between therapies as well as variation in the content[33].

For most treatment approaches for upper limb dysfunction in children with CP there is a paucity of evidence. Growing evidence was found for the use of casting combined with occupational therapy, as well as for BTX-A combined with occupational therapy[34], although there were only a small number of trials investigating these interventions, and some had very small samples. Many of the effect sizes for individual treatments had wide confidence intervals indicating a variable response to therapy[33].

A large effect size was noted for **botulinum toxin type A** combined with **occupational therapy** at 1 month, and this was partially maintained at 6 months[34].

Behavioural therapies such as NDT and standard occupational therapy may have small effects that appear to be enhanced by augmentation with additional intervention (e.g. bivalved casts)[35]. Newer therapies such as BTX-A have a greater magnitude of effect at 1 month, although the results are not sustained to the same level at 6 months follow-up. Further research is required to evaluate the effects of combinations of treatments over longer time intervals, utilizing a broader range of outcome measures[34]. To date, no large randomized studies of functional outcome have been completed with comparison to placebo therapy or 'no' occupational therapy. One difficulty is that ethical considerations may not permit such studies in young children with CP. Another difficulty is interpreting the content of therapy as well as the intensity delivered across trials[36].

Two very detailed studies with a range of validated objective outcome measures evaluating the efficacy of **conductive education (CE)** programmes against traditional **NDT programmes** of rehabilitation have been completed which examine many aspects of function, including upper extremity measures[36].

In two large studies, the effects of **standard occupational therapy** on the acquisition of fine motor skills and functional outcomes were studied over 1 year[34]. Attainment of visual motor skills were influenced by the intensity of sessions with play goals, fine motor skills were influenced by peer interaction,

while play goals and functional outcomes were influenced by emphasis on self-care activities.

The main generalized approaches (pharmacotherapy and surgery) to spasticity management in children with CP are **continuous intrathecal baclofen (ITB)**[37] and selective dorsal rhizotomy (SDR)[33]. The predominant effect is in the lower limbs, however, anecdotal reports of higher placement of the ITB catheter tip have suggested improvements in the upper limbs. Several reports have documented a reduction in spasticity with intrathecal baclofen treatment, but none has shown improvements in range of motion in the upper limbs or signs of improved functional skills in comparative trials[33].

Prospective studies without control groups investigating the effects of **selective dorsal rhizotomy** surgery for the upper limbs have yielded equivocal results[38]. Although there have been some subjective reports of improvements in arm function and activities of daily living (ADL) in small numbers of children with CP, larger investigations have demonstrated only small changes in functional performance. In more severely impaired children there has been one subjective report of improved posture in the affected upper limb as well as reduced arm pain. The only study to compare continuous intrathecal baclofen with selective dorsal rhizotomy in matched pairs showed that upper limb spasticity improved with both of these interventions, although this was not translated to improvements in the performance of functional tasks such as reaching, grasping and dressing[33].

A relatively new area of treatment for the upper limb in children with CP is **neuromuscular electrical stimulation (NMES)** of antagonist muscles. In two

case studies, positive improvements in bimanual hand function were reported. In a larger study, improved functional outcomes were demonstrated with combined use of NMES and dynamic bracing. More recently, improvements in speed of completion of functional tasks such as turning over cards, stacking draughts and placing objects in a container was demonstrated with NMES alone[33].

A new approach is the use of **Botulin Toxin A (BTX-A)** in the upper limb in children with CP. Wall et al. were the first to report use of BTX-A in the upper limbs of five children with CP. Injection to the adductor pollicus was coupled with rigid splinting and led to improvements in hand function (key grip, precision grip), precision pinch, palmar grip and the performance of bimanual tasks. These functional improvements were carried over to effective use of the hemiplegic hand at school, home and play. BTX-A have been shown to be effective in reducing muscle stiffness using resonant frequency[33].

Recent training studies in animals and in adults who have had a stroke suggest that 'forced use training' or 'constraint induced movement therapy' may be more effective than conventional upper limb treatment. This group of cognitive neurorehabilitation therapies has evolved to encompass the issues of 'learned nonuse'. The elements of constraint induced (CI) movement therapy are constraint of the unaffected limb to encourage use of the affected limb, massed practice of the affected limb, and use of intensive shaping techniques to train use of the affected limb. The details of this new treatment approach are discussed in the following paragraph[33].

In conclusion, management of the upper limb in children with CP is both resource-intensive and costly[33]. As well as the healthcare costs, a heavy time commitment is required from both the people with CP and their carers to ensure that therapy goals are achieved and maintained. Despite the investment of time, resources, personnel and funding, there remains a paucity of randomized clinical trials evaluating management options[33]. The interventions currently with the best evidence are occupational therapy and serial casting, although outcomes of these remain similar, with only small treatment effects. There is also growing evidence to support the use of BTX-A for reducing upper limb spasticity and improving function in children with CP. The effects of BTX-A are most evident during the period of maximum chemodenervation, in the first 3–4 weeks after injection. Intramuscular injection of BTX-A alone is not guaranteed to enable a child to use the hemiplegic limb and it is recommended that it be used in conjunction with physiotherapy and occupational therapy training. Upper limb surgery aims to correct deformity, improve cosmesis and improve functional outcomes. These outcomes with upper limb surgery may be of an order of magnitude greater than occupational therapy or BTX-A; however, no randomized or controlled trials have been undertaken[33].

Effective use of the upper limb impacts on educational outcomes, independence in activities of daily living and vocational options for many children with CP. Development of effective therapy regimes and evaluation of their efficacy with randomized controlled trials therefore require immediate attention[33].

Constraint Induced Movement Therapy

The biological basis

Both CI therapy and forced use are based on earlier primate unilateral deafferentation studies. Monkeys were observed not to use the deafferented limb unless the intact limb was restrained, and they practiced tasks using the involved limb for to 2 weeks. The animals were also observed using the deafferented limb if movement of the limb was encouraged via shaping, a behavioural training technique in which a desired motor behaviour is approached in small steps by successive approximations. As these monkeys regained functional use of the deafferented limb following restraint or shaping techniques, lack of use of the involved limb was considered a result of initial unsuccessful attempts to use it. Taub defined this behaviour as *"learned non-use"* and proposed that restraint of the intact limb or use of shaping techniques would overcome the learned non-use and lead to increased "real-life" function in the involved limb. Further studies with deafferented monkeys were conducted to delineate the learned non-use and forced use paradigms. Constraint of the less affected upper extremity of monkeys deafferented in uterus and at birth also shows increased use of the deafferented extremity, suggesting that learned non-use can be prevented if the constraint is applied early during development.

Influences on neural plasticity

Since CIMT has been shown to modify brain activity, especially in the affected motor and premotor cortexes, and interconnections from undamaged hemispheric structures can be engaged, there is a need to explore mechanisms through which

CIMT can induce neuroplasticity. Further questions involve the possible presence of neural substrates that impede movement initiation and whether these substrates might be susceptible to modification with CIMT.

The perspective of Taub and coworkers is that specific behavioral retraining will reduce basic impairments as more normal function is restored. Under the learned nonuse paradigm, cortical or subcortical pathology affecting motor output (as well as reduced limb cortical representation) would result in poor function, even if the potential for use existed. Frustration, fatigue, and teaching of compensatory strategies (defined as learning to use the better upper extremity in the interest of time, convenience, and demonstration of ability) inevitably would produce learned nonuse behavior and, consequently, little initiative to use the impaired hand.

The additional factors supplied by Sunderland and Tuke[39] are referred to as "compensatory learning". This form of compensation is different from the compensatory use of the better limb. Specifically, compensatory learning includes behavioural factors, such as attention, motivation, and perceived sense of effort, that contribute to a patient's reacquisition of unique motor skills through attention, motivation, effort, and control over motor outflow from preserved or accessible pathways. This new skill capability thus may facilitate restoration of the cortical representation of movement through task practice. Therefore, this model would suggest that overcoming learned non-use and improved compensatory learning both contribute to limb use after CIMT. One could deduce that factors such as attention and sense of effort are emergent behaviours that are manifested during

CIMT training. Although this behavioural linking of concepts is indeed intriguing, the model does call into question a fundamental concern about whether all non-use is indeed learned. Several factors are still unclear, for example the variations in neuronal synaptic behaviour (neuromodulation), alterations in neurotransmitter regulation, and the impact of previous behaviours (movement experience) on skill reacquisition.

Recently, neuroimaging techniques, in particular the functional Magnetic Resonance Imaging (fMRI), have been used to study the cortical reorganization following rehabilitation treatment and it opened new opportunities to verify the changes induced by different approaches. You and colleagues[40] reported in an hemiplegic child a shift in the functional MRI laterality index to the controlateral hemisphere after virtual reality treatment with bimanual activities.

In a study carried out by Sutcliffe and colleagues[41], an hemiplegic child treated with CIMT showed at fMRI bilateral sensorimotor activation before and after treatment and a shift in the laterality index from ipsilateral to controlateral hemisphere after therapy.

In CP children, cortical modifications usually occur in the very early phases both in the affected and unaffected hemispheres. In some patients, the ipsilateral corticospinal projections – normally transient – are not withdrawn, but persist and they allow the patient to control the paretic hand ipsilaterally, while in other patients the crossed projections are preserved so that they can control their hand with the affected hemisphere. In this second case, the sensorimotor loop is preserved and seems to be crucial for effective motor learning during CIMT.

Some Authors have hypothesized that patients with different types of corticospinal organization - whether the patient has an ipsilateral or a controlateral control of the affected limb - could respond differently to CIMT. The results suggest that CIMT can influence the time required to execute the task (e.g. Contra group patients are faster that Ipsi group patients)[42 43].

Clinical evidence of efficacy in adults

Forced use and Constraint-Induced Movement Therapy (CIMT) are recent therapeutic interventions for individuals with hemiplegia that involve restraint of the non-involved upper extremity and intensive practice with the involved upper extremity. Increasing evidence indicates that these interventions are effective in reducing motor deficits in the involved upper extremity and increasing functional independence in adults with hemiplegia resulting from stroke.

Two early studies in adults with hemiplegia examined the effects of forced use on the involved upper extremity. Subsequent studies involving adults following stroke utilized restraint in addition to the shaping technique as a clinical intervention to examine changes in involved upper-extremity function. Gradually the intervention was refined and eventually termed "constraint-induced movement therapy". Forced use and CI therapy involve restraint and practice using the involved upper extremity.

Although restraint is common to both techniques, the types of practice provided during the restraint period are different. By definition, placing a restraint on the non-involved upper extremity would result in practice of the involved hand and arm for any movement performed. The practice is unstructured, and the intensity

of the practice is dependent on the individual wearing the restraint. Constraint-induced therapy, however, involves a structured practice period (typically 6 hours in duration) that includes shaping and repetitive task practice.

A recent review by Cochrane examining 19 RCTs on 619 adults concluded that CIMT has moderately positive effects on disability at the end of treatment[44]. These benefits were demonstrated on other outcomes such as improvement of limb motor function and motor impairment. Patients who seem to benefit most are those with active wrist and finger extension, with limited pain or spasticity. Nonetheless, it is still to be cleared up if CIMT maintains efficacy in the longer term follow-up and if the effect observed can be entirely attributed to CIMT itself rather than on the amount and quality of repetitive exercise.Repetitive task practice involves functional tasks that are performed continuously over a specific period, and overall feedback is provided at the end of the task. Subsequent studies of CI therapy examined the efficacy of this intervention for improving involved upper extremity use with different types of restraint, different types of intervention, different outcome measures, and in people with chronic, acute, and sub-acute stroke.

Neuroimaging and transcranial magnetic stimulation studies of the brain prior to and after CI therapy have demonstrated differences in cortical organization around the infarct site after the intervention. These differences led to hypotheses regarding central nervous system (CNS) plasticity in adulthood and the role of CI therapy in cortical reorganization. Overall, the results of these adult studies

suggest that following stroke, CI therapy and forced use may be able to improve upper extremity function.

Clinical evidence of efficacy in children

Recently, forced use and constraint-induced therapy have been applied to children with hemiplegia, with moderate success. More than half the studies to date are case studies, however, and most of those remaining are small-scale studies.

The aim consists of an attempt of reversing the behavioral suppression of movement in the affected upper limb. According to a recently published Cochrane review[45], evidence on this treatment is very poor and limited, since all currently available trials reveal methodological limitations and a need for additional research to support the application of this treatment. To date, three trials have been published in the international literature [101, 46,].

The term CIMT describes an intervention that can be applied with numerous variants with regard to: method of restraint, length of restraint (per day, number of weeks), type and duration of therapy, intervention environment (home, school, or clinic), and intervention provider (therapist, parent, or teacher).

As extensively underlined in the recent Cochrane review[101], all currently available trials in children differ significantly in terms of methodological quality, sample sizes, treatment and assessment tools. The first significant variant regards the method used to restrain the non-affected limb: a broad range of techniques has been used from a glove or mitt[47], to slings[48, 49], short arm casts[50] and long arm casts[51]. Secondly, treatment programs vary in intensity and typology, ranging from 2 months of intervention 7 days per week[107], 2 hours per day[103] to twice

weekly in 30 minute-sessions for 6 weeks[106]. Moreover, there is inconsistency in the length of time the child's non-affected limb is restrained, varying from 6 hours per day, all day[106, 107], for a period of 10 days[105], to two months[103]. Furthermore, treatment programs range from no increase in routine occupational therapy or physiotherapy[106] to eight hours of therapy per day[52], although there is currently no evidence that improvement is correlated to the time spent wearing the restraint during the treatment session[103]. The treatment setting can either be the home[48, 53], pre-school[103], a day camp[54], the hospital or university clinic[49 55] or a combination of these environments. In general, all the settings described modulate differently the role and type of intervention required from parents or caregivers. Nonetheless, there is still insufficient support for the use of a specific device, technique or program[101].

Moreover, Taub & Wolf[56] suggested that the impact on CIMT outcomes is probably related more to intensity of treatment, than to the treatment principle itself.

Although limited information is currently available on this issue, children's response to treatment may also be influenced by age, diagnosis, severity of motor and sensory impairment, co-morbidities, presence and impact of mirror movements, cognitive abilities and behavior[101, 103].

The clinical significance of study results so far is unclear also due to the lack of valid and reliable tools to measure the outcome, particularly the functional use of the hemiplegic hand in bimanual tasks[101, 103].

In most cases for the comparison group no treatment or very basic treatment is provided, leading to a possible overestimation of the surplus value of CIMT (usually combined with an intensive rehabilitation program) compared to other treatment options. In our opinion, this comparison does not allow to distinguish the Constraint's effects from those of intensive rehabilitation and therefore assess the real effectiveness of Constraint Therapy.

The last published randomized controlled trial[102] raises the question of whether similar intensive practices can be elicited without the restraint and whether this might result in even better functional results. This hypothesis was recently supported by Gordon and colleagues[57], who published a randomized trial demonstrating that bimanual intensive treatment results in a better outcome if compared to no treatment.

Nonetheless, results of currently available clinical studies have poorly contributed to estimate the effectiveness of CIMT in cerebral palsy, also due to small study sample size resulting in inadequate power to detect statistical difference between the groups compared[101].

In conclusion, presently the optimal ingredients for successful CIMT practice are not known.

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CHAPTER 2. AIMS OF THE THESIS PROJECT

In the light of the new advances in the under standing the mechanisms of neural plasticity, adaptation and reorganization of brain structures after injury, the thesis project aims at exploring the possible new treatment and rehabilitation approaches for the management of hemiplegic cerebral palsy in children. In particular, the safety and efficacy of a new treatment approach, Constraint Induced Movement Therapy has been studied and compared to a bimanual intensive rehabilitation approach and to traditional rehabilitation programs.

All the researches presented hereby have been conducted with 21 rehabilitation centres belonging to a national network, i.e. the Italian Group of Cerebral Palsy (*Gruppo Italiano Paralisi Cerebrali Infantili*, G.I.P.C.I).

The Objectives of the project are:

1. to verify the efficacy and safety of Constraint Induced Movement Therapy for children aged 2-8 years affected by hemiplegic cerebral palsy on upper limb function (set as primary endpoint);
2. to verify the persistence in time of the effects of Constraint Induced Movement Therapy for children aged 2-8 years affected by hemiplegic cerebral palsy;
3. to compare the efficacy of this new rehabilitation approach with a bimanual intensive rehabilitation program and with the traditional rehabilitation programs currently provided in the Italian rehabilitation centres for children affected by hemiplegic cerebral palsy;

4. to study the influence of secondary outcome measures such as gross motor function, cognitive level, behaviour, familial stress on treatments overall effect;
5. to study consistency, reliability and agreement among assessors of the primary outcome measure (i.e. the upper limb function) utilizing both validated and non validated assessment tools;
6. to explore the opinions of professionals involved in the clinical trial on the need, role and aims of conducting clinical research in rehabilitation and in local health services.

CHAPTER 3. THESIS RESULTS AND PROJECT PLAN

During the three-year period the clinical trial has been projected, designed and implemented.

In **Chapter 4** of this thesis, the planning phase will be illustrated showing the final project.

The subsequent chapters represent the results of the thesis and are constituted by the collection of papers that have been produced during the three years of the PhD Program, utilizing the data deriving from the research project shown in Chapter 4.

In particular, in **Chapter 5**, the methodological choices and the drawing of the study design are illustrated. Discussion on the possible options of different study designs have been illustrated, also taking into account the organizational characteristics of the rehabilitation services, in particular those participating to the research project. These results have been published in the *American Journal of Physical Medicine and Rehabilitation* in 2009 (Facchin P, Rosa Rizzotto M, Turconi AC, Pagliano E, Fazzi E, Stortini M, Fedrizzi E, GIPCI Study Group. Multi-Site Trial on Efficacy of Constraint Induced Movement Therapy in Children with Hemiplegia: Study Design and Methodology. Am J Phys Med Rehabil. 2009;88(3):216-30).

In **Chapter 6**, we illustrated the process of the agreement phase among professionals involved in the research project regarding the primary outcome measures. Two scales have been considered and have been used by assessors the evaluate 44 children videotaped. The results of this analysis have been

subsequently used to estimate the level of agreement among assessors and the factor influencing their evaluation. This material has been submitted for publication in the international journal *Physical Therapy.*

In **Chapter 7**, the results of the immediate post-treatment phase will be shown and discussed, comparing the results regarding the primary endpoint and outcome measures with those of the available research studies currently published in the international literature. This paper is currently under revision in the *American Journal of Physical Medicine and Rehabilitation.*

Chapter 8 is composed by the main results of the 3-months-after-treatment follow-up assessment. The primary outcome measures will be described and analyzed in the light of secondary outcome measures. These results have been submitted to the international journal *Developmental Medicine and Child Neurology*.

Finally, in **Chapter 9**, the results of a survey are presented regarding the opinions of professionals on the advantages/disadvantages of carrying out research projects in the rehabilitation services. The survey was conducted with a self-administered questionnaire developed ad hoc, with the professionals involved in the clinical trial. This survey is currently in press in the *European Journal of Physical Therapy and Rehabilitation.*

CHAPTER 4. PLANNING A CLINICAL TRIAL: THE PROJECT

This chapter includes the final version of the research project as it was accepted and approved by the ethical committee of the participating centres.

PROGETTO DI RICERCA

CONSTRAINT THERAPY NELLA FORMA EMIPLEGICA DI
PARALISI CEREBRALE INFANTILE:
SPERIMENTAZIONE SULLA EFFICACIA E SICUREZZA DEL TRATTAMENTO

Razionale

Molti sono ancora oggi i punti critici intorno alle paralisi cerebrali, in particolar modo per quanto concerne gli aspetti eziopatogenetici, l'inquadramento clinico, la classificazione, le storie naturali, ecc. Certamente i quesiti intorno all'efficacia e alla struttura stessa dei trattamenti sono quelli di massimo interesse e per i quali le evidenze scientifiche paiono essere più povere e discusse.

Relativamente recentemente sono apparsi in letteratura dapprima segnalazioni singole[58, 59, 60], poi trial clinici[61, 62, 63, 64] su un nuovo approccio terapeutico per i pazienti emiplegici, basato sulla costrizione al movimento dell'arto superiore non

plegico. Questo trattamento trova delle basi biologiche che derivano da studi sull'animale condotti a partire dagli anni '70 e '80[65, 66], che dimostravano che in primati arti superiori deafferentati attraverso una rizotomia dorsale non venivano più utilizzati per il movimento, potendo però ottenere un loro riutilizzo obbligando l'animale ad un loro uso forzato. Da quel momento si è sviluppata la teoria dell'"apprendimento al non uso"[67, 68], chiamata in causa per spiegare il non uso dell'arto superiore plegico in pazienti adulti con stroke. Più recentemente altri ricercatori[69] hanno dimostrato sperimentalmente nell'animale come le aree lesionate dopo stroke siano passibili di un rimaneggiamento plastico in seguito a una riabilitazione precoce comprendente movimento forzato dell'arto plegico. Su queste basi è stata introdotta la terapia basata sul movimento forzato dell'arto plegico ottenuta grazie alla costrizione dell'arto normale. Gli studi sopra citati hanno le caratteristiche di prevedere trattamenti per tempi relativamente brevi (2 o 4 settimane), di dimostrare netti miglioramenti nell'uso dell'arto plegico nei pazienti trattati e di riguardare unicamente adulti in fase cronica dopo una lesione cerebrale da stroke. L'impressione diffusa di una reale efficacia del trattamento associata alla relativa facilità nel metterlo in atto e limitata durata temporale richiesta hanno fatto sì che l'utilizzo di questo trattamento si diffondesse nella pratica clinica con una velocità ed estensione non proporzionata alla solidità delle evidenze scientifiche a disposizione. Solo recentemente è partito un trial randomizzato della Società Americana di Neuroriabilitazione con una potenza sufficiente per valutare in maniera adeguata l'efficacia di questo trattamento nei pazienti adulti con stroke. Le considerazioni metodologiche alla base del disegno

sperimentale sono apparse recentemente in letteratura[70] e dimostrano come la valutazione reale dell'efficacia del trattamento richieda un arruolamento di un numero ben superiore a 200 pazienti. Oltre alla numerosità dei pazienti arruolati, altri punti critici nel compiere tali sperimentazioni riguardano la misura dell'outcome, la definizione del trattamento sperimentato, in particolare la sua durata e tipologia di costrizione dell'arto non plegico, la tipologia del trattamento a confronto, ivi comprese le modalità e le scadenze dei trattamenti di controllo.

Nonostante queste notevoli incertezze, la terapia costrittiva è stata usata anche per il trattamento di bambini emiplegici. Dapprima sono stati riportati in letteratura singoli casi clinici[71, 72], poi sono stati riprodotti due trial clinici[73, 74], tutti concordemente riportanti efficacia del trattamento. I trial riferiti hanno peraltro una consistenza numerica estremamente bassa (25 e 18 casi rispettivamente), utilizzano scale di valutazione differenti e trattamenti a confronto diversi. In particolare, il trattamento costrittivo utilizzato è differente per tipologia, tempo di utilizzo nella giornata e durata in settimane di trattamento. Anche il movimento forzato dell'arto plegico è stimolato diversamente nei due trial. Infine, il trattamento a confronto è definito come normale trattamento in un caso e nessun trattamento nell'altro. Si può quindi concludere che la forza delle evidenze scientifiche attualmente a disposizione è alquanto modesta.

Accanto a questi elementi di incertezza sussistono degli elementi di preoccupazione, che riguardano l'outcome a distanza dei bambini trattati. I trial sopra descritti fanno un controllo di risultato a 6 mesi dalla fine del trattamento, dimostrando la permanenza di un outcome più positivo nei trattati rispetto agli

altri, a dimostrazione di una stabilità dei risultati ottenuti. Queste evidenze unitamente alla relativa facilità e brevità del trattamento lo rendono certamente molto appettibile e giustificano la sua estensione nella pratica clinica, nonostante non siano disponibili a tutt'ora evidenze cliniche sufficientemente probanti[75], e siano anzi stati condotti studi sperimentali che dimostrano la sua possibile pericolosità a distanza. Molto recentemente, infatti, sono stati condotti studi sperimentali sull'animale che hanno dimostrato che la restrizione forzata dell'uso dell'arto non plegico determina un'alterazione strutturale della connessione del sistema nervoso centrale con i neuroni spinali, inducendo un rimaneggiamento delle interazioni sinaptiche che tende a rimanere stabile nel tempo[76]. Ciò indurrebbe secondo gli stessi Autori una menomazione dell'arto normale permanente nel tempo. Accanto a questi sospetti rischi del trattamento sono ipotizzabili degli interrogativi sull'impatto che esso avrebbe nell'intero sviluppo del bambino a distanza, in particolar modo per quanto attiene lo schema corporeo e la capacità di lateralizzazione con le loro complesse ricadute nel loro sviluppo globale e nelle performance a distanza, tra cui per esempio l'apprendimento e le abilità di lettura e scrittura. Infatti, se il trattamento è sufficientemente efficace da determinare un risultato persistente nel tempo è possibile che il rimaneggiamento plastico determinato dalla costrizione dell'arto sano nelle zone controlaterali cerebrali possano essere altrettanto stabili nel tempo.

In conclusione, allo stato attuale delle conoscenze non si possono assumere delle decisioni sufficientemente supportate scientificamente: la constraint-therapy può apparire un trattamento promettente, ma necessita certamente di studi clinici

controllati più consistenti degli attuali e follow-up dell'outcome a medio e lungo termine più complessivo e indagante diversi assi di sviluppo[77].

Obiettivi

Obiettivo principale del presente progetto di ricerca è verificare l'efficacia sulla performance motoria dell'arto superiore plegico (end-point principale) del trattamento di constraint therapy in confronto ad un altro trattamento di controllo senza costrizione, analogamente intensivo. L'efficacia sarà misurata al termine della terapia e a 3, 6 e 12 mesi. Essa verrà misurata sia come outcome motorio dell'arto plegico e delle performance motorie complessive del bambino, sia come outcome cognitivo e comportamentale,

Tenendo in considerazione le osservazioni riferite nel paragrafo precedente, con lo stesso protocollo sperimentale si intendono ottenere informazioni riguardo agli altri punti definiti come critici rispetto allo stato attuale delle conoscenze. Obiettivi secondari dello studio sono:

1. la valutazione di due strumenti per la misurazione dell'outcome motorio dell'arto plegico, in particolare utilizzando sia una scala di misura italiana (scala Besta[78]), caratterizzata dalla capacità di rilevare la funzione mono- e bi-manuale in condizioni di attività e di gioco spontanee, sia una frequentemente utilizzata in letteratura come la QUEST[79];
2. la valutazione delle correlazioni interne agli item componenti ciascuna scala oggetto di studio, al fine di ottenere degli elementi sintetici che approssimino la valutazione dell'intera scala e il confronto tra questi elementi sintetici,
3. la valutazione della concordanza inter-osservatore delle scale studiate,

4. la valutazione del gradimento e dell'eventuale stress familiare legati ai diversi trattamenti.

Materiali e metodi

Il progetto è coordinato dall'Unità di Epidemiologia e medicina di Comunità del Dipartimento di pediatria dell'Università di Padova (Responsabile Prof.ssa Facchin).

23 Centri italiani[1] facenti parte del Gruppo Italiano Paralisi Cerebrali hanno aderito alla proposta di studio sperimentale. Caratteristiche per l'arruolamento dei soggetti sono le seguenti:

1. età compresa tra 1 e 8 anni;
2. diagnosi di paralisi cerebrale, supportata da elementi anamnestici e clinici, oltre che da documentazione neuroradiologica;
3. forma clinica di emiplegia;
4. non essere mai stati in precedenza sottoposti a terapie costrittive.

Differente gravità clinica o presenza di patologie connesse alla paralisi cerebrale o comorbidità non costituiscono causa di esclusione dall'arruolamento, ma vengono a descrivere l'ambito di variabilità clinica da sottoporre alla terapia sperimentale.

Tutti i pazienti arruolabili, dopo che i genitori avranno ricevuto una specifica e dettagliata informazione e avranno espresso per iscritto il loro consenso informato, verranno immessi in 2 gruppi differenti di trattamento, in seguito definiti come Gruppo A – sperimentale e Gruppo B – controllo.

[1] Bergamo, Bosisio Parini (LC), Casalmaggiore, Conegliano, Pieve di Soligo, Cremona, Milano, Genova, Istituto Besta (MI), Ostuni, Padova, Pavia, Treviso, Udine, Varese, Vicenza, Lecco, Torino, Venezia, Monza, AIAS (MI), Viterbo, Bambin Gesù (Roma)

Il Gruppo A verrà sottoposto a un trattamento combinato con terapia costrittiva e terapia intensiva di supporto all'apprendimento motorio secondo gli schemi seguenti:

1. terapia costrittiva: l'arto "sano" verrà trattenuto con uno split in materiale termoplastico che coinvolga la mano – polso - avambraccio, ma che lasci libera la spalla, fissato con una fasciatura. Questa costrizione verrà posta in atto per 3 ore al giorno per 7 giorni alla settimana per 10 settimane;
2. riabilitazione intensiva: durante le settimane di costrizione il bambino sarà sottoposto a una terapia intensiva di supporto all'apprendimento motorio, costituita da: 3 accessi per settimana presso il Centro di riferimento con attività suddivisa in un'ora e mezza di terapia individuale e seguita da un'ora e mezza di attività guidata con genitore, attività legata al gioco o ad azioni comunemente svolte nella vita quotidiana come fare merenda, ecc. In particolare, verranno svolte attività di esplorazione multimodale, attività motorie grossolane, comprendente le prassie semplici che implicano il reclutamento e il direzionare l'arto e il raggiungere l'oggetto, attività di motricità fine, comprendenti la presa e manipolazione mono-manuale e la singolarizzazione delle dita, attività di equilibrio, sostegno e difesa posturo-cinetica ed infine attività di autonomia nella vita quotidiana, come cura della persona ed alimentazione. La tabella allegata riporta lo schema analitico delle attività previste;
3. trattamento a domicilio: 4 volte la settimana (i giorni in cui non c'è attività presso i Centri) il bambino dovrà svolgere a domicilio un'ora e mezza di attività

simile a quella che svolge presso i Centri e un'ora e mezza di gioco e attività della vita quotidiana secondo le prassi e gli schemi indicati al punto 2.

Il Gruppo B verrà sottoposto solo al trattamento di riabilitazione intensiva secondo quanto indicato ai punti 2 e 3 sopra descritti, aggiungendo alle attività mono-manuali quelle analogamente condotte bi-manualmente, con particolare riguardo alle prassie semplici e complesse, alle attività di esplorazione e manipolazione.

L'assegnazione ai trattamenti verrà effettuata in base al Centro di reclutamento. Poiché risulta complesso e concretamente poco fattibile l'assegnamento casuale semplice del trattamento ad ogni soggetto, essendo frequentemente i bambini emiplegici coinvolti in attività riabilitative di gruppo all'interno dello stesso Centro, si è preferito utilizzare i Centri come cluster intermedi e i soggetti come unità statistica finale. Per tale motivo, per ogni Centro verrà predefinito il trattamento da effettuare e all'interno di tale Centro tutti i soggetti arruolati attueranno lo stesso tipo di trattamento. L'eventuale distorsione sul risultato data dall'effetto Centro verrà valutata e corretta in sede di analisi dei dati. La randomizzazione dei trattamenti per Centro terrà conto del numero dei casi ipoteticamente reclutabili da ognuno di essi.

Il trattamento verrà sospeso solo qualora il bambino dimostri di non tollerare in maniera assoluta la costrizione proposta e/o i genitori non seguano con sufficiente compliance i trattamenti domiciliari e/o presso i Centri.

Per ogni soggetto reclutato per il trattamento per il Gruppo A o B prima di iniziare tali trattamenti verranno eseguite le seguenti valutazioni:

raccolta di dati anamnestici e clinici indicanti, oltre che i principali dati anagrafici, il livello di gravità di compromissione motoria, la presenza di disabilità aggiuntive e/o patologie completanti il quadro di comorbidità complessivo;

esame obiettivo e neurologico completo, comprendente anche la valutazione della stereognosi e dello schema corporeo, attraverso il Test della Figura Umana a partire dai 4 anni;

valutazione delle abilità motorie globali con la *Gross Motor Function Measure* (GMFM)[80];

scala di sviluppo o valutazione di livello con la scala *Griffith*[81] fino ai 5 anni e successivamente con le scale *Wechsler* (*Wippsi*[82] fino a 7 anni e *Wisch-R*[83] successivamente);

valutazione della funzionalità dell'arto superiore attraverso la scala *Quality of Upper Estremity Skills Test* (QUEST[79]) e la scala Besta[78];

scala di stress familiare (*Parenting Stress Index*[84]) e scala delle autonomie redatta dall'Istituto Besta e compilata da parte dei genitori.

Successivamente alla fine del trattamento e a 3, 6, 12 mesi dal suo termine verranno svolte le seguenti valutazioni:

1. esame obiettivo e neurologico completo, comprendente anche la valutazione della sterognosi e dello schema corporeo, attraverso il Test della Figura Umana a partire dai 4 anni;
2. valutazione delle abilità motorie globali con la *Gross Motor Function Measure* (GMFM)[80];

3. a 12 mesi dalla fine del trattamento, scala di sviluppo o valutazione di livello con la scala *Griffith* fino ai 5 anni e successivamente con le scale *Wechsler*[83], *Wippsi*[82] fino a 7 anni e *Wisch-R* successivamente;
4. valutazione della funzionalità dell'arto superiore attraverso la scala *Quality of Upper Estremity Skills Test* (QUEST)[79] e la scala Besta[78];
5. scala delle autonomie redatta dall'Istituto Besta e compilata da parte dei genitori;
6. scala di valutazione del comportamento del bambino (*Child Behavior Checklist*[85]).

Alla fine del trattamento viene inoltre valutato il gradimento alla terapia attraverso un questionario appositamente apprestato e la scala di stress familiare.

In tutte le scadenze di valutazione (all'inizio e alla fine del trattamento, e a 3, 6, 12 mesi) verranno effettuate videoregistrazioni secondo un protocollo standard (protocollo GIPCI) riguardante l'applicazione delle scale QUEST e Besta per l'arto superiore.

Durante tutto il periodo di trattamento ogni centro organizzerà delle riunioni settimanali per monitorare le attività domiciliari in corso, rispondere a domande e perplessità o difficoltà esposte dai genitori e supportare le attività che essi dovranno svolgere con il bambino. A tale riguardo verrà anche predisposta una tabella pratica e concreta che elencherà possibili proposte di attività riabilitative da svolgere a domicilio per facilitare il lavoro dei genitori.

Fasi e tempi della ricerca

La ricerca si articolerà in 4 fasi, 2 preliminari precedenti l'attuazione della vera e propria sperimentazione clinica, la terza di sperimentazione e la quarta di follow-up e valutazione dell'outcome.

La prima fase preliminare consiste nell'inventario dei casi di paralisi cerebrale forma emiplegica già seguiti dai Centri coinvolti nello studio e teoricamente disponibili per l'arruolamento. Per ciascuno dei casi verranno raccolti una serie di informazioni quali dati anagrafici, l'anamnesi, la gravità motoria e patologie e disabilità associate. Obiettivo di questa fase è la definizione della variabilità clinica presumibilmente interna alla casistica reclutabile e lo studio della distribuzione del numero e della tipologia dei casi per Centro, preliminari alla randomizzazione dei trattamenti.

La seconda fase preliminare comprende la formazione degli operatori dei Centri agli strumenti di valutazione ed ai trattamenti riabilitativi intensivi oltre che allo studio della concordanza intra-operatori per quanto attiene le due scale di misurazione della funzione degli arti superiori. La formazione degli operatori avverrà attraverso due metodologie differenziate. La prima riguarda la formazione all'uso delle scale QUEST e Besta e consisterà nella attuazione di più riunioni seminariali nelle quali verranno presentate ed illustrate le due scale ed il loro uso, anche attraverso la visione ed il commento congiunto di casi videoregistrati. Successivamente le videoregistrazioni di 3 nuovi casi per ciascuna scala verranno inviate ad ogni centro assieme ai formulari già compilati per ciascun caso. Ciò permetterà ad ogni operatore di sperimentare le due scale e di autovalutarsi. Successivamente, la videoregistrazione di un quarto caso per ogni scala sarà

ugualmente inviata e permetterà una valutazione autonoma di ogni operatore coinvolto. Questa valutazione sarà confrontata esternamente rispetto ad un gold standard inizialmente non noto all'operatore.

Per quanto attiene invece la formazione alle attività di riabilitazione, verrà predisposto un gruppo di lavoro di terapisti provenienti dai Centri coinvolti che avrà il compito di standardizzare proposte di attività, procedure, materiali e contesto, oltre che di stendere lo schema a tabella da consegnare ai genitori.

Infine, si procederà allo studio della concordanza inter-operatore. Ogni Centro effettuerà 2 videoregistrazioni di 2 differenti casi predisposti per la valutazione delle scale QUEST e Besta e invierà tali videoregistrazioni a tutti gli altri centri senza alcuno schema di valutazione allegato.

Le valutazione di scala compilate da tutti i centri verranno elaborate analizzando sia la concordanza totale, sia le concordanze tenuto conto del fattore Centro e del fattore bambino.

La terza fase consisterà nella sperimentazione vera e propria dei trattamenti. Ciascun caso verrà arruolato nel trattamento del gruppo A o del gruppo B in base a quanto indicato dal centro coordinatore. Il trattamento verrà condotto secondo gli schemi descritti nella sezione di Materiali e Metodi.

Il reclutamento dei casi avverrà tra quelli inventariati nella prima fase preliminare e che avranno espresso adesione dopo consenso informato e continuerà per tutto il periodo dell'attuazione dei trattamenti sperimentali, comunque non si concluderà prima di aver raggiunto il numero di casi predefinito e descritto nella sezione

Analisi Statistica, stimato in circa 1 anno. Attualmente la casistica reclutabile è pari a 118 casi.

La quarta fase consisterà nella valutazione dell'efficacia e in parte sarà temporalmente sovrapposta alla fase di sperimentazione. Inizierà prima dell'attuazione vera e propria dei trattamenti con la valutazione delle condizioni pre-trattamento e continuerà con i tempi e i modi indicati nella sezione Materiali e Metodi fino a che saranno trascorsi i 12 mesi dalla conclusione del trattamento dell'ultimo caso arruolato.

Analisi Statistica

Analisi della concordanza inter-osservatore e valutazione delle scale QUEST e Besta

Poiché le scale di misura prese in considerazione conducono a punteggi su una scala continua, verrà utilizzato, ai fini della concordanza, l'usuale coefficiente campionario di correlazione intraclasse[86], oltre che modelli a componenti della varianza[87], che stimano il coefficiente di correlazione intraclasse come complemento a 1 della quota di varianza spiegata.

Recentemente sono stati sviluppati modelli, basati sul metodo delle equazioni di stima generalizzate[88], che consentono di valutare la concordanza in presenza di covariate dei casi e/o dei valutatori[89, 90].

A seguito di analisi preliminari dei dati, si farà perciò ricorso anche a questi ultimi metodi.

Con criteri del tutto analoghi si procederà all'analisi dell'esistenza di un effetto "Centro", grazie alla disponibilità di due misurazioni, per caso, in ogni Centro. In

tal caso le misure che potranno essere prese in considerazione saranno i valori medi per Centro (qualora l'effetto valutatore non sia significativo).

Le procedure sopra descritte saranno attivate sia con riferimento alla scala "Besta", sia con riferimento alla scala QUEST.

Una volta definita la variabilità di valutazione tra gli osservatori, verranno anche studiati i rapporti tra i vari item all'interno di ciascuna scala e tra le due scale QUEST e Besta.

Trattandosi di punteggi, l'analisi statistica è effettuata mediante il coefficiente di correlazione di Pearson, calcolato sui punteggi complessivi, e, quando possibile, per aree tematiche. Fra le due scale considerate, ciò è ad esempio possibile per la parte relativa alla prensione.

Effettuate quindi dapprima la valutazione della variabilità di misura delle scale e poi la coerenza di giudizio tra le due scale e la inter-dipendenza interna a ciascuna scala tra i vari item analizzati, si passerà successivamente alla valutazione esterna delle scale di misura tramite un osservatore indipendente che andrà ad analizzare le videoregistrazioni effettuate in un campione di pazienti selezionati per ogni Centro. Questa valutazione esterna, ritenuta gold standard, consentirà di avere una stima dell'eventuale distorsione nella valutazione di efficacia dei trattamenti prodotta da ciascun Centro e all'interno dei Centri da ciascun osservatore.

Stima del numero di casi necessari e confronto dell'efficacia dei trattamenti

Siano:

$$\pi_i = \frac{\text{(punteggio ottenuto al termine della terapia intensiva) - (punteggio prima della terapia)}}{\text{(punteggio prima della terapia)}}$$

$$\pi_{cimt} = \frac{\text{(punteggio ottenuto al termine della CIMT) - (punteggio prima della terapia)}}{\text{(punteggio prima della terapia)}}$$

Al fine di determinare il numero di casi necessari per il disegno sperimentale, è necessario definire[91]:

- Una stima di Π_i
- la soglia minima richiesta di differenza significativa fra le probabilità di miglioramento relative ai due trattamenti, ovvero $\Delta = \Pi_{cimt} - \Pi_i$.

  Ad esempio, Δ=0,3 significa che si richiede che il disegno sperimentale evidenzi come significative percentuali di miglioramento della CIMT rispetto alla terapia intensiva di almeno il 30%. Ovviamente, maggiore si richiede sia Δ, e minore sarà la numerosità necessaria a evidenziarla come significativa.
- la potenza del test (1-β), ovvero la probabilità di affermare correttamente che la differenza Δ esiste in misura non inferiore alla soglia considerata. Generalmente la potenza del test viene posta pari all'80-90%
- l'errore di primo tipo (α), ovvero la probabilità di dichiarare erroneamente che la differenza è significativa, quando invece non lo è. Viene usualmente posto pari al 5%.

Sulla base degli esiti degli incontri svolti con i referenti di tutti i Centri, le scelte effettuate sono:

$\Pi_i = 0{,}15$

$\Delta = 0{,}30$

$1-\beta = 0{,}90$

$\alpha = 0{,}05$

da cui si ricava una numerosità per gruppo pari a 54 casi.

La numerosità di base necessaria è dunque pari a 108 casi. Dovendo prevedere una quota di drop-out fisiologico, stimata nel 10%, la numerosità complessiva si assesta su circa 118 casi.

Il confronto fra l'efficacia del trattamento intensivo e della CIMT sarà in prima battuta effettuato mediante l'usuale test T per campioni indipendenti, considerando come parametro da porre a confronto la differenza fra il punteggio ottenuto con la scala di misura dopo la terapia e prima della terapia. L'ipotesi da testare è quindi:

$\Delta i = \Delta cimt$ contro $\Delta i < \Delta cimt$

dove:

Δi = (punteggio ottenuto al termine della terapia intensiva) – (punteggio prima della terapia)

$\Delta cimt$ = (punteggio ottenuto al termine della CIMT) – (punteggio prima della terapia)

Questo metodo potrebbe rivelarsi non sufficiente, per due motivi:

1. diversi fattori, oltre al trattamento, potrebbero influenzare l'esito (ad esempio l'età del caso)
2. i dati sono in realtà correlati entro cluster, identificati dal Centro.

Per poter tenete in considerazione questi due fattori sarà necessario procedere con metodi statistici appropriati. Il riferimento è ai modelli di regressione per dati correlati entro cluster, le cui procedure di stima si basano sulle già citate equazioni di stima generalizzate.

Grazie a tale approccio sarà possibile stimare l'effetto dei due trattamenti contestualmente alla presenza di altri fattori, e valutare anche la loro significatività. Inoltre, le stime sono più accurate: il tenere in considerazione la correlazione entro cluster porta infatti a stime differenti delle varianze dei parametri e, di conseguenza, degli intervalli di confidenza e della significatività.

Risorse umane ed economiche

Tutti i Centri partecipanti offrono il loro contributo, mettendo a disposizione del personale esperto per l'espletamento di tutte le fasi del progetto.

È previsto un impegno economico aggiuntivo, assicurato dalla Fondazione Mariani, per l'attività di coordinamento delle varie fasi del progetto, di raccolta e analisi dei dati, di studio della concordanza delle scale e valutazione degli effetti dei trattamenti. Questa attività è stata assegnata all'Osservatorio della Patologia in Età Pediatrica della Regione Veneto, coordinato dalla prof.ssa Paola Facchin.

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CHAPTER 5. A CLINICAL TRIAL IN THE FIELD OF REHABILITATION: METHODOLOGICAL CONSIDERATIONS

This paper was published in the *American Journal of Physical Medicine and Rehabilitation* and outlines the main methodological critical aspecs encountered design the clinical trial on CIMT.

Title

Multi-Site Trial on Efficacy of Constraint Induced Movement Therapy in Children with Hemiplegia: Study Design and Methodology

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Abstract

In the last decades, several treatment approaches have been used to improve upper limb function in hemiplegic CP. Only recently has Constraint Induced Movement Therapy (CIMT) emerged as a treatment approach for children with hemiplegic CP with the aim of reversing the behavioral suppression of movement in the affected upper limb.

To date, evidence on this treatment has been very poor and limited, since all currently available trials reveal methodological limitations and a need for additional research to support the application of this treatment technique. This paper presents the methodological choices, design and main characteristics of an ongoing controlled clinical trial on the effectiveness and safety of CIMT combined with an intensive rehabilitation program, and compared with 2 comparison groups: one treated with an intensive rehabilitation program and the other with standard treatment. 21 rehabilitation sites are currently recruiting patients with hemiplegic cerebral palsy, aged between 2 and 8 years, who have never undergone constraint therapy. Primary outcome measures include 2 major domains: UE motor ability (QUEST) and hand function assessment evaluating both grip function and spontaneous use of the affected side (Besta Scale). Secondary outcome measures concern overall function, behavior, compliance and satisfaction with treatment program of both child and family. Patients' follow-up is of 12 months after treatment.

Key Words: Hemiplegia, Cerebral Palsy, Constraint Induced Movement Therapy, Outcomes

Background

Hemiplegic cerebral palsy (CP) is the most common syndrome in children born at term, and it is second in frequency only to diplegia in preterm infants. In Italy, the incidence rate 0.3-0.5/1000 newborns[92, 93].

Although almost all hemiplegic children achieve independent walking, impaired arm and hand function are the main problems in about half of affected children[94], particularly with regard to bimanual fine motor activity and reduced motor ability with increasing age. These factors contribute to disability in activities of daily living (ADL) and everyday functional activities[95].

During the past decade, considerable effort has been devoted to establishing novel approaches to overcome children's impairments and compromised ability to use their upper extremities to control and manipulate their environment[96].

Several Authors suggested that hemiplegic children learn to disregard the affected arm and tend to use their non-affected arm as the dominant hand, even when functional loss is mild[97]. The term *developmental disregard* was introduced to describe all hemiplegic children disregarding and learning not to use the affected limb during their developmental motor function. This suggestion was confirmed by a follow-up study of functional outcome carried out on hemiplegic children, whose results showed that hand function was better on request rather than during spontaneous use in bilateral manipulation[95].

Several treatment approaches have been used to improve upper limb function in hemiplegic CP. A review conducted by Boyd[96] listed different treatment

modalities such as splinting, passive stretching, spasticity medication with Baclofen and with Botulin Toxin A, and surgery.

More recently, a novel approach – Constraint Induced Movement Therapy (CIMT) - based on the behavioral research conducted with non-human primates by Taub[98] in the 1980s - has been proposed. This therapy involves restraint of the non-affected arm to encourage performance of therapeutic tasks with the affected arm, which children normally tend to disregard. CIMT has been used in several studies with adult populations presenting with different acquired conditions such as stroke, traumatic brain injury, and focal hand dystonia[99]. The results of the EXCITE trial, recently published show significantly larger improvements in the group of patient undergoing CIMT both immediately after treatment and after 12 months. The improvement regards quality and speed of paretic limb movement and amount of paretic arm use in ADL[100].

Evidence of Constraint Therapy in children

Only recently has CIMT emerged as a treatment for children with hemiplegic CP with the aim of reversing the behavioral suppression of movement in the affected upper limb. According to a recently published Cochrane review[101], evidence on this treatment is very poor and limited, since all currently available trials reveal methodological limitations and a need for additional research to support the application of this treatment. To date, three trials have been published in the international literature whose main characteristics are summarized in Table 5.1[101, 102].

The term CIMT describes an intervention that can be applied with numerous variants with regard to: method of restraint, length of restraint (per day, number of weeks), type and duration of therapy, intervention environment (home, school, or clinic), and intervention provider (therapist, parent, or teacher).

As extensively underlined in the recent Cochrane review[101], all currently available trials differ significantly in terms of methodological quality, sample sizes, treatment and assessment tools. The first significant variant regards the method used to restrain the non-affected limb: a broad range of techniques has been used from a glove or mitt[103], to slings[104, 105], short arm casts[106] and long arm casts[107]. Secondly, treatment programs vary in intensity and typology, ranging from 2 months of intervention 7 days per week[107], 2 hours per day[103] to twice weekly in 30 minute-sessions for 6 weeks[106]. Moreover, there is inconsistency in the length of time the child's non-affected limb is restrained, varying from 6 hours per day, all day[106, 107], for a period of 10 days[105], to two months[103]. Furthermore, treatment programs range from no increase in routine occupational therapy or physiotherapy[106] to eight hours of therapy per day[108], although there is currently no evidence that improvement is correlated to the time spent wearing the restraint during the treatment session[103]. The treatment setting can either be the home[109, 110], pre-school[103], a day camp[111], the hospital or university clinic[112, 113] or a combination of these environments. In general, all the settings described modulate differently the role and type of intervention required from parents or caregivers. Nonetheless, there is still insufficient support for the use of a specific device, technique or program[101].

To date, treatment principles have been based on two different approaches, which vary according to the professionals involved[101]: on one hand, psychologists utilize the operant movement conditioning[105, 107], and on the other, occupational therapists and physiotherapists adopt a motor learning and motor control approach, practicing repeatedly highly motivating tasks[103]. This difference could be another variant of CIMT, although Taub & Wolf[114] suggested that the impact on CIMT outcomes is probably related more to intensity of treatment, than to the treatment principle itself.

Although limited information is currently available on this issue, children's response to treatment may also be influenced by age, diagnosis, severity of motor and sensory impairment, co-morbidities, presence and impact of mirror movements, cognitive abilities and behavior[101, 103].

The clinical significance of study results so far is unclear also due to the lack of valid and reliable tools to measure the outcome, particularly the functional use of the hemiplegic hand in bimanual tasks[101, 103].

Another crucial point to be taken into consideration regards the treatment provided to comparison groups. In most cases no treatment or very basic treatment is provided, leading to a possible overestimation of the surplus value of CIMT (usually combined with an intensive rehabilitation program) compared to other treatment options. In our opinion, this comparison does not allow to distinguish the Constraint's effects from those of intensive rehabilitation and therefore assess the real effectiveness of Constraint Therapy.

The last published randomized controlled trial[102] raises the question of whether similar intensive practices can be elicited without the restraint and whether this might result in even better functional results. This hypothesis was recently supported by Gordon and colleagues[115], who published a randomized trial demonstrating that bimanual intensive treatment results in a better outcome if compared to no treatment.

Nonetheless, results of currently available clinical studies have poorly contributed to estimate the effectiveness of CIMT in cerebral palsy, also due to small study sample size resulting in inadequate power to detect statistical difference between the groups compared[101].

Aims

These considerations have led us to a key question: is it possible to overcome these methodological problems and design a trial that can give strong evidence on CIMT effect? The aim of this paper is to present the methodological choices, design and main characteristics of a controlled clinical trial that is currently ongoing and whose recruitment is still open (although some patients have already completed the whole follow-up phase). The trial aims to study the effectiveness and safety of CIMT (defined as restraint combined with an intensive rehabilitation program) compared with 2 comparison groups: one treated with an intensive rehabilitation program and one with traditional treatment.

Experimental design

The study has been designed as a multicenter, prospective, controlled clinical trial on the efficacy of Constraint Induced Movement Therapy (CIMT) (consisting of

the bandage of the unaffected arm with a specific device combined with a intensive rehabilitation program (IRP) for the affected arm) (Group 1). At the end of the recruitment process, the results of this study group will be compared with those of two comparison groups, one undergoing bimanual IRP (Group 2), and the other receiving traditional rehabilitation program (Group 3). Recruitment of Group 1, Group 2 and Group 3 is currently ongoing and treatment programs are carried out in the same intervention period.

CIMT comprehends 2 major therapeutic elements, the restraint of the non-affected limb and the massive practice of movements of the affected limb. The comparisons between group 1 vs 2 may highlight the effect of restraint and the comparisons between group 1 vs 3 and group 2 vs 3 may show the effect of massive practice of movements.

The traditional rehabilitation treatment (defined in the next paragraph) has been considered as the baseline treatment, allowing us to estimate if there is a surplus value in providing intensive treatment and which children would benefit the most.

Due to possible organizational difficulties within the rehabilitation services and the subsequent impossibility to randomize patients by treatment group in every single clinical center, the Authors have chosen a cluster randomization design[116, 117], i.e. typology of trials in which groups or clusters rather than individuals are randomly allocated to different treatments. Cluster randomized trials are increasingly being utilized in the evaluation of health care interventions and the methodology for analyzing cluster randomization trials has been rapidly developing in the last decade[118, 119].

A crucial measure is the intra-cluster correlation coefficient. This coefficient measures the degree of similarity among responses to treatment *within a cluster*[120]. If we consider two hypothetical extreme situations, we can trace two different scenarios:

1. the variability in treatment response is null within the clusters and maximum among the clusters: in this case clusters could be considered as a single individual for the trial;
2. the variability in treatment response within the clusters and among the clusters are similar: in this case, the individuals are randomly distributed in the clusters and the statistical power randomizing the clusters is similar to the one obtained by randomizing individuals.

The measure identifying this "cluster-effect" is *IF*, the ratio between intra-cluster variability and inter-cluster variability of treatment effect outcome measure[120].

Since it is very difficult to obtain accurate estimation of intra-cluster correlation, we have utilized a range of hypothesis to estimate intra-cluster coefficient, in order estimate the sample size and the power of the trial[121].

To verify if the individuals were randomly distributed within the clusters, we utilized the IF of the main covariates such as age, severity of impairment, IQ and parents' education level. No significant differences among variabilities inter and intra-clusters were observed in children enrolled in the trial.

Sample Size and Power

Following the second hypothesis previously described, with a delta value set at 30%, ($1-\beta = 0,80$, $\alpha = 0,05$, $\pi i = 0,15$), we estimated a sample to be recruited of 111 participants, considering a 10% drop out.

If at the end of the trial the intra-cluster correlation would be much higher than expected, the trial will be still valid but with a lower power and an α error tending to a constant value[121].

37 cases have been enrolled in 7 centers for CIMT, 37 cases in 7 centers for IRP and 37 case in 7 centres for traditional treatment.

Statistical analysis

The effect of intervention will be assessed using a Generalized Estimation Equation, extension of logistic regression[120].

Inclusion and Exclusion Criteria

Patient inclusion criteria are: age range between 2 and 8 years, diagnosis of hemiplegic cerebral palsy (anamnestic, clinical and neuroimaging documentation to be collected) according to Hagberg's classification[122]. To avoid the confounding effects of other intervention studies, potential participants have been or will be excluded from the study if they have previously undergone restraint therapy or have received or will receive injections of anti-spasticity drugs into UE musculature (e.g., botox). Differing clinical severity and/or comorbidity with other diseases (e.g. epilepsy, mental retardation…) do not constitute an exclusion criteria, but have been used to describe clinical variability.

Participants' motor criteria are divided into 3 groups: 1) mild, 2) moderate, and 3) severe motor impairment, based on and modified from criteria set by Beckung et al[123] and Eliasson et al[124]. Operational definitions of degrees of severity were set as shown in Table 5.2.

Before starting the research program, all potentially eligible patients and their families have been or will be fully informed about the trial and treatments and, if assenting, have been or will be asked to express a formal written consent.

Participating centers

21 clinical sites located in 8 Italian regions take part in this research project. At least 2 clinicians per center are involved in the research project, a physician (neuro-pediatrician or physiatrist) and a physiotherapist. All the centers involved in the research study belong to the Italian Group of Cerebral Palsy (G.I.P.C.I.), which was founded in 1994 and is composed of physiotherapists, physicians and psychologists. The group has worked for 15 years in defining the decision-making process and clinical management of children with cerebral palsy.

When the recruitment process will be completed, 2 supervisors of outcome measures will examine videotapes of all evaluations of patients from each treatment group and they will be blinded to treatment allocation.

Before commencing the trial, a Steering Committee composed of the principal investigator of each clinical site and the Data Management Center made decisions relating to the study conduct. The DMC is located at the Epidemiology and Community Medicine Unit of the Pediatrics Department of Padua University. The

DMC established a number of role-specific electronic mailing lists to facilitate communications among the various sites.

The present project was examined by an ethics committee that approved the study recommending to pay particular attention and care to the information given to families and children about the research program and treatment options, including the burden of the treatment program, the involvement of families and the safety of treatment.

Baseline information

Baseline information on each recruited patient is planned to be collected before commencing the trial: anamnestic and main clinical data, personal information, level of UE motor impairment severity, the presence of other diseases and/or disabilities (see Annex 5.1). The data collected from patients recruited so far are summarized in Table 5.3.

Treatment groups: main characteristics

Group 1. Constraint Induced Movement Therapy (CIMT) (glove plus Intensive Rehabilitation Program). Children are to wear 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, and, thereby, prevents the ability to grasp (Figure 5.1).

The thumb is kept in a fixed position tight against the index finger. The children can, however, use the hand for support or for breaking a fall. The intervention is planned to last 10 weeks, 7 days a week. Children are expected to wear the glove

for 3 hours a day consecutively. During this interval the child is expected to perform the therapeutic training under the supervision or the therapist and/or parents and without removing the glove.

During the treatment period, children undergo an intensive rehabilitation program based on unimanual activities. They are treated for hand impairment according to a motor learning approach during play sessions and activity of daily living (ADL). Sessions are held 3 times weekly at the Rehabilitation Center: an individual therapist encourages the child to solve tasks requiring the unilateral use of the paretic hand. Task goals refer to 4 main domains: (1) perceptual motor activities; (2) activities of reaching, grasping, holding and manipulating; (3) postural and balance activities; (4) self-care and daily living activities (Table 5.4).

Sessions are planned to last 3 hours: during the first part of the session (1 hour and ½) the therapist interacts with the child proposing unimanual activities of an appropriate level of difficulty, in relation to age and motivation. In the second part of the session (1 hour and ½) parents, who cooperate during all the 3 hours sessions, are instructed to interact with their own children by proposing them unilateral tasks in play and daily living activities. Parents are trained to carry out similar 3-hour sessions at home on the remaining 4 days, as showed at the Rehabilitation Center (specific unilateral tasks during play and daily living activities).

Group 2. Bimanual Intensive Rehabilitation Program (IRP). Children are treated for hand impairment according to the same approach described above, and with the same schedule (3 hours a day, 3 times a week, half sessions with the therapist

and half sessions with the parents) at the Rehabilitation Center: the only differences are that children do not wear the glove and are encouraged to solve tasks requiring the use of both hands.

Parents are trained to carry out similar 3-hour sessions at home on the remaining 4 days, as showed at the Rehabilitation Center (specific bimanual tasks during play and daily living activities).

Task goals refer to the same 4 main developmental domains, but they imply a bimanual use in play and daily living activities (Table 5.5).

Group 3. Traditional treatment. This group includes children affected by cerebral palsy currently treated in territorial Rehabilitation Services. They usually undergo 1-hour standard rehabilitation sessions once or twice a week and the session frequency differs in relation to child's age. Infants receive physiotherapy, mainly a neurodevelopmental treatment twice a week, while preschool and school-age children attend occupational therapy once a week (40-60 min).

Primary Outcome Measurements

During the five evaluation sessions (one before and one after the treatment program, and three follow-up evaluations at 3, 6, 12 months after treatment), primary outcomes are assessed in 2 major domains: UE motor ability (QUEST[125]) and hand function assessment evaluating both grip function and the spontaneous use of the affected side (Besta Scale[126]).

QUEST (Quality of Upper Extremity Skills Test) is an international validated scale exploring four main domains: dissociated movement, grasp, protective extension and weight bearing. The dissociated movement domain includes items

that counter typical patterns of spastic synergy, representing each joint of the upper limb. Grasp items are based on normal hand grasps as described in developmental literature, arranged in a hierarchical and developmental framework. Weight bearing and protective extension are based on normal developmental sequence and are scored hierarchically based on the degree of abnormality as represented by joint positions. All items are scored for both arms using a dichotomous scale and percentage scores are calculated[127].

The Besta Scale is an instrument that was developed in 1985 at the Developmental Neurology Division of the Istituto Neurologico (Neurological Institute) *"Carlo Besta"* in Milan, to assess quality of grip (hand function on request) and spontaneous hand use (bilateral manipulation), and their changes in relation to age and degree of impairment. The first version of this assessment protocol was described in 1986, in a study in which clinical characteristics were analyzed in relation to aetiological factors and computed tomography findings in 30 children with congenital hemiplegia[128]. After modification, the instrument was used in a prospective study to evaluate changes in hand impairment and bilateral manipulation skills over time[129]. The interrater reliability was assessed with a pilot study conducted on 15 children with hemiplegia under 7 years of age and 15 children with hemiplegia over 7 years of age. Interobserver agreement of grip scores was excellent[95].

In the scale, grip assessment is performed in a standardized setting, asking the child to pick up different sized cubes on request. The quality of grip is videotaped and scored in a hierarchical way (from 0 to 3). Spontaneous use is assessed during

structured activities requiring both hands and being standardized according to age. The scoring system for the quality of manipulation is based on variability and stereotypy of movement pattern[130]: score 0, no use of impaired limb; score 1, use of impaired limb in a stereotyped pattern (wrist support) for holding; score 2, cooperation of the impaired hand in manipulation by holding with a restricted number of stereotyped patterns; score 3, cooperation of the impaired hand with holding and manipulation, using a varied repertoire of patterns[126].

During the evaluation sessions, both tests are administered, video-recorded, scored on subsequent viewing and videotapes are to be posted to the DMC for quality evaluation control.

Secondary Outcome Measurements

Besides the general assessment of patients (anamnesis, objective and neurologic exams), evaluation sessions include additional tests assessing: a) the patients' cognitive level with the Wechsler/ Griffiths scales (according to patient age), b) general motor development with the Gross Motor Function Measure, c) the level of familial stress with the Parenting Stress Index[131], d) parents evaluation of the child's autonomy in daily living activities using the Parents Besta Scale[132], e) the Child Behavior Checklist[133], f) and treatment satisfaction and compliance perceived by parents using an ad hoc scale.

The purpose of including these other instruments in the evaluation sessions is to assess the child's overall development and if it is influenced by the treatment assigned.

The timing of secondary outcome measures evaluation is described in figure 5.2 and table 5.6.

Safety measures

To evaluate the safety of the interventions carried out, the following measures have been utilized:

- since the use of a restraint in the non-affected limb could cause a motor impairment (as some studies on animal models have assumed[134]) and compromise the non-affected-side ability, the function of the non affected limb is monitored through the QUEST and Besta Scales;
- another parameter is the behavioural change in the child, that is assessed using the Child Behaviour Checklist. This scale can detect sudden modifications of child behaviour, mood, or response to stress during and after the restraint of the non affected limb. The Child Behavior Checklist[133] (CBCL) was designed to address the problem of defining child behavior problems empirically. It is based on a careful review of the literature and carefully conducted empirical studies. It is designed to assess in a standardized format the behavioral problems and social competencies of children as reported by parents;
- performing intensive treatment lasting 3 hours a day per 10 weeks can load on family life and increase the level of family stress. This evidence is evaluated through Parenting Stress Index[131].

Baseline, Post-Immediate, and Follow-up Evaluations

The timeline for baseline, post-treatment/control period, and follow-up evaluations is outlined in figure 2 and table 6. Only primary outcomes are evaluated at each evaluation visit. Evaluation visits are planned at baseline, end of treatment, and after 3, 6 and 12. The study plan provides that the follow-up ends at month 14.5 from the baseline date.

Training, standardization and agreement

Before starting the controlled trial, a specific training program was provided to familiarize professionals with testing and training procedures in order to develop a homogeneous administration and videotaping of the QUEST and Besta Scale tests, as well as the parents of recruited children.

Professionals - Principal Investigator

First of all, the principal investigators of the participating centers were equipped with a training package including: a presentation module illustrating the sections of each scale (QUEST and Besta Scale) and describing the scoring procedures with practical video-recorded examples, which included the videos of 3 children with different levels of hemiplegia, 2 of which were scored and the third was blind (with the scoring enclosed in a sealed envelope).

After the self-training phase, a meeting with scale experts was organized for the principal investigators in order to discuss issues related to administration. recording procedure and scoring process.

The project included an assessors' agreement phase. The main goal of this phase was represented not only by the need of providing a standardized training for all

assessors, but also to be able to measure the variability of primary outcome measures in order to use this coefficient as an estimation of the variability of the "instrument of measure" of primary end-point. Each clinical centre provided the video-recording of the administration of the 2 tests (QUEST and Besta Scale) to 2 children of their hemiplegic population, in all 42 cases (2 per each centre) who undergone the administration and video-recording of 2 test: in all 84 videos, 42 Besta scale and 42 QUEST scale). The coordinating centre sent the 84 videos to all the 21 participating centre and all videos were scored by the principal investigator (a total amount of 84 assessments, 2 per all 42 children video-recorded). All evaluations were collected and analysed by the coordinating centre in order to evaluate the agreement among the investigators involved, considering separately in the analysis each item scored, partial scoring values of scales sections and total scoring values of Besta and QUEST scales.

2 training core members of staff evaluated the videotapes to assess the quality of procedures employed by each clinical center and exclude participants that were not sufficiently trained, and they also rated the videotapes.

Periodical meetings were held during the second project year among all the representatives of the participating centers. These meetings included participant chart reviews, focus groups with research participants, and key informative interviews with Training Core staff. Information gathered during these meetings, along with data collected with the standardization procedures, was included in a trial evaluation process.

Professionals- Therapists

All the therapists involved in the trial belong to the G.I.P.C.I. group and they are trained to use the same motor learning approach during play and ADL since 15 years. All therapists involved in the treatment development have been trained and have been equipped with a manual listing the theoretical framework of rehabilitation programs to be carried out and many practical examples of activities and tasks (both unimanual and bimanual) to be developed during the treatment sessions. The manual had a DVD attached showing some examples and activities. New personnel employed was trained in the same way. Nevertheless, in order to further standardize the administration of the therapeutic training, all the therapists of the participating Centers had several meetings in order to verify the standardization of therapeutic procedures among the therapists through practical activities with simulated and real cases. Table 4 and 5 show the theoretical framework and some practical examples of activities and tasks of experimental treatment.

Parents

The activities and tasks proposed and developed during the intensive treatment sessions were shown and taught to parents that are asked to attend all the treatment sessions. The family compliance to the suggestions given by the therapist during the treatment sessions was verified periodically and, in the recruitment phase, the family undertook to develop all the activities at home for the duration required. The compliance was an essential requirement for the child recruitment in the clinical trial. Moreover a manual and several videos showing the therapeutic activities were published and handed out to families in order to

equip parents with an instrument to carry out the activities at home during play and daily living.

Standardization

On what attains the assessment procedures the standardization was guaranteed by:

1. Strict timing in tests administration during the trial, constantly verified by the DMC;
2. Common training period for the scales administration and videorecording procedure;
3. Analysis of interobserver variability through the inter-scorer agreement;
4. Mandatory videorecording of the administration scales monitoring primary endpoint (Besta and QUEST) for all the trial assessment phases;
5. Evaluation of 2 expert external supervisors of all the videos recorded during the trial and the agreement phases, blinded to treatment allocation.

On what attains the treatment procedures the standardization was guaranteed by:

1. the 15-years belonging to a common working group on cerebral palsy (G.I.P.C.I.), sharing a practical and theoretical framework of all therapists;
2. Clear and detailed definition of the treatment programs of the 3 groups, specified for age classes;
3. Pre-trial common training period for the treatment procedure for all the therapists involved in the study;
4. 2 manuals + DVD for therapists and for parents showing some examples of training activities and tasks both in the rehabilitation center setting and at home;

5. mandatory participation of the parents to the treatment sessions at the rehabilitation center to learn the activities and tasks to be repeated at home.

Discussion

Clinicians involved in rehabilitation agree on the need for scientifically credible evidence which shows that interventions are safe, effective and worthwhile. In the last decade, research in the field of rehabilitation has been increasingly interested in Randomized Clinical Trials (RCTs) as the preferred design for outcome studies. Nevertheless, in medical rehabilitation the design and conduct of RTCs imply many challenges. Among the others, Fuhrer[135] mentioned the following: (a) difficulties in blinding the administrators of interventions or the recipients; (b) resistance of candidate participants to being randomly assigned to experimental or control groups; (c) the unacceptability, ethically or otherwise, of using control conditions that withhold or delay treatment; (d) the extreme complexity of some interventions that makes it difficult to monitor the fidelity with which they are administered; (e) an insufficiency of eligible participants in any one setting, necessitating difficult-to-administer, multisite trials; (f) the relatively lengthy follow-up interval of some rehabilitation trials that makes them vulnerable to participant attrition.

In pediatric rehabilitation, other challenges are to be added, such as the overlap between intervention effects and natural process of function development, and the marked variability of the clinical picture among participants of different ages and the degree of functional impairment. Moreover, in infancy and childhood, the biological evidence of many developmental disorders is still very poor and

therefore it is often very difficult to define the "rationale" of assessment and treatment methodology.

In the field of hemiplegic cerebral palsy another challenge is represented by its rarity (0.3-0.5/1000 Italian newborns[92, 93]) and therefore by the difficulty to collect large samples of participants for research programs. Moreover, assessment tools of upper limb function, which is the principal goal of the rehabilitation treatment in this form of CP, are very few, and mainly derive from adult protocols.

How can these problems be tackled and managed when designing a trial on the efficacy and safety of CIMT in hemiplegic children? The Cochrane review recently analyzed several clinical aspects of three trials on CIMT in hemiplegic children, namely the method of constraint, frequency and intensity of practice, intervention environment and social context, intervention principles, individual characteristics of children and outcome measures[101]. All these aspects varied significantly in the three trials published[99, 103, 106] particularly in relation to intensity of treatment. Moreover, the samples of children were very small, lowering the power of the studies. Finally, in our opinion, the comparison between children treated with a combination of Constraint of the non affected hand and intensive practice of the affected hand, and children not treated at all is not correct, because it does not allow to distinguish between the effect to be attributed to the restraint and that to be attributed to the intensity of treatment, thus presumably overestimating the effect of CIMT.

For all these reasons, it is very difficult to assess the real efficacy of CIMT itself. In fact, although the results of Eliasson[103] did not support its efficacy, Taub &

Wolf[114] had previously formulated the hypothesis that the intensity and not the principle of treatment could have an impact on outcomes. The RCT results published by Gordon and colleagues[115] on the efficacy of a hand-arm bimanual intensive therapy in hemiplegic children seem to confirm this idea, i.e. the efficacy of intensive treatment alone would improve bimanual hand use, and elicited practice rather than restraint may be responsible for improved motor performance. These encouraging results on small samples of patients need to be urgently confirmed by studies on larger samples of cases, in order to have enough power to exclude the null hypothesis and give clear significant results that do not need further investigation. For this reason, our study has chosen to enroll 37 patients per group, for a total amount of 111 patients.

To overcome many of the problems posed by conducting a trial in the domain of pediatric rehabilitation such as the need to collect large samples, the GIPCI group chose to conduct the trial on CIMT in hemiplegic children as a multisite clinical trial. According to Meinert[136], a trial must possess three characteristics to be considered multiple site in nature. First, the data ought to be acquired from two or more settings that are organizationally independent. Second, a common intervention and data collection protocol ought to be used, and third, data management and analysis ought to be centralized. All these characteristics have been respected in the design of our research study.

As Fuhrer[137] suggested, the advantages of multisite trials are the collection of larger samples, the rapidity in study completion and enhancement of generalizability of findings. Our MSCT in fact involves 21 Rehabilitation Centers,

most of them located in Northern Italy, which deal with the treatment of CP children in ordinary clinical practice. Therefore, this trial may have the advantage of giving a measure of the effectiveness of the treatment, and particularly of determining whether interventions have beneficial results in the real context where new cases with hemiplegic cerebral palsy will have to be treated[138].

However, multisite clinical trials are more challenging in terms of organization, management and administration. The main problem concerns intervention fidelity that is the degree to which the essential features of experimental and control interventions are implemented and planned.

Another relevant aspect of this trial is the choice of outcome measures, which is justified not only by the need for objective and reproducible measurements, but also by the usefulness of considering primary hand function outcomes as strictly related to secondary outcomes, namely the child's overall development, familial environment and quality of life. This choice is based on the principle that any modification determined by a rehabilitation intervention is the result of a balance between changes in hand and limb function, global motor and cognitive development and the child's quality of life. For example, this mutual influence can paradoxically result in a positive effect of the affected limb, but in a negative effect on overall motor development, as demonstrated in animal models[134].

The participation of many Centers in our trial has raised several questions when planning the trial, particularly with regard to the practitioners' different experiences and skills, the diversity in treatment setting, the difference in the use of outcome measures.

To overcome these problems, one year has been entirely dedicated to planning and implementing the study design and to training all the professionals (physicians and therapists) involved in the research project. The protocol features, including enrolment criteria, outcome measures, method of constraint, principles of treatment, intensive practice and parent cooperation, have been specified, discussed and explained, also with the use of videorecordings. In each Center a doctor is responsible for assessment and treatment fidelity and many meetings have been organized to verify the homogeneity of assessment and interventions. The inter-scorer agreement on the main outcome measures of upper limb function and the standardization of treatment practice were lengthy processes, but were worthwhile because they enhanced the practitioners' expertise and awareness. Another important innovation of this research study regards the deep involvement of parents in treatment sessions and their training in order to continue the exercises at home: their involvement plays a key role in the treatment program and in changing their attitude towards the value of treatment and the role of daily activities and actions in improving the use of the affected hand and their children's quality of life.

The effort of staff members involved in the research project is focused on monitoring the quality of protocol implementation over time, checking the experimental and control interventions carried out and introducing corrective factors, if necessary.

In conclusion, the planning and implementation of this multisite study on the safety and efficacy of CIMT in hemiplegic children has so far achieved a first

important goal, besides defining the study design: it has increased the knowledge and expertise of many clinicians involved in pediatric rehabilitation with regard to research study methodologies and practices.

According to the Authors of the review recently published by Cochrane[101], *"...given the paucity of evidence, the use of CIMT in children with cerebral palsy should still be considered experimental. Further adequately powered RCTs, using valid and reliable outcome measures, are required to explore the effectiveness of CIMT for children with hemiplegic cerebral palsy. Future research in CIMT should investigate the most efficient, cost-effective, least invasive and family-friendly treatment protocol that can be easily replicated in a clinical setting."*

As already underlined, research in children has always been neglected in comparison to adults, due to ethical reasons regarding the use of children for experimental purposes. The consequence of this attitude has been the utilization of treatment and assessment tools and techniques whose efficacy has not yet been tested in pediatric patients or evidence is very scarce. The Authors believe that discussing and working on pediatric research methods represents an urgent need in rehabilitation research.

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Tables & Figures

Table 5.1. Currently available clinical trials on CIMT

Author	PY	Design	Methods	Participants	Interventions	Control group	Assessment tools	Cochrane review
Charles [10]	2007	Randomized controlled trial	Randomization. Blinding of 5 outcome assessors. Follow up at 1 and 6 months.	N: 22 Children Sex: 8 F, 14 M Mean Age: 6y 8m Range age: 4-8 y Diagnosis: hemiplegic CP Levels of severity: moderate	*Type of constrain* Use of a sling on the non-involved upper extremity for the entire time during an intervention session *Treatment duration* 10 out of 12 consecutive days during summer or school vacation, 6h wearing the sling and 6 hours with no sling *Treatment setting* Columbia University *Treatment program* Individualized instructions from a trained interventionist involving specific practice of designated target movements. Children engaged in play and functional activities with 2 types of structured practice	Any treatment	▪ Jebsen-Taylor Test of Hand Function ▪ Bruininsk Oseretsky Test of Motor Proficiency ▪ Caregiver Functional Use Survey (CFUS) ▪ Hand-held dynamometer ▪ Modified Ashworth scale	NO
Eliasson [11]	2005	Controlled Clinical Trial.	No randomization. Blinding of outcome assessors. Follow up at 2 and 6 months.	N: 45 children Treatment group: 21 control group: 20 Sex: 20 M, 21 F Age: 18-51 months Diagnosis: hemiplegic CP. Levels of severity: all	*Type of constraint* Use of a fabric glove with a built in stiff volar plastic splint on the "dominant " unaffected hand, preventing finger flexion and thumb movement. *Treatment duration* 2 months of intervention 7 days per week, 2 hours per day which could be split into different sessions. *Treatment setting* Child's usual environment (home/pre-school). Therapist supervision once weekly. *Treatment programme* Principles of motor learning, knowledge of motor control, with activities of an appropriate level of difficulty, and repetition	Traditional services	▪ Assisting Hand Assessment (AHA)	YES
Sung [14]	2005	Randomised controlled trial with no	Follow up at 6 weeks.	N: 31 children Treatment group: 18 Control group: 13	*Type of constraint* Application of a short-arm Scotchcast from below the elbow to the fingertips on the unaffected upper limb.	Traditional services	▪ Box and Blocks Test ▪ Erhardt	YES

Author	PY	Design	Methods	Participants	Interventions	Control group	Assessment tools	Cochrane review
		blinding of assessors		Sex: 15 M, 16 F Age: < 8 years Diagnosis: hemiplegic CP Levels of severity: mild, medium.	*Treatment duration* Twice weekly in 30 minute session for 6 weeks for both groups. *Treatment setting* Hospital setting. Provided by an occupational therapist *Treatment programme* Individualised functional Occupational therapy (OT), and Activites of Daily Living.		Developmental Prehension Assessment ▪ WeeFIM.	
Taub & DeLuca [15]	2004	Single blind randomised controlled crossover trial with blinding of Child Arm Use Test assessors	Follow up at 3 & 6 weeks and 3 & 6 months (CIMT group only)..	N: 18 children Treatment group: 9 Control group: 9 Sex: 13 M, 5 F Age: 7-96 months (mean 41.5 months) Diagnosis hemiplegic CP Levels of severity: all	*Type of constraint* Involved extremity casted from upper arm to fingertips with lightweight bivalved fibreglass cast. *Treatment duration* 6 hours per day for 21 days *Treatment setting* Hospital setting *Treatment programme* Child behaviour shaping, presenting activities to the child in ways that provided immediate, frequent, and repetitive rewards for the child's efforts and increasingly functional use of the more-impaired extremity.	Traditional services	▪ Quality of Upper Extremity Skills Test (QUEST) ▪ Child Arm Use Test (CAUT) ▪ Pediatric Motor Activity Log (PMAL) ▪ Emerging Behaviors Scale (EBS)	YES

Table 5.2. Levels of severity of UE motor impairment

Group I	The paretic hand manipulates without restrictions but with limitations in more advanced fine motor skills
Group II	The paretic hand has only holding function during bimanual manipulation
Group III	The paretic hand has no functional ability

Table 5.3. Recruited patients: baseline demographic information (collected with a dedicated recruitment questionnaire (Annex I)

Variable	**Distribution**
Age (y)	
Average	4y 8m
Range	2-7
Gender	
Male	43 (%)
Female	42 (%)
Level of severity	
I	52%
II	39%
III	9%

Table 5.4. Unimanual activities (CIMT group)

Domain	Repetitive activities	Whole task practice	Elicited movements
Perceptual motor tasks	Blind objects search and recognition Tactile exploration of different materials and surfaces, objects with different weight and consistency Pattern recognition of drawings traced on the palm of the affected hand	• Non structured play activities *Examples* 2-3 yrs plasticine 4-6 yrs wheat, cream 7-8 yrs pasta, rice	Stereognosis, adaptive grasp, finger singolaritation, grasp, fingers singolarization, supination
Holding and manipulative tasks	Activities targeted to: string, lift, move, get and throw objects of different dimensions and shapes	• Structured play activities. *Examples* 2-3 yrs drawing; painting (finger paints) 4-6 yrs puzzles; Lego building 7-8 yrs memory cards	Wrist extension, finger singolarization, release, thumb opposition
Posture and balance	Grab and carry small objects from/to different places and levels (high, low, front, back, up, down)	• Movement games *Examples* 2-3 yrs play ball 4-6 yrs play skittles 7-8 yrs play bowls and darts	Shoulder flexion and abduction, wrist extension, prono-supination forearm
Self-care and ADL		*Examples* 2-3 yrs Drink with the glass; smear face with cream or soap 4-6 yrs comb or brush hair; brush teeth 7-8 yrs spoon or fork use; dust a surface	Precision grip, adaptive grip, release, prono-supination

Table 5.5. Bimanual activities (control group 1)

Domain	Repetitive activities	Whole task practice	Elicited movement of affected hand	Evoked use
Perceptual motor task	Fill up/empty big bottles or containers with wheat, rice, pasta, water, etc.	• Non structured play activities *Examples* 2-3 yrs smear both upper limbs with cream, soap or colour 4-6 yrs paint palm and fingers of the affected hand with the other hand and make handprints 7-8 yrs play wind or percussion instruments	Perceptive exploration, supination precision grip, release, finger singolaritation	Cooperation in bimanual task as assisting hand for holding and manipulation
Holding and manipulative tasks	Several symmetrical and asymmetrical activities (cork and uncork bottles, take off/put on top on marking pens, tear a piece of paper cut out a picture etc.)	• Structured play activities *Examples* 2-3 yrs playing dolls; drawing; painting 4-6 yrs Lego blocks 7-8 yrs puzzle, packaging; do the washing, spread out the washing, ironing linen, make pizza, cut fruits for food salad	Adaptive grip, supination, release, bimanual coordination	Cooperation in bimanual task as assisting hand for holding and manipulation
Posture and balance	Grab and carry big objects from/to different places and levels (high, low, front, back, up, down)	• Movement games *Examples* 2-3 yrs play with a big ball 4-6 yrs tricycle, pull a chart 7-8 yrs play basket, bicycle	Shoulder flexion, abduction, wrist extension and supination, bimanual coordination	Cooperation in bimanual task as assisting hand for holding and manipulation
Self care		*Examples* 2-3 yrs Drink with a big cup; break bread or sweets; wash hands and face 4-6 yrs take off the shoes and socks 7-8 yrs take off the shoes and socks, cooperate in bimanual ADL such as bring the plates, fold napkins, dry up kitchenware	Adaptive grip, prono-supination, release, bimanual coordination	Cooperation in bimanual task as assisting hand for holding and manipulation

Table 5.6. Assessment protocol

Timing	Assessment tools/Outcome measures
t_o (baseline)	Anamnesis / Objective Exam Neurologic Exam Wechsler/ Griffiths Gross Motor Function Measure Parenting Stress Index QUEST Besta Scale Besta Scale for parents
t_1	Anamnesis / Objective Exam Neurologic Exam Gross Motor Function Measure Parenting Stress Index Child Behavior Checklist Treatment Satisfaction and Compliance Scale QUEST Besta Scale Besta Scale for parents
t_2	Anamnesis / Objective Exam Neurologic Exam Gross Motor Function Measure Child Behavior Checklist QUEST Besta Scale Besta Scale for parents
t_3	Anamnesis / Objective Exam Neurologic Exam Gross Motor Function Measure QUEST Besta Scale Besta Scale for parents
t_4	Anamnesis / Objective Exam Neurologic Exam Gross Motor Function Measure QUEST Besta Scale Besta Scale for parents

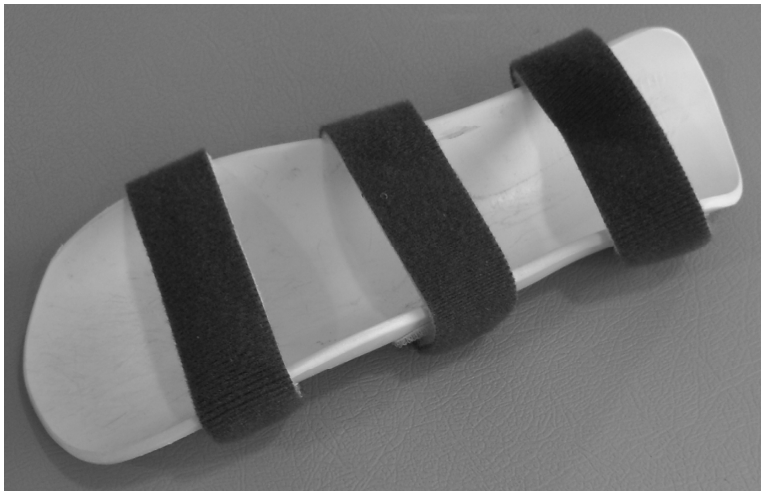

Figure 5.1. The stiff-plastic glove used to cast the unaffected arm

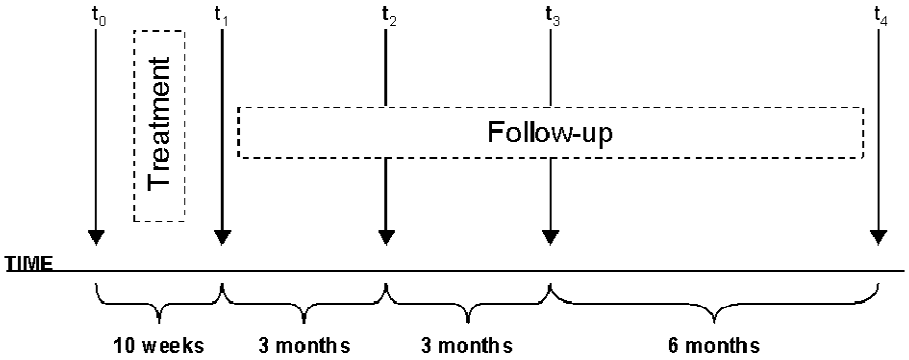

Figure 5.2. Timing of assessment sessions: the pre and post-treatment and the follow-up phases.

Annex 5.1 – Baseline information collected per each eligible case

Rehabilitation Center
Patient Initials
Date of birth
Sex
Gestational Age
Side of hemiplegia
Age of onset (months)
Level of severity
Plausibile pre/peri-natal cause or acquired cause
Cognitive disturbances
Stereognosis alterations
Speech/ language delay
Mood disturbances
Visual Impairment
Visual attention disorders
Hearing impairment
Associated malformations
Skeletal
Visceral
Presence of epilepsy
Other comorbidities
MRI results (leucomalacia, cerebral malformation, other cerebral alterations)
CT scan; Ultrasound, SPECT results

CHAPTER 6. THE PRIMARY OUTCOME MEASURE: AGREEMENT AMONG ASSESSORS

This paper has been submitted to the international journal *Physical Therapy.*

Title

Comparison of Quality of Upper Extremity Skills Test (QUEST) and Besta Scale in hemiplegic cerebral palsy

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Background

Cerebral palsy represent the most common cause of disability in children with neurologic impairment. It result from a wide spectrum of central nervous system diseases and, depending on the etiology, are classified as primary or secondary.

The prevalence of movement disorders in children, their clinical presentation and course, and their prognosis and management substantially differs from those of adults. The presentation is frequently insidious, and may be characterized at onset by mild hypotonia. The clinical picture may be more complex, rapidly changing, and often characterized by the association of different types of movement abnormalities. The pattern of movement disorders may be highly influenced by age at onset and by the stage of development at which the disease occurs. Moreover, the occurrence of movement disorders affects the course of neuromotor and adaptive development.

The recognition of the pattern of movement disorders and the possibility of grading their severity are relevant for the clinician when planning rehabilitative and pharmacologic interventions, monitoring the results of treatment, and predicting outcomes.

Several instruments and rating scales are currently used to assess movement disorders in children with hemiplegic cerebral palsy, in particular one of the most "measured" performance regards the outcome of the upper limb function, such as in the case of Melbourne[139] or Peabody Developmental Motor Scales[140].

The available measurement tools are characterized by the possibility to obtain a synthetic measure of hand function that is useful to monitor the clinical course of

the affection and the influence of the rehabilitation treatment proposed on the severity of the impairment.

In general, all available tools require the execution of specific tasks and action by the child (for example grasp a cube, hold a pencil, draw a circle) as asked by the therapist. Furthermore, the majority of the scales are build to assess each hand separately. This characteristic is useful while studying the motor performance of the affected hand, but does not measure its real use in bimanual activity. Finally, the measurement of the involvement of the affected hand in bimanual activities is usually assessed in standardized actions, rather than in the common activities the child carries out in his/her daily living.

To our knowledge, none of the assessment tools currently available test the spontaneous use of the impaired hand in the evaluation session. Very often the attention is devoted to explore the capacity the child has to carry out a certain tasks (best performance), instead of understanding how and how often the child utilizes the hand during ADL and play activities.

Another major reason of complaint is that some of these scales were mainly designed for and are limited to adult patients, being very difficult to apply in paediatric populations. An assessment scale specifically designed for movement disorders in paediatric populations is crucial. This scale should take into account and measure movement-disorder severity, and also the impact of the disorder on child development and functioning, aspects that are highly age-specific and relevant to all types of movement disorders.

In the assessment of the function of the affected limb in the child hemiplegic cerebral palsy, the learned non-use or the developmental disuse are fundamental to be taken in consideration since they characterize the disease's natural history. As these children develop they tend to acquire ever greater skill with the unaffected hand and increasingly neglect the impaired hand. As a consequence, such children show good hand function if required to use the impaired hand during a therapy session, but hardly ever use it in spontaneous manipulation during play or ADL.

As demonstrated in a prospective study on 31 children with hemiplegic cerebral palsy[141], to evaluate the real disability of the affected hand, grip assessment is insufficient and an instrument assessing spontaneous hand use in bilateral manipulation is required for meaningful clinical assessment of hand function and disability.

Recently, a new tool for hand function assessment, the Assisting Hand Assessment (AHA)[142], was developed to measure how effectively the involved hand is used for bimanual activity. It is based on observations of actions performed in relevant activities and is meant to reflect the child's usually performance, and not the best capacity. The rating scale categories a graded in a scale of effectiveness (4 = effective, 3 = somewhat effective, 2 = ineffective, 1 = does not do). The activities proposed deal with play session and daily living actions, stratified by age, in order to assess spontaneous use in bimanual activities.

However, the scoring system does not evaluate the effectiveness of movement, but the quality of patterns and mostly the variability or the stereotypy in grasping patterns.

Despite the application of these assessment tools on the single patient, their applicability should be easily extended to groups of patients in order to compare the trend of impairment in larger samples and deeply understand the natural history: The possibility to compare test results is meaningful also to conduct valid a reliable clinical research to assess new treatment options and to compare two or more rehabilitation approaches.

Aims of the study

The aims of the study were to evaluate the inter-rater reliability of QUEST and Besta Scale and to assess the relationship between the scales.

This phase was utilized not only to be able to measure the variability among assessors of primary outcome measures in order to use this coefficient as an estimation of the variability of the measurement tool of primary end-point, but also by the opportunity of providing further standardized training for all assessors participating to the clinical trial (if needed).

Materials and Methods

Patients

Participants were included in the study if they were diagnosed with hemiplegic cerebral palsy, aged between 2 and 10 years, and able to understand the test instructions.

Besta and QUEST scale were administered to 39 patients and the administration was video-recorded. Each video was evaluated by 20 assessors belonging to 20 different rehabilitation centers. Per each patient information was collected on age, sex, side of the hemiplegia, and severity of impairment (Table 6.1).

The levels of severity of UE motor impairment were divided into three groups, according to the following criteria. In the group 1 the paretic hand manipulates without restrictions but with limitations in more advanced fine motor skills, in the group 2, the paretic hand has only holding function during bimanual manipulation and in the group 3, the paretic hand has no functional ability.

Chi squared test was utilized to verify if there was an equal distribution among the age classes and severity classes and the equal distribution was confirmed (p value = 0.6622).

The measurement tools

The **Besta Scale** is an instrument that was developed in 1985 at the Developmental Neurology Division of the Istituto Neurologico (Neurological Institute) *"Carlo Besta"* in Milan, to assess quality of grip (hand function on request) and spontaneous hand use (bilateral manipulation), and their changes in relation to age and degree of impairment. The first version of this assessment protocol was described in 1986, in a study in which clinical characteristics were analyzed in relation to aetiological factors and computed tomography findings in 30 children with congenital hemiplegia[143]. After modification, the instrument was used in a prospective study to evaluate changes in hand impairment and bilateral manipulation skills over time[144]. To assess the inter-rater reliability of these

instruments a pilot study was conducted in 1993 on 15 children with hemiplegia under 7 years old and 15 children with hemiplegia over 7 years old. The videotapes of grip assessment and bilateral manipulation activity assessment for each child were scored by three observers (an occupational therapist, a paediatric neurologist, and a medical student), and the K statistic was calculated. Inter-observer agreement of grip scores was excellent (K = 0.95). For bilateral manipulation scores the agreement was also good to excellent, with K ranging from 0.75 to 0.89 for the assessment of younger children and from 0.69 to 0.90 for children over 7 years of age.

In the scale, grip assessment is performed in a standardized setting, asking the child to pick up different sized cubes on request. The quality of grip is videotaped and scored in a hierarchical way (from 0 to 3). Spontaneous use is assessed during structured activities requiring both hands and being standardized according to age. The scoring system for the quality of manipulation is based on variability and stereotypy of movement pattern[145]: score 0, no use of impaired limb; score 1, use of impaired limb in a stereotyped pattern (wrist support) for holding; score 2, cooperation of the impaired hand in manipulation by holding with a restricted number of stereotyped patterns; score 3, cooperation of the impaired hand with holding and manipulation, using a varied repertoire of patterns. The assessment was video-recorded and scored on subsequent viewing.

Grip. The assessment was performed in a standardized setting. The child sat in a chair at a table adjusted to his or her height. Three cubes of different sizes (side measurements 4, 2.5, and 1cm) were placed on the table and the child was asked

to pick up the cubes first with the unaffected hand and then with the impaired hand. There was no time limit. The performance was video-recorded. The scoring system for grip impairment was as follows: 0, inability to grip cube; 1, grasping or whole-hand grip; 2, radial or three-finger grip; 3, pincer grip.

Spontaneous use of affected hand during bilateral manipulation. Use of the affected hand during bilateral manipulation was assessed during structured activities requiring both hands, standardized according to age. For children up to age 7 years the tasks were to throw a large ball, to tear a sheet of paper into many pieces, to unscrew and screw the cap of a bottle, and to open a packet tied with adhesive tape. Children over the age of 7 years had to open a packet tied with string in a single knot, to wrap an object in paper forming a parcel, to cut out geometrical figures and stick them onto a sheet of paper, and to fold a piece of paper and place it in an envelope. The assessment was video-recorded and scored on subsequent viewing.

Stereognosis. Stereognosis was usually assessed at the age of 4 years because younger children often do not cooperate or do not have sufficient attention. The procedure used is part of a test battery for evaluating the gnosic competence of preschool children. A set of 5 familiar objects was used: a small spoon, a coin, a brush, a small ball, and a doll. The objects were put on the table in front of the child who could touch and recognize them. A second set of identical objects was used to assess tactile recognition without vision. The objects were first placed in the unaffected hand in random order and the child had to point to the object on the table corresponding to one in the hand. The objects were then placed in the

affected hand in random order, and if necessary the child was helped to manipulate and explore them with the fingers. Stereognosis was considered normal when all 5 objects were identified, and was considered absent otherwise.

The **QUEST scale**[146] is used to evaluate quality of upper extremity function in four main domains: dissociated movement, grasp, protective extension, and weight bearing. The validation studies have been completed with children with cerebral palsy aged 18 months to 8 years. It is articulated in 36 items assessing dissociated movements, grasp, protective extension, and weight bearing. A separate scoring is given to

The scale administration requires 30 - 45 minutes and it is administered within a play context. Items are related to quality of movement, not to chronological age.

In the literature, three reliability studies have been completed with children with cerebral palsy and the observer reliability of the QUEST and its domains ranges from 0.51 to 0.96 with all coefficients except one greater than 0.70. Test-retest reliability of QUEST and its domains ranges from 0.75 to 0.95. Concurrent validity with the Peabody Developmental Motor Scales (PDMS) - fine motor is 0.84. Correlations between QUEST domains and sub-scores of the PDMS range from 0.58 to 0.84.

The grasp domain correlates highly with all areas for the PDMS while protective extension is lower.

Construct validity with therapist's judgement of child's level of hand function - 0.72 for left hand function, and 0.58 for right hand function. Correlation between chronological age and QUEST score was 0.33.

Professionals training

A specific training program was provided to familiarize professionals with testing procedures in order to develop a homogeneous administration and videotaping of the Besta Scale and QUEST tests.

The principal investigators of the participating centers were equipped with a training package including: a presentation module illustrating the sections of each scale (QUEST and Besta Scale) and describing the scoring procedures with practical video-recorded examples, which included the videos of 3 children with different levels of hemiplegia, 2 of which were scored and the third was blind (with the scoring enclosed in a sealed envelope).

After the self-training phase, a meeting with scale experts was organized for the principal investigators in order to discuss issues related to administration. recording procedure and scoring process.

2 experienced training core members of staff evaluated the videotapes to assess the quality of procedures employed by each clinical center and exclude participants that were not sufficiently trained, and they also rated the videotapes.

Periodical meetings were held during the second project year among all the representatives of the participating centers. These meetings included participant chart reviews, focus groups with research participants, and key informative interviews with Training Core staff. Information gathered during these meetings,

along with data collected with the standardization procedures, was included in a trial evaluation process.

Video-recording standardized protocol

Each clinical centre provided the video-recording of the administration of the 2 tests (QUEST and Besta Scale) to 2 children of their hemiplegic population, in all 42 cases (2 per each centre) who undergone the administration and video-recording of 2 test: in all 84 videos, 42 Besta scale and 42 QUEST scale). The coordinating centre sent the 84 videos to all the 21 participating centre and all videos were scored by the principal investigator (a total amount of 84 assessments, 2 per all 42 children video-recorded). All evaluations were collected and analysed by the coordinating centre in order to evaluate the agreement among the investigators involved, considering separately in the analysis each item scored, partial scoring values of scales sections and total scoring values of Besta and QUEST scales.

Statistical Analysis

Patients' data were collected in a database and kept up to date using Microsoft Access® software (Microsoft Corp., Redmond, WA, USA). The statistical analysis was done with the SAS® package, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Summary statistics of the overall scores are presented as mean ± SD ratings. Inter-rater reliability of Besta scales and QUEST was assessed by Kendall’s coefficient of concordance (K) and intraclass correlation coefficient (ICC) respectively.

Kappa statistic is used to compute estimates and tests of agreement among multiple raters when ratings are on ordinal scale[147]. Kendall's coefficient of concordance is comprised between 0 (= no agreement) and 1 (=perfect agreement) and indicates the degree of agreement according to this range: "0-0.2"=slight; "0.2-0.4"=fair; "0.4-0.6"=moderate, "0.6-0.8"=substantial, "0.8-1"=almost perfect[148]. SAS "%MAGREE macro" was utilized to compute Kendall's coefficient[149].

The ICC coefficient is used to test inter-rater agreement on continuous ratings. ICC may be conceptualized as the ratio of between subjects variance to total variance. ICC has a range of 0–1, with 1 representing perfect inter-rater agreement[150,151]. Beside the ICC coefficient, in the tables the sources of variance are reported (Sum of Squares, SS), one due to rated subjects and one due to raters, and the ratio between the two SS. SAS "%INTRACC macro" was utilized to compute ICC[152,153].

Patients were stratified by age in three age classes ("2-3", "4-5","6-10") and by severity of impairment ("1" mild impairment, "2" medium impairment, "3" severe impairment).

Besta scale was analyzed both item by item (23 item; range 0-3) and on the 5 global mean scores (1 overall mean score and 4 sub-sections mean scores):

- Assessment on the grasp function of the paretic hand on request (4 items);
- Qualitative assessment of the spontaneous use of the paretic hand in bimanual manipulatory activities(4 items);

- Qualitative assessment of the use of the paretic hand in feeding and clothing Activities of Daily Living in younger children(11 items);
- Qualitative assessment of the use of the paretic hand in feeding and clothing Activities of Daily Living in younger children (4 items).

For QUEST the analysis has been carried out on the 5 subscale scores (range 0-100) calculated according to the algorithm give by the scale scoring system.

- Dissociated movements (A);
- Grasping (B);
- Weight bearing (C);
- Protective extension (D);
- Global score.

In order to be able to calculate the scoring of the two hands separately, all items with a positive answer (modality “yes”) were summed up attributing a “+1” each. The items have been grouped homogeneously into five categories:

- Dissociated movements: shoulder, elbow, wrist and fingers (28 items);
- Dissociated movements combine with grasping of a cube (4 items);
- Grasping of a cube of 2.5 cm, a pencil and a matita and a felt pen (12 items);
- Weight bearing (24 items);
- Protective extension (18 items).

For every subject, given a value of 1 for every positive response per single item, extra scores were calculated separating the results of the affected and the unaffected hand.

Results

Mean scores and SD: Besta and QUEST

Besta scale. 780 scales have been elaborated. The global mean score was calculated in 5.43 (± 2.3 SD). As expected, the global score decreases with the increasing of severity of impairment (7.34→ 5.41→ 2.44) and increases with the increase of child's age (4.66→ 5.52→5.82) (Table 6.2). The same behaviour is observed in each sub-scale mean score. In general, SD are relatively small showing a limited variation in scoring by assessors. The trend of scores is plausible from a biological/clinical point of view.

QUEST. A different behaviour is observed in QUEST scale: the global score tends to increase with age (71.0→ 74.5 → 76.8) (except from protective extension for which a decreasing is observed) and decrease with severity (85.7→ 73.7 → 58.7) (Table 6.3). Looking at age the scale seems to underestimate the tasks performing of children age 4-5 years, despite the level on impairment, especially for the dissociated movements. In some case the SD is high or very high indicating an extreme variability in scoring or performing.

The separate analysis of affected and unaffected limb shows that some sections of the test are very confusing not separating the performance as biologically expected. For example, in weight bearing area, the scoring of 6-9 years old children is completely overlapped and confused. In children aged 4-5 years with a

level of impairment of 3, the score is always the lower. On the contrary, the unaffected side of the same age children (4-5) is always scored as the highest, except from weight bearing. An interesting result regards the scoring of the unaffected hand of the children with a level 3 impairment: in these cases the hand is judged as performing better than the unaffected hand in general. The most regular trends are observed in dissociated movements and grasp function (Table 6.4, Figure 6.1). In children aged 6-9 years in weight bearing, the assessors seem not to be able to distinguish the performance of the three levels of severity confusing them with the unaffected limb (Figure 6.1).

Kendall's K coefficient

In Besta Scale, the calculation for the K coefficient shows a value of 0.47 for the overall global score. In the global value of single items the K has the highest value for wearing pants (0.64) and wearing shoes (0.63). The lowest agreement is calculated for grasp a bilia and take off the sweater (0.35) (Table 6.5).

In general, K is higher in ADL (both in younger and in older), while it is lower in grasp and spontaneous use.

The analysis stratified for level of severity shows the following (Table 6.5):

- Severity 1: minimum agreement is observed in grasping cube of different measures (0.11-0.12), while maximum agreement is observed in wearing pants, socks and shoes (0.82).
- Severity 2: minimum agreement is observed in tear tissue paper and wrap a packet (0.09), while maximum agreement is observed in grasping cube of different measures (0.44-0.51) and use fork and knife (0.52).

- Severity 3: minimum agreement is observe for the item take off socks (0.22) and maximum for cut with fork and knife. In general a good agreement is observed for ADL in younger ages.

The analysis stratified for age shows that the agreement is higher for 4-5 years-aged for the grasping function (Table 6.5), while for all other subscales the agreement increases with age (i.e. the older the child the higher is the inter-rater agreement).

Intraclass Correlation Coefficient (ICC)

In the global score and sub-scales scores the ICC ranges from 0.59 to 0.71, showing a good agreement among assessors (demonstrated also by the rate SS observer/ SS patient always below 1).

Looking at the distribution of age the total ICC increases as the child gets older, showing an higher agreement among assessors while the child grows, for all the sections of the scale (Table 6.6). For younger children the assessment is highly affected in the scoring of dissociated movements and weight bearing, probably because in this age these tasks are performed with difficulties.

For the level of severity, there is a higher agreement for patients with the highest level of impairment. This is particularly relevant for 6-9 years age group (Table 6.6).

Unexpectedly, the assessment of the unaffected limb has some spikes of extreme variability, particularly for dissociated movements & grasping (total scores) and for grasping in the less severe children (Table 6.7).

The agreement among observers for the affected limb is better than the unaffected one, particularly for grasping function (very high for all the age groups). According to severity, the agreement is better if compared to the other categories for children with a less severe impairment (Table 6.8).

Discussion

In this study we examined the interrater reliability of the Besta Scale and the QUEST in a group of young children with hemiplegic CP.

Agreement between continuous data measured from different observers or measurement methods is a question that has received a great deal of consideration from the scientific community. The Intraclass Correlation Coefficient is one of the most popular aggregate procedures used to measure agreement when data are on a continuous scale. The Intraclass Correlation Coefficient (ICC) measures the amount of overall data variance due to between-subjects variability. Since the ICC is defined using variance components, several expressions of ICC can be found in the literature depending on the measurement model selected to fit the data. But at the same time, this flexibility of the ICC causes confusion or misunderstanding, because the underlying measurement model.

For the QUEST, the interrater reliability of the total score and the domains was very high and in agreement with the study of De Matteo and of Klingels. The domains showing a clearly lower reliability are the Protective Extension and the Weight Bearing.

A clear advantage of QUEST is represented by the possibility to assess separately the two upper limbs. In this way a focus on the affected limb can be done and this

results particularly useful while assessing the limb performance before and after treatment.

Also Besta scale showed good agreement results, particularly regarding the ADL for older children and spontaneous use for more severe cases.

Besta scale was conceived in a way that not the best performance was to be evaluated, but the capability. In other words, the assessor should be able to score the ability of continuing to perform the task in time (not just once). This characteristic could affect the agreement among assessors, since not just the quality of the movement but also its reproduction in time are to be judged. The scale scoring systems seems to be able to respond in a good way to this difficulty.

A limitation of this study is the administration of the QUEST to children younger than 4 years. In these cases the level of development of motor function is too immature and therefore it is difficult to distinguish the impossibility to perform the task required due to age from the disability determined by the cerebral palsy. In this way, the agreement among observers might be affected and biased by age as a confounding factor.

It is crucial to gain more insight into the performance of bimanual activities, not only in an assessment setting, but also during dailies activities performed spontaneously. Particularly to improve the understanding of this second aspect further studies are need to explore the quality of Besta scale. In fact, by comparing the results of the capacity of the hemiplegic side with the performance of the hemiplegic side in bimanual activities, instructive conclusions can be drawn about the developmental non-use of the hemiplegic side.

In conclusion, this study demonstrated that QUEST and Besta scale are reliable measurement scales to evaluate unilateral upper limb function and bimanual spontaneous use (Besta) in young children with hemiplegic cerebral palsy.

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Tables & Figures

Table 6.1. Assessed patients: Demographic characteristics

Variables		**N**
Cases		39
Sex (Males/Females, %M/ %F)		
Male	(n, %)	21 *(52)*
Female	(n, %)	18 *(48)*
Age		
2-3 yrs	(n, %)	9 (*23)*
4-5 yrs	(n, %)	16 (*41)*
6-10 yrs	(n, %)	14 (*36)*
Side affected (right/left)		
Right	(n, %)	20 *(51)*
Left	(n, %)	19 *(49)*
Severity of impairment*		
1	(n, %)	13 *(33)*
2	(n, %)	18 *(46)*
3	(n, %)	8 *(21)*

Assessors	20
Experienced assessors	2
Besta Assessments	780
QUEST Assessments	780

(* for severity classes see Facchin et al. *Am J Phys Ther Rehab*. 2009)

Table 6.2. Besta Scale: mean scores and Standard deviation (SD) (range: 0-3)

	TOTAL		SEVERITY						AGE					
			1		2		3		2-3		4-5		6-10	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
*Assessment on the **grasp function** of the paretic hand on request*														
Grasp a bilia	1.99	0.8	2.54	0.5	2.08	0.4	0.95	0.9	1.74	0.8	2.04	1.0	2.06	0.6
Grasp a cube 1.5 cm	2.01	0.8	2.56	0.5	2.09	0.4	1.00	0.9	1.77	0.8	2.07	1.0	2.08	0.6
Grasp a cube 2.5 cm	1.99	0.8	2.52	0.5	2.08	0.4	0.99	0.9	1.77	0.8	2.06	1.0	2.04	0.6
Grasp a cube 4 cm	1.96	0.9	2.56	0.5	2.04	0.5	0.86	0.9	1.78	0.9	2.01	1.0	2.01	0.7
Mean score	**1.99**	**0.8**	**2.55**	**0.5**	**2.07**	**0.4**	**0.95**	**0.9**	**1.78**	**0.8**	**2.05**	**1.0**	**2.05**	**0.6**
*Qualitative assessment of the spontaneous use of the paretic hand in **bimanual manipulatory activities***														
Hold/throw a big/small ball; Unwrap a packet	1.93	0.9	2.64	0.5	1.84	0.6	0.99	0.8	1.72	0.7	1.92	1.0	2.07	0.7
Tear tissue paper; Wrap a packet	2.06	0.7	2.49	0.6	2.04	0.5	1.35	0.7	2.07	0.6	2.07	0.8	2.03	0.7
Grasp/drink from baby's bottle/bottle; uncork/fill in a bottle; Fold a sheet	1.86	0.9	2.50	0.6	1.86	0.6	0.98	0.8	1.61	0.8	1.92	0.9	1.95	0.8
Grasp a doll; unwrap a packet; Paste paper shapes on the corresponding outlines	1.98	0.9	2.68	0.5	1.93	0.5	0.96	0.9	1.87	0.8	2.11	0.9	1.91	0.8
Mean score	**1.96**	**0.7**	**2.57**	**0.4**	**1.93**	**0.4**	**1.06**	**0.7**	**1.83**	**0.6**	**2.00**	**0.8**	**2.00**	**0.6**
*Qualitative assessment of the use of the paretic hand in feeding and clothing **Activities of Daily Living***														
Drink from a cup (>18 m)	1.81	1.1	2.66	0.6	1.78	0.9	0.66	0.8	1.53	1.0	1.97	1.1	1.81	1.1
Drink form a big glass (>18 m)	1.10	1.2	1.53	1.4	1.07	1.1	0.56	0.8	1.00	1.2	1.16	1.3	1.09	1.2
Slice the bread (>18 m)	1.95	0.8	2.47	0.5	2.07	0.5	1.07	0.8	1.84	0.6	1.94	0.9	2.19	0.6
Fold a napkin (> 3 yrs)	1.86	1.0	2.62	0.5	1.75	0.8	0.64	0.9	1.66	1.1	1.94	1.0	1.87	1.0
Cut with fork and knife (> 6 yrs)	2.12	0.6	2.79	0.4	1.82	0.4	1.95	0.2	.	.	.	.	2.12	0.6
Wash hands (> 2 yrs)	1.80	1.0	2.55	0.7	1.71	0.8	0.89	0.7	1.41	1.0	1.96	1.0	1.96	0.8
Wash face (> 2 yrs)	1.21	1.3	2.06	1.2	0.75	1.0	0.22	0.5	1.24	1.2	1.31	1.2	0.94	1.3
Take off the shoes (> 2 yrs)	1.10	1.2	2.17	1.1	0.73	1.0	0.25	0.7	1.00	1.2	1.24	1.2	0.89	1.3
Take off the socks (>18 m)	1.21	1.3	2.19	1.1	0.90	1.1	0.21	0.6	1.08	1.2	1.30	1.3	1.16	1.3
Take off the sweater (> 3 yrs)	1.56	1.2	2.62	0.6	1.21	0.9	0.10	0.3	1.40	1.0	1.78	1.2	1.21	1.2
Take off the trousers (> 2 yrs)	1.32	1.2	2.50	0.8	0.94	1.0	0.07	0.4	1.05	1.2	1.49	1.2	1.21	1.3
Mean score	**1.49**	**0.9**	**2.35**	**0.5**	**1.33**	**0.6**	**0.52**	**0.5**	**1.26**	**0.8**	**1.63**	**0.9**	**1.45**	**0.9**
Wear a sweater	1.94	1.0	3.00	0.2	1.79	0.7	0.39	0.5	.	.	.	.	1.94	1.0
Wear trousers	2.17	0.8	3.00	0.2	1.96	0.5	0.14	0.4	.	.	.	.	2.17	0.8

	TOTAL		SEVERITY						AGE					
			1		2		3		2-3		4-5		6-10	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Wear socks	2.01	1.0	3.00	0.2	1.99	0.6	0.00	0.0	.	.	.	.	2.01	1.0
Wear shoes	1.75	1.1	3.00	0.2	1.56	0.8	0.00	0.0	.	.	.	.	1.75	1.1
Mean score	**1.93**	**0.9**	**3.00**	**0.2**	**1.83**	**0.5**	**0.13**	**0.2**	**.**	**.**	**.**	**.**	**1.93**	**0.9**
Global Mean score	**5.43**	**2.3**	**7.34**	**1.6**	**5.41**	**1.1**	**2.44**	**1.9**	**4.66**	**1.9**	**5.52**	**2.5**	**5.82**	**2.2**

Table 6.3. QUEST: mean scores and SD (range: 0-100)

		SEVERITY							
		1		**2**		**3**		**TOTAL**	
	AGE	mean	SD	mean	SD	mean	SD	mean	SD
Dissociated movements	2-3	84.1	7.6	73.4	13.7	70.1	12.6	74.6	13.2
	4-5	85.9	14.8	70.2	14.8	56.7	8.2	74.5	17.6
	6-9	94.2	6.2	78.6	10.4	65.9	7.9	81.3	13.0
	TOTAL	**88.2**	**12.4**	**74.6**	**13.3**	**64.2**	**11.6**	**76.9**	**15.4**
Grasp	2-3	80.9	9.3	63.8	16.8	47.8	17.0	62.0	19.7
	4-5	85.9	13.0	71.8	16.6	46.3	15.4	73.2	20.7
	6-9	89.4	10.8	69.2	14.5	56.7	12.4	73.2	17.3
	TOTAL	**86.3**	**12.1**	**68.9**	**16.0**	**49.5**	**15.8**	**70.6**	**19.9**
Weight bearing	2-3	86.0	19.8	77.5	40.1	64.2	40.3	74.7	37.5
	4-5	94.2	8.8	79.5	18.5	53.1	32.4	81.0	24.0
	6-9	52.9	81.9	84.3	15.4	81.4	12.3	75.1	47.1
	TOTAL	**80.4**	**49.5**	**81.2**	**24.0**	**64.4**	**34.0**	**77.4**	**36.8**
Protective extension	2-3	75.6	24.0	66.8	29.6	64.5	20.3	67.9	25.7
	4-5	68.7	36.8	45.2	63.1	44.0	31.1	55.2	49.1
	6-9	35.3	77.7	66.7	22.8	36.0	32.6	53.3	48.6
	TOTAL	**59.7**	**53.8**	**59.4**	**43.3**	**49.8**	**30.2**	**57.5**	**44.9**
Global Score	2-3	81.6	12.0	72.2	13.0	62.9	14.1	71.0	14.9
	4-5	85.0	10.2	73.2	11.3	52.8	8.2	74.5	15.5
	6-9	89.0	9.0	74.7	11.7	60.8	10.7	76.8	14.1
	TOTAL	**85.7**	**10.4**	**73.7**	**11.8**	**58.7**	**12.2**	**74.5**	**15.0**

Table 6.4. QUEST: mean scores (ranges respectively: 0-28, 0-4, 0-12, 0-24, 0-18)

		Unaffected limb		**Unaffected limb Severity 3**		**Affected limb Severity 1**		**Affected limb Severity 2**		**Affected limb Severity 3**	
	AGE	median	SD	median	SD	median	SD	median	SD	median	SD
Dissociated movements	2-3	20.4	6.9	16.8	6.2	19.3	3.7	12.8	4.9	9.6	5.2
	4-5	20.5	8.4	25.7	2.6	18.3	8.9	9.6	6.8	4.1	3.9
	6-9	26.0	3.0	26.4	2.3	23.2	4.4	16.1	6.1	9.9	3.6
	TOTAL	**22.5**	**7.1**	**22.5**	**6.2**	**20.0**	**7.4**	**13.2**	**6.7**	**7.6**	**5.1**
Dissociated movements & grasp	2-3	3.8	0.7	3.8	0.7	3.6	0.9	2.8	1.2	0.9	1.4
	4-5	3.6	1.0	3.8	0.6	3.6	1.0	3.0	1.3	0.6	1.0
	6-9	3.7	0.9	3.9	0.4	3.5	1.2	2.6	1.3	1.5	1.5
	TOTAL	**3.7**	**0.9**	**3.8**	**0.6**	**3.6**	**1.0**	**2.8**	**1.3**	**1.0**	**1.3**
Grasp	2-3	8.4	3.0	7.0	2.5	8.0	2.3	3.6	2.0	1.5	2.3
	4-5	9.8	3.0	10.5	2.5	8.5	2.9	6.3	3.0	0.6	1.1
	6-9	11.2	1.7	11.2	1.4	9.6	2.4	4.9	2.8	2.2	2.0
	TOTAL	**10.0**	**2.7**	**9.3**	**2.9**	**8.8**	**2.7**	**5.1**	**2.9**	**1.3**	**2.0**
Weight bearing	2-3	17.7	7.6	14.9	8.0	23.7	3.4	16.7	6.8	13.0	9.3
	4-5	21.0	6.8	21.1	6.5	24.0	2.3	16.1	8.1	9.2	7.9
	6-9	22.7	6.4	24.8	0.8	19.3	10.3	22.5	4.8	23.9	1.5
	TOTAL	**20.9**	**7.0**	**19.6**	**7.5**	**22.5**	**6.4**	**19.1**	**7.2**	**14.3**	**9.4**
Protective extension	2-3	12.6	4.2	11.1	3.3	13.3	3.2	10.3	3.7	9.3	4.5
	4-5	13.4	5.5	13.4	4.6	13.5	5.8	11.0	6.1	3.3	4.7
	6-9	14.0	5.6	9.8	3.5	12.7	7.4	13.3	5.0	6.4	6.0
	TOTAL	**13.5**	**5.2**	**11.6**	**4.1**	**13.2**	**6.0**	**11.8**	**5.3**	**6.4**	**5.6**

Table 6.5. K for Besta Scale

		SEVERITY			AGE		
	TOTAL	**1**	**2**	**3**	**2-3**	**4-5**	**6-9**
*Assessment on the **grasp function** of the paretic hand on request*							
Grasp a bilia	0.35	0.15	0.29	0.34	0.34	0.35	0.28
Grasp a cube 1.5 cm	0.43	0.11	0.44	0.49	0.26	0.49	0.34
Grasp a cube 2.5 cm	0.46	0.12	0.50	0.52	0.32	0.52	0.36
Grasp a cube 4 cm	0.45	0.11	0.51	0.53	0.35	0.49	0.33
Mean score	**0.42**	**0.12**	**0.43**	**0.47**	**0.32**	**0.46**	**0.33**
*Qualitative assessment of the spontaneous use of the paretic hand in **bimanual manipulatory activities***							
Hold/throw a big/small ball; Unwrap a packet	0.43	0.22	0.17	0.60	0.36	0.40	0.45
Tear tissue paper; Wrap a packet	0.40	0.37	0.09	0.42	0.27	0.43	0.43
Grasp/drink from baby's bottle/bottle; uncork/fill in a bottle; Fold a sheet	0.37	0.36	0.14	0.35	0.26	0.31	0.48
Grasp a doll; unwrap a packet; Paste paper shapes on the corresponding outlines	0.43	0.34	0.12	0.47	0.48	0.38	0.39
Mean score	**0.41**	**0.32**	**0.13**	**0.46**	**0.35**	**0.38**	**0.44**
*Qualitative assessment of the use of the paretic hand in feeding and clothing **ADL younger***							
Drink from a cup (>18 m)	0.49	0.36	0.41	0.52	0.28	0.47	0.65
Drink form a big glass (>18 m)	0.42	0.37	0.28	0.51	0.36	0.44	0.38
Slice the bread (>18 m)	0.49	0.37	0.46	0.51	0.40	0.43	0.57
Fold a napkin (> 3 yrs)	0.53	0.40	0.50	0.71	0.52	0.49	0.57
Cut with fork and knife (> 6 yrs)	0.57	0.34	0.52	0.82	-	-	0.57
Wash hands (> 2 yrs)	0.44	0.38	0.37	0.28	0.32	0.42	0.50
Wash face (> 2 yrs)	0.46	0.38	0.44	0.29	0.47	0.46	0.34
Take off the shoes (> 2 yrs)	0.41	0.41	0.25	0.38	0.26	0.43	0.45
Take off the socks (>18 m)	0.42	0.34	0.34	0.22	0.33	0.42	0.41
Take off the sweater (> 3 yrs)	0.35	0.23	0.23	0.09*	0.28	0.31	0.34
Take off the trousers (> 2 yrs)	0.42	0.31	0.32	0.01*	0.37	0.40	0.35
Mean score	**0.45**	**0.35**	**0.37**	**0.47**	**0.36**	**0.43**	**0.47**
*Qualitative assessment of the use of the paretic hand in feeding and clothing **ADL older***							
Wear a sweater	0.52	0.79	0.28	- *	-	-	0.52
Wear trousers	0.64	0.82	0.42	- *	-	-	0.64
Wear socks	0.60	0.82	0.37	- *	-	-	0.60
Wear shoes	0.63	0.82	0.39	- *	-	-	0.63
Mean score	**0.60**	**0.82**	**0.37**	**- ***	**-**	**-**	**0.60**
Global Mean score	**0.47**	**0.39**	**0.34**	**0.47**	**0.35**	**0.42**	**0.46**

Table 6.6. ICC for QUEST Scale

		SEVERITY															
		1				2				3				TOTAL			
	AGE	ICC	SS pat	SS obs	SS obs/ SS pat	ICC	SS pat	SS obs	SS obs/ SS pat	ICC	SS pat	SS obs	SS obs/ SS pat	ICC	SS pat	SS obs	SS obs/ SS pat
Dissociate movements	2-3	0.01	49	1.240	25.44	0.04	688	5.745	8.35	0.11	544	5.512	10.14	0.25	5.958	8.853	1.49
	4-5	0.42	11.042	4.488	0.41	0.15	3.600	8.124	2.26	0.24	734	1.109	1.51	0.57	52.107	8.424	0.16
	6-9	0.30	747	735	0.98	0.70	10.045	2.416	0.24	0.66	949	971	1.02	0.82	34.735	2.648	0.08
	TOTAL	**0.43**	**15.931**	**4.067**	**0.26**	**0.34**	**19.085**	**10.428**	**0.55**	**0.43**	**7.485**	**4.452**	**0.59**	**0.59**	**100.453**	**14.432**	**0.14**
Grasp	2-3	0.00	3	2.245	895.30	0.20	4.448	3.913	0.88	0.07	1.281	6.119	4.78	0.48	31.073	5.892	0.19
	4-5	0.28	6.780	2.086	0.31	0.37	9.400	8.994	0.96	0.13	1.641	4.899	2.99	0.63	79.951	8.644	0.11
	6-9	0.34	2.292	3.025	1.32	0.48	13.235	6.242	0.47	0.53	1.908	2.481	1.30	0.66	50.473	5.405	0.11
	TOTAL	**0.28**	**10.918**	**2.919**	**0.27**	**0.36**	**29.999**	**11.961**	**0.40**	**0.20**	**7.611**	**7.198**	**0.95**	**0.61**	**177.954**	**13.112**	**0.07**
Weight bearing	2-3	0.48	5.646	4.206	0.74	0.02	2.580	34.200	13.25	0.45	36.101	18.761	0.52	0.21	56.161	27.377	0.49
	4-5	0.25	2.314	2.235	0.97	0.42	14.130	8.226	0.58	0.14	7.822	19.999	2.56	0.54	90.649	15.621	0.17
	6-9	1.00	480.229	881	0.00	0.57	19.008	4.329	0.23	0.22	303	4.426	14.61	0.97	549.611	6.684	0.01
	TOTAL	**0.97**	**569.174**	**4.255**	**0.01**	**0.17**	**38.521**	**23.031**	**0.60**	**0.35**	**62.330**	**22.653**	**0.36**	**0.71**	**702.901**	**34.579**	**0.05**
Protective extension	2-3	0.60	11.581	3.764	0.32	0.34	20.135	14.891	0.74	0.37	5.970	9.113	1.53	0.39	40.632	18.887	0.46
	4-5	0.18	35.622	27.356	0.77	0.86	377.399	23.640	0.06	0.00	1.903	15.408	8.10	0.62	457.539	30.540	0.07
	6-9	0.92	393.256	12.652	0.03	0.58	40.207	12.415	0.31	0.40	13.470	10.439	0.78	0.84	508.819	22.171	0.04
	TOTAL	**0.72**	**503.797**	**27.637**	**0.05**	**0.77**	**472.976**	**32.490**	**0.07**	**0.30**	**43.436**	**15.769**	**0.36**	**0.69**	**1.031.607**	**50.976**	**0.05**
Global score	2-3	0.56	2.215	1.743	0.79	0.33	3.410	3.791	1.11	0.55	4.257	4.239	1.00	0.56	18.059	7.000	0.39
	4-5	0.34	4.107	2.837	0.69	0.43	4.541	4.915	1.08	0.27	612	1.664	2.72	0.74	50.293	7.195	0.14
	6-9	0.38	1.992	1.478	0.74	0.69	11.845	3.717	0.31	0.72	2.193	1.363	0.62	0.78	38.015	5.151	0.14
	TOTAL	**0.39**	**9.817**	**4.394**	**0.45**	**0.50**	**20.136**	**9.934**	**0.49**	**0.55**	**10.224**	**5.356**	**0.52**	**0.71**	**109.775**	**16.763**	**0.15**

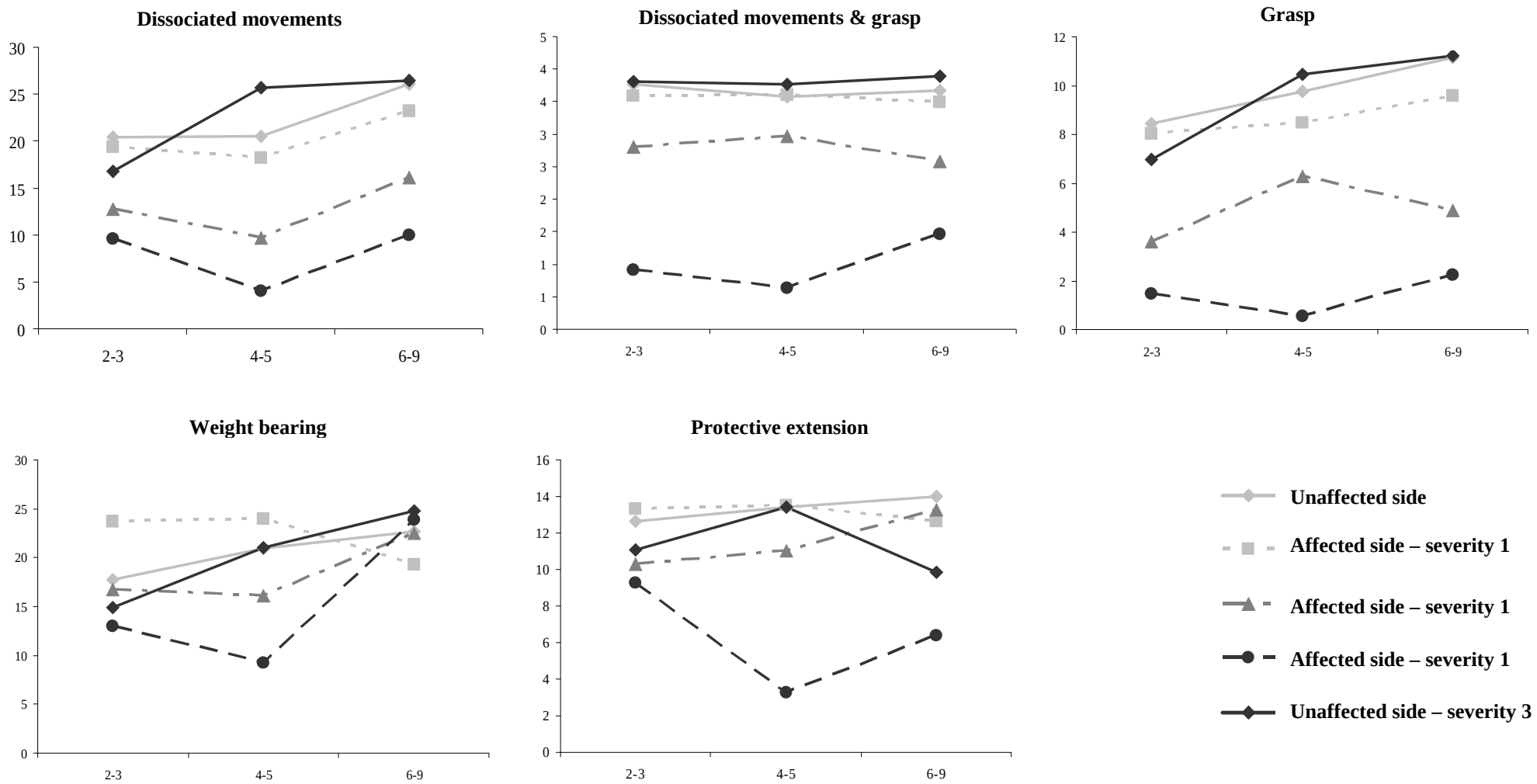
Table 6.7. ICC and the unaffected limb for QUEST Scale

		SEVERITY															
		1				2				3				TOTAL			
	AGE	ICC	SS pat	SS obs	SS obs/ SS pat	ICC	SS pat	SS obs	SS obs/ SS pat	ICC	SS pat	SS obs	SS obs/ SS pat	ICC	SS pat	SS obs	SS obs/ SS pat
Dissociated Movements	2-3	0.31	28	144	5.13	0.67	1.974	967	0.49	0.27	305	1.293	4.24	0.58	3.964	1.462	0.37
	4-5	0.82	8.138	603	0.07	0.71	4.810	1.218	0.25	0.05	19	124	6.53	0.77	15.507	1.352	0.09
	6-9	0.14	164	325	1.99	0.19	146	204	1.39	0.09	10	120	12.16	0.18	451	383	0.85
	TOTAL	**0.76**	**9.350**	**828**	**0.09**	**0.73**	**12.415**	**1.467**	**0.12**	**0.65**	**3.390**	**860**	**0.25**	**0.72**	**25.430**	**2.545**	**0.10**
Dissociated Movements & grasp	2-3	0.00	0	11	295.69	0.00	1	7	6.99	0.00	0	9	42.85	0.00	1	12	12.00
	4-5	0.15	19	30	1.57	0.06	11	32	3.05	0.00	1	8	13.00	0.10	35	35	1.00
	6-9	0.26	25	22	0.91	0.04	6	32	5.25	0.00	0	4	8.29	0.15	35	37	1.06
	TOTAL	**0.16**	**45**	**30**	**0.66**	**0.05**	**23**	**42**	**1.82**	**0.02**	**1**	**10**	**7.06**	**0.09**	**76**	**69**	**0.91**
Grasp	2-3	0.00	0	59	127.42	0.30	181	219	1.21	0.15	44	148	3.39	0.37	490	262	0.53
	4-5	0.15	121	322	2.66	0.60	630	112	0.18	0.36	103	103	1.00	0.42	964	385	0.40
	6-9	0.00	1	54	65.07	0.41	157	57	0.36	0.26	9	36	3.98	0.29	168	99	0.59
	TOTAL	**0.14**	**180**	**248**	**1.38**	**0.53**	**1.354**	**245**	**0.18**	**0.57**	**698**	**151**	**0.22**	**0.45**	**2.453**	**618**	**0.25**
Weight bearing	2-3	0.03	8	223	27.98	0.36	1.031	1.065	1.03	0.68	2.341	385	0.16	0.57	5.146	903	0.18
	4-5	0.11	64	223	3.46	0.65	4.520	781	0.17	0.65	1.408	286	0.20	0.66	8.810	458	0.05
	6-9	1.00	7.700	12	0.00	0.18	248	174	0.70	0.00	0	17	57.32	0.89	9.158	111	0.01
	TOTAL	**0.90**	**8.935**	**152**	**0.02**	**0.59**	**9.386**	**937**	**0.10**	**0.73**	**6.197**	**309**	**0.05**	**0.70**	**26.212**	**929**	**0.04**
Protective extension	2-3	0.11	34	255	7.54	0.18	176	498	2.83	0.21	95	251	2.66	0.25	711	523	0.74
	4-5	0.56	1.548	357	0.23	0.68	3.101	240	0.08	0.46	471	280	0.60	0.59	5.373	413	0.08
	6-9	0.85	3.592	156	0.04	0.48	948	172	0.18	0.48	141	180	1.28	0.75	5.955	267	0.04
	TOTAL	**0.69**	**5.380**	**462**	**0.09**	**0.57**	**5.117**	**435**	**0.08**	**0.44**	**1.025**	**440**	**0.43**	**0.59**	**12.476**	**878**	**0.07**

Table 6.8. ICC and the affected limb for QUEST Scale

		SEVERITY															
		1				2				3				TOTAL			
	AGE	ICC	SS pat	SS obs	SS obs/ SS pat	ICC	SS pat	SS obs	SS obs/ SS pat	ICC	SS pat	SS obs	SS obs/ SS pat	ICC	SS pat	SS obs	SS obs/ SS pat
Dissociated Movements	2-3	0.00	0	273	1136.97	0.14	157	844	5.38	0.01	35	881	25.15	0.48	2.363	1.380	0.58
	4-5	0.78	7.665	744	0.10	0.60	2.660	1.051	0.40	0.16	114	286	2.51	0.79	19.602	1.130	0.06
	6-9	0.40	460	463	1.01	0.79	4.063	508	0.13	0.36	96	238	2.49	0.80	9.623	713	0.07
	TOTAL	**0.73**	**9.322**	**1.043**	**0.11**	**0.67**	**9.476**	**1.490**	**0.16**	**0.38**	**1.380**	**787**	**0.57**	**0.76**	**35.501**	**2.490**	**0.07**
Dissociated Movements & grasp	2-3	0.00	0	25	189.45	0.31	25	28	1.14	0.65	58	24	0.41	0.71	276	52	0.19
	4-5	0.12	16	33	2.05	0.29	50	39	0.79	0.39	25	6	0.22	0.61	440	39	0.09
	6-9	0.28	27	23	0.85	0.29	69	51	0.73	0.70	32	36	1.12	0.46	237	68	0.29
	TOTAL	**0.14**	**43**	**39**	**0.90**	**0.29**	**156**	**84**	**0.54**	**0.52**	**131**	**31**	**0.24**	**0.58**	**993**	**124**	**0.12**
Grasp	2-3	0.16	8	146	18.34	0.43	108	72	0.66	0.29	82	71	0.86	0.70	1.185	157	0.13
	4-5	0.58	568	219	0.39	0.66	634	115	0.18	0.28	18	17	0.94	0.81	3.692	225	0.06
	6-9	0.46	138	145	1.05	0.64	708	111	0.16	0.78	95	27	0.29	0.79	2.645	167	0.06
	TOTAL	**0.52**	**792**	**384**	**0.48**	**0.65**	**1.796**	**209**	**0.12**	**0.44**	**261**	**54**	**0.21**	**0.79**	**8.258**	**463**	**0.06**
Weight bearing	2-3	0.01	13	183	14.02	0.35	951	1.021	1.07	0.75	3.493	411	0.12	0.64	7.083	816	0.12
	4-5	0.00	27	149	5.55	0.76	5.544	352	0.06	0.27	442	2.117	4.79	0.73	15.311	691	0.05
	6-9	1.00	7.605	11	0.00	0.30	1.088	327	0.30	0.00	0	40	945.91	0.78	9.403	245	0.03
	TOTAL	**0.88**	**8.756**	**103**	**0.01**	**0.60**	**10.734**	**665**	**0.06**	**0.70**	**8.928**	**1.187**	**0.13**	**0.71**	**35.101**	**1.120**	**0.03**
Protective extension	2-3	0.05	24	218	9.00	0.31	293	197	0.67	0.43	439	215	0.49	0.38	1.139	279	0.24
	4-5	0.58	2.380	469	0.20	0.82	3.416	152	0.04	0.10	66	749	11.28	0.73	9.943	796	0.08
	6-9	0.92	3.587	88	0.02	0.38	1.465	343	0.23	0.74	982	108	0.11	0.70	7.523	290	0.04
	TOTAL	**0.69**	**6.026**	**383**	**0.06**	**0.59**	**5.738**	**397**	**0.07**	**0.55**	**2.505**	**497**	**0.20**	**0.68**	**19.289**	**959**	**0.05**

Figure 6.1. QUEST. Mean scores of affected hand and unaffected hand distributed by age (2-3; 4-5; 6-9) and by severity of impairment



CHAPTER 7. BEFORE AND AFTER TREATMENT COMPARISON: PRELIMINARY RESULTS

This paper has been submitted to the *American Journal of Physical Therapy and Rehabilitation*

Title

Multisite Trial on Efficacy of Constraint-Induced Movement Therapy in Children with Hemiplegia: Preliminary Results.

Running head

Trial on safety and efficacy of CIMT in children: Preliminary Results

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Background

In children with hemiplegic cerebral palsy (CP), the impairment of upper extremity both in strength and motor control represents an obstacle to exploration, self care and all major activities of daily living, and it has been the main target of several treatment approaches used to improve upper limb function. A review conducted by Boyd et al. [154] in 2001 listed different treatment modalities besides physiotherapy such as splinting, passive stretching, spasticity medication with Baclofen and with Botulin Toxin A, and surgery. Such treatments focus on teaching compensatory skills and prevent deformity, but none of them seems to influence significantly the primary disorder.

More recently, a novel approach – Constraint Induced Movement Therapy (CIMT) has been proposed in these cases. This approach is based on the behavioral research conducted by Taub[155] in the 1980s with non-human primates who underwent deafferentation of a single forearm, followed by intensive forced training of deafferented limb and combined with the restraint of the intact limb. Although varying in its implementation, this treatment is characterized by two elements: a method of restraint in use of the unimpaired limb combined with an intensive practice and with repetitive tasks. In this way the constraint of the non-affected arm is made to encourage performance of therapeutic tasks with the affected arm, which children normally tend to disregard.

CIMT has been used in several studies with adult populations presenting with different acquired conditions such as stroke, traumatic brain injury, and focal hand dystonia[156]. In particular, the results of the EXCITE trial, recently published show

significant larger improvements in the group of patient undergoing CIMT both immediately after treatment and after 12 months. The improvement regards quality and speed of paretic limb movement and amount of paretic arm use in ADL[157]. However a recent review by Cochrane examining 19 RCTs on 619 adults concluded that CIMT has moderately positive effects on disability at the end of treatment[158]. These benefits were demonstrated on other outcomes such as improvement of limb motor function and motor impairment. Patients who seem to benefit most are those with active wrist and finger extension, with limited pain or spasticity. Nonetheless, it is still to be cleared up if CIMT maintains efficacy in the longer term follow-up and if the effect observed can be entirely attributed to CIMT itself rather than on the amount and quality of repetitive exercise. Therefore it is difficult to distinguish the effects of the constraint from those of intensive rehabilitation. Taub and Wolf [159] suggested that the impact on CIMT outcome could be related more to intensity of treatment than to the treatment principle itself.

The past published randomized controlled trials[160, 161, 162, 163, 164, 165] do not give an answer to this question, because in most cases no treatment or very basic treatment was provided to the comparison groups, leading to a possible overestimation of the value of the CIMT compared with other treatment.

The question to be solved is whether similar intensive practice can be elicited with bimanual training without the restraint of the unaffected hand and whether this might result in similar functional results. This hypothesis was supported by Gordon et al.[166] who published in 2007 a randomized trial demonstrating that

bimanual intensive treatment results in a better outcome if compared with no treatment.

More recently Gordon[167], using a quasi-randomized trial, reported that both CIMT and bimanual training lead to improved performance of upper extremity function in children with hemiplegia: the efficacy of CIMT was compared with Hand-Arm Bimanual Intensive Therapy (HABIT) in tw5o groups of 8 hemiplegic children and the outcome measures showed similar improvement in both groups.

The Authors concluded that the amount of improvement is not dependent on use of a restraint and that the goal of Upper Extremity rehabilitation should be the increasing of the functional independence by improving the use of both hand in cooperation. Nonetheless, the small sample size and the lack of data on long term retention of the reported gains in the study result in inadequate power and limitations of this preliminary report.

Only recently CIMT has emerged as a treatment for children with hemiplegic CP with the aim of reversing the behavioral suppression of movement in the affected upper limb.

According to a Cochrane review on CIMT in pediatric age[168], evidence on this treatment is very poor and limited, since all currently available trials reveal methodological limitations and need for additional research to support the application of this treatment in pediatric age. To date, four trials have been published in the international literature[160, 161, 164, 165].

The study group of Gordon & Charles demonstrated that CIMT treatment showed a significant measurement occasion effect, that was mantained at 3 weeks' post

treatment. The control group used for comparisono purpouse showed no significant changes over time.

According to research studies conducted by Eliasson and collegues, Children who received CIMT improved their ability to use their hemiplegic hand significatively, particularly those with a high level of severity in hand function impairment seemed to benefit most. Furthermore, older children seemed to improve more than younger with CIMT, as did children with cortical/subcortical lesion if compared to children with periventricular white matter lesions (this result was not statistically significant). The effect size of CIMT was high after treatment and medium at 6 months.

Studies published by Sung showed a significant treatment effect at 6 weeks on one outcome measure (self care component), while for all other measures it was demonstrated a trend favoring forced use, but no significant treatment effect.

A research published by Taub & DeLuca demonstrated significant measurement occasion effect after CIMT, that was maintained 3 weeks after treatment end, while in control group had no significant changes across measurements occasions were observed.

Nonetheless, as concluded in the Cochrane review, these results have to be taken cautiously since the studies are underpowered and differ significantly in terms of methodological procedures, as method of restraint, length of restraint, type and duration of therapy, intervention environment and intervention provider. Moreover, the differences in measurement tools adopted and the scarcity of valid and reliable tools to measure the outcome in children on the functional use of

hemiplegic hand in bimanual task of ADL, makes even more difficult to verify the effectiveness of CIMT approach.

Furthermore, the influence of several factors on response to treatment is still not fully understood, such as the roles of child's age, severity of motor and sensory impairment, presence of comorbidities, child's cognitive abilities and compliance to restraint of the unaffected arm.

Recently the attention of research studies has been devoted to understand the process of corticospinal reorganization following the injury and to clear how CIMT can effectively influence, modulate or modify this phenomenon.

In CP children, these cortical modifications usually occur in the very early phases both in the affected and unaffected hemispheres. In some patients, the ipsilateral corticospinal projections – normally transient – are not withdrawn, but persist and they allow the patient to control the paretic hand ipsilaterally, while in other patients the crossed projections are preserved so that they can control their hand with the affected hemisphere. In this second case, the sensorimotor loop is preserved and seems to be crucial for effective motor learning during CIMT.

Some Authors have hypothesized that patients with different types of corticospinal organization - whether the patient has an ipsilateral or a controlateral control of the affected limb - could respond differently to CIMT. The results suggest that CIMT can influence the time required to execute the task (e.g. Contra group patients are faster that Ipsi group patients)[169 170].

As suggested by Martin and colleagues, the use of a restraint in the non-affected limb could cause a motor impairment, as some analysis on animal models have shown[171], and compromise the non-affected-side ability.

Neuroimaging techniques, in particular the functional Magnetic Resonance Imaging (fMRI), have been used to study the cortical reorganization following rehabilitation treatment and it opened new opportunities to verify the changes induced by different approaches. You and colleagues[172] reported in an hemiplegic child a shift in the functional MRI laterality index to the controlateral hemisphere after virtual reality treatment with bimanual activities.

In a study carried out by Sutcliffe and colleagues[173], an hemiplegic child treated with CIMT showed at fMRI bilateral sensorimotor activation before and after treatment and a shift in the laterality index from ipsilateral to controlateral hemisphere after therapy. To date, however the fMRI is available only for children over 7-8 years of age and in an experimental context, and therefore its clinical use is very limited.

Aim of the study

Aim of this study is to measure the effect of CIMT on patients with hemiplegic CP immediately after the end of 10-weeks intensive treatment practice. The result are to be compared with two comparison groups of patients: in one children are treated with an Intensive Rehabilitation Program of bimanual training and in the other with a traditional treatment. This design choice allows us to distinguish the constraint's effects from those of intensive rehabilitation, and assess the real effectiveness of hand restraint.

In the present paper we present the preliminary results of the trial, specifically the comparison of the primary outcome measures in the 3 groups of hemiplegic children at baseline and post-treatment period.

Materials and Methods

Study design

The study has been designed as a multicenter, prospective, cluster-randomized controlled clinical trial. The effect of CIMT (intended as restraint of unaffected limb combined with unimanual intensive rehabilitation program, *group 1*), is compared with a comparison group undergoing bimanual Intensive Rehabilitation Program (bimanual IRP, *group 2*), and a second comparison group receiving a traditional rehabilitation program (standard treatment ST, *group 3*). The comprehensive description of study design and methodology of the trial has been previously published[174]. The comparisons between group 1 vs 2 may highlight the effect of restraint and the comparisons between group 1 vs 3 and group 2 vs 3 may show the effect of intensive practice of movements and exercises. The traditional rehabilitation treatment has been considered as the baseline treatment.

Due to possible organizational difficulties within the rehabilitation services and the subsequent impossibility to randomize patients by treatment group for 3 different treatment approaches in every single clinical center, the Authors have chosen a cluster randomization design[175, 176 177, 178].

21 clinical sites located in 8 Italian regions took part in the research project. At least 2 clinicians per center were involved in the research project, a physician (neuro-pediatrician or physiatrist) and a physiotherapist. All the centers involved

in the research study belong to the Italian Group of Cerebral Palsy (G.I.P.C.I.). 2 supervisors of outcome measures examined videotapes of all evaluations of patients from each treatment group and they were blinded to treatment allocation.

Sample Size and Power

A sample of 111 participants has been recruited (with an estimated 10% drop out), with a delta value set at 30%, ($1-\beta = 0.80$, $\alpha = 0.05$, $\pi_i = 0.15$). 37 cases have been enrolled in 7 centers for CIMT, 37 cases in 7 centers for IRP and 37 case in 7 centers for traditional treatment.

Inclusion and Exclusion Criteria

Patient inclusion criteria were: age range between 2 and 8 years, diagnosis of hemiplegic cerebral palsy (anamnestic, clinical and neuroimaging documentation to be collected) according to Hagberg's classification[179]. To avoid the confounding effects of other intervention studies, potential participants have been excluded from the study if they have previously undergone restraint therapy or have received injections of anti-spasticity drugs into UE musculature (e.g., botox). Differing clinical severity and/or comorbidity with other diseases (e.g. epilepsy, mental retardation) do not constitute exclusion criteria, but have been used to describe clinical variability.

Participants' motor criteria were divided into 3 groups: 1) mild, 2) moderate, and 3) severe motor impairment, based on and modified from criteria set by Beckung et al[180] and Eliasson et al[181].

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.

Treatment groups: main characteristics

Group 1. Constraint Induced Movement Therapy (CIMT) (glove plus unimanual Intensive Rehabilitation Program). 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, and prevents the ability to grasp.

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 or the therapist and/or parents and without removing the glove. During the treatment period, children underwent an intensive rehabilitation program based on unimanual activities. Sessions were held 3 times weekly (lasted 3 hours divided in 1 hour and ½ with the therapist and 1 hour and ½ with parents) at the Rehabilitation Center: an individual therapist encouraged the child to solve tasks requiring the unilateral use of the paretic hand. Parents were trained to carry out similar 3-hour sessions at home on the remaining 4 days, as showed at the Rehabilitation Center (specific unilateral tasks during play and daily living activities).

Group 2. Bimanual Intensive Rehabilitation Program (IRP). Children were treated for hand impairment according to the same approach described above, and with the same schedule (3 hours a day, 3 times a week, half sessions with the

therapist and half sessions 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. Parents were trained to carry out similar 3-hour sessions at home on the remaining 4 days, as showed at the Rehabilitation Center (specific bimanual tasks during play and daily living activities).

Group 3. Standard treatment (ST). This group includes children affected by cerebral palsy currently treated in territorial Rehabilitation Services. They usually undergo 1-hour standard rehabilitation sessions once or twice a week and the session frequency differs in relation to child's age. Infants receive physiotherapy twice a week, while preschool and school-age children attend occupational therapy once a week (40-60 min).

The full description of treatment sessions for each group has been previously and published[174] and is fully illustrated in Annex 7.1.

Primary Outcome Measurements

Primary outcomes were assessed in 2 major domains: UE motor ability (QUEST[182]) and hand function assessment evaluating both grip function and the spontaneous use of the affected side (Besta Scale).

QUEST (Quality of Upper Extremity Skills Test) explores four main domains: dissociated movements, grasp, protective extension and weight bearing. All items were scored for both arms using a dichotomous scale and percentage scores were calculated[183]. This characteristic allowed us to assess separately the function of each hand (affected and unaffected).

The Besta Scale was developed in 1985 to assess quality of grip (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 Annex 7.2. Several studies have been perform to test validity, reliability and inter-observer agreement[184, 185, 186].

In the scale, grip assessment is performed in a standardized setting, asking the child to pick up different sized cubes on request. The quality of grip is videotaped and scored in a hierarchical way (from 0 to 3). Spontaneous use is assessed during structured activities and activities of daily living (ADL) requiring both hands and being standardized according to age. The scoring system for the quality of manipulation is based on variability and stereotypy of movement pattern according to Touwen[187].

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

Secondary Outcome Measurements

Besides the general assessment (anamnesis, objective and neurologic exams), in order to assess the child's overall development and if it is influenced by the treatment assigned, the evaluation sessions before and after treatment included additional tests assessing: a) the patients' cognitive level (Wechsler/ Griffiths scales, according to patient age), b) general motor development (Gross Motor Function Measure), c) the level of familial stress (Parenting Stress Index[188]), d) parents evaluation of the child's autonomy in daily living activities (Parents Besta

Scale), e) the child behavioral changes (Child Behavior Checklist[189]), f) and treatment satisfaction and compliance perceived by parents (ad hoc questionnaire).

Training, standardization and agreement

Before starting the controlled trial, a specific training program was provided to familiarize professionals (both principal investigator and therapist) with testing and training procedures in order to develop a homogeneous administration and videotaping of the QUEST and Besta Scale tests[174]. A specific training at the Rehabilitation Center and a dedicated booklet with a DVD (Figure 7.1) was provided to 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 planned to be collected before commencing the trial: anamnestic and main clinical data, personal information, level of UE motor impairment severity, the presence of other diseases and/or disabilities. The data collected from patients recruited so far are summarized in Table 7.1.

To verify non-random distribution of patients within the cluster – e.g. in order to measures the degree of similarity among responses to treatment *within a cluster* - the intra-cluster correlation coefficient was estimated[190] and the "cluster-effect" was estimated calculating *IF,* the ratio between intra-cluster variability and inter-cluster variability of treatment effect outcome measure[174, 191].

To verify if the individuals were randomly distributed within the clusters, we utilized the IF of the main covariates such as age, severity of impairment, IQ and parents' education level. No significant differences among variables inter and intra-clusters were observed by age class, level of severity of hemiplegia and IQ values, in enrolled children (Table 7.1).

Primary outcomes analysis

The analysis regarding the primary outcome measures has been carried out considering the differences on the global score of both Besta Scale and QUEST before and after treatment for each treatment group. Moreover, the subscales have been studied separately in order to verify the effect on specific skills and patterns of movement (e.g. fine grasp or weight bearing for QUEST and spontaneous use in ADL for Besta Scale). Wilcoxon signed-rank test for non parametric paired samples t-test was utilized to test statistical significance.

For the comparison among treatment groups (1 vs 2 vs 3; 1 vs 2, 2 vs 3 and 1 vs 3) percentualized differences on the global and subscale scored have been calculated. Respectively, Kruskal-Wallis Test for non parametric version of ANOVA was utilized to test statistical significance for 3-groups comparison (1 vs 2 vs 3) and Mann-Whitney test for non parametric independent samples t-test for paired groups comparisons (1 vs 2, 2 vs 3 and 1 vs 3).

Results

Between march 2006 and January 2009, 105 patients were recruited and assigned to the treatment groups Constraint Induced Movement Therapy (n=39), bimanual Intensive Rehabilitation Program (n=33) and Standard Treatment (n=33). At

baseline, there were no significant differences between the study groups on demographic (age), severity of impairment and cognitive level characteristics (Table 7.1). One patient recruited in the IRP group withdrew the program because the family moved and did not undergo the post-treatment assessment.

Effects of 3 treatment approaches on primary outcomes

Before and after treatment, for all the treatment approaches changes were observed in the primary upper-extremity outcome variables. The changes are much more relevant for the children undergoing an intensive rehabilitation program - both CIMT and bimanual IRP – if compared with the ST group (Table 7.2). The changes are statistically significant in the global score before and after treatment of the 2 groups (CIMT and IRP group) of children assessed with the Besta Scales ($\mathbf{\Delta_{CIMT}}$=0.23 p=0.002; $\mathbf{\Delta_{IRP}}$=0.23 p<0.0001), and QUEST scale ($\mathbf{\Delta_{CIMT}}$=7.12 p<0.0001; $\mathbf{\Delta_{IRP}}$=4.43 p=0.0143). Compared to IRP and ST, in children treated with constraint (CIMT group) the improvement in grasp function is more relevant and statistically significant in both assessment tools (Besta: $\mathbf{\Delta_{CIMT}}$=0.30 p=0.0019; QUEST: $\mathbf{\Delta_{CIMT}}$=7.12 p=0.0003). Moreover, all the specific dimensions explored by QUEST show a higher significant change only for CIMT group. On the contrary, in children treated with bimanual intensive rehabilitation (IRP group) the improvement is more significant in activities of spontaneous use ($\mathbf{\Delta_{IRP}}$=0.28 p=0.0005) and ADL ($\mathbf{\Delta_{IRP}}$=0.25 p=0.0001) at Besta scale.

3 treatment approaches: comparison analysis (1 vs 2 vs 3)

Comparing the 3 treatment groups of children at QUEST, the statistical analysis shows a significant difference in the global score ($\mathbf{\Delta_{CIMT}}$=11.3 vs $\mathbf{\Delta_{IRP}}$=6.5 vs

Δ_{ST}=2.0; p=0.0049) and in protective extension (Δ_{CIMT}=21.6 vs Δ_{IRP}=5.1 vs Δ_{ST}=-2.6; p=0.0391) (Table 7.3).

Comparing the outcome of the affected limb vs the non affected limb at QUEST scale, the results show a significant improvement in children treated with CIMT for the affected hand, particularly for the grasp function (p<0.0001). On the contrary, children treated with bimanual intensive treatment (IRP) show a significant improvement in the non affected hand after 10-weeks of treatment, while CIMT patients show a worse function for grasp ($\Delta\%_{CIMT}$=-2.4 $\Delta\%_{IRP}$=5.7 $\Delta\%_{ST}$=-2.9; p=0.0521) (Table 7.3).

At Besta Scale, no significant differences were observed except from the comparisono of 3 treatment groups in the ADL in older children. In this case, the CIMT group showed a worsening in score($\Delta\%_{CIMT}$=-6.9), IRP showed no improvement ($\Delta\%_{IRP}$=0.0) while ST showed an improvement ($\Delta\%_{ST}$=7.0). This difference was significant (p=0.0365) (Table 7.3).

3 treatment approaches: comparison analysis (1 vs 2; 2 vs 3; 1 vs 3)

CIMT vs Standard Treatment. In this analysis, the results previously noted were confirmed. In particular, the CIMT group shows a significant improvement in global score and in grasp function in both outcome measures compared to Standard treatment (Table 7.4).

IRP vs Standard Treatment. The bimanual intensive rehabilitation is more effective compared to standard treatment, mostly in global scores and in ADL in younger children (Table 7.4).

CIMT vs IRP. This comparison demonstrated that CIMT is more effective in improving grasp function in Besta scale, while there is no significant difference in any of the dimensions of QUEST scale.

Discussion

In the past decade, in the international literature a growing attention has been devoted to study the Constraint Therapy as a new rehabilitation approach both for adults with an acute cerebral injury (such as stroke) and in children with hemiplegic cerebral palsy. Its pediatric application represents a 'paradigm shift', as noted by Brady&Garcia[192], in rehabilitation of hemiparesis, emerging from the confluence of behavioral learning theory and discoveries in neurosciences regarding neuro-plasticity.

While in adults population CIMT efficacy has been documented[157], in children the evidence on this approach is still debated, as stated by the Cochrane review recently published[168]. Many aspects (namely the method of constraint, frequency and intensity of practice, intervention environment and social context, intervention principles, individual characteristics of children and outcome measures) varied significantly in the three trials published[160, 166, 167] particularly in relation to intensity of treatment and in samples size.

Our multisite clinical trial for the first time has compared two groups of children with hemiplegia treated with intensive rehabilitation practice - one with restraint of the affected hand and unimanual rehabilitation treatment (CIMT group) and one with bimanual rehabilitation treatment without restraint (IRP group) - using

an adequate sample size of patients. Moreover, a third control group of children, considered as a baseline standard treatment, was recruited for comparison purpose, for a total recruitment of 105 children.

The design characteristics allowed to utilize the results to analyse the efficacy and safety of constraint therapy with a sufficient power and to distinguish the plus value given by the intensity of the practice (given the presence of 3 separate treatment groups).

Our results demonstrate that a substantial improvement of paretic hand function was observed in children treated both with restraint of the unaffected hand and intensive unilateral practice and those treated with intensive bilateral practice without restriction, while children of the standard group showed minimal or no changes of hand function. The higher effect of intensive treatment has already been suggested and seems to be apparently stronger for younger children[193].

These results are in accordance with those reported by Gordon and colleagues that underline the importance of intensity of treatment on the outcome rather that the restraint itself in improving motor performance[194]. This interesting result if confirmed, would change radically the approach to rehabilitation in children.

Secondly, children treated with Constraint of the unaffected hand and intensive unilateral practice (CIMT group) showed a significant improvement in comparison with children treated with intensive bilateral practice (IRP group) on what attains fine grasp abilities of the affected hand assessed both with QUEST and Besta Scale. This datum is of particular interest if its presence will be

observed at 3, 6 and 12 months after the end of treatment, during the follow-up phases of trial.

According to recent studies on cats, the activity-based therapy on an intensive treatment basis seems to lead to important changes in the cortical reorganization process[195].

All the aspects related to early motor system development and brain plasticity should be carefully considered, exploring mechanisms through which CIMT can induce neuroplasticity (both in function and in structure), produce gains/losses in motor function, and ultimately which children would benefit most[169 196 197]. All recent advances in the understanding of post-lesional reorganization processes seem to demonstrate that there are different patterns of possible development after injury (some of them aberrant) and that several factors related to the type and the dimension of the lesion and to the child himself– not least genetic and environmental factors – may influence the future development of hand function and in the end the possible beneficial effect of CIMT or intensive practice[198, 199, 200].

The results of a recent study by Sutcliffe and colleagues[201] suggest that a shift to or persistence of controlateral cortical activity for affected hand movement is important for constraint therapy mechanism of action and that developmental disregard may be a predictor of positive response to treatment.

Similar plasticity patterns have been observed and demonstrated in children with strabismus, where controlled daily monocular deprivation leads to improved

performance of the impaired eye without deterioration of the well sighted eye or the case of amblyopia[202].

These preliminary results on animals seem to demonstrate that CIMT result particularly efficient for limited treatment periods and to permit sufficient plasticity on the affected side[203], in the development of particular abilities, in the precocious development phases. It is suggested that activity-based therapy should be synchronized with specific corticospinal system developmental periods[195].

This could explain the figures regarding the ADL where an improvement is demonstrated in younger children. On the contrary, in older children an apparent worsening is shown in ADL in CIMT group. This datum should be deeply explored in subsequent follow-up phases and should be further understood.

At stake, Authors suggest to modulate the intervention with a cost-benefit approach, particularly in younger children where the risks of compromising the uninjured side are higher and the recovery possibilities of the affected side are wider.

CIMT is mostly effective in ameliorating pinch type and the hand performance on request and not in global movement and on spontaneous use. In particular for QUEST – that is an impairment-based measure with a small number of items that address activity performance-, the improvements observed in results may reflect gains in range of motion and biomechanical alignment as a result of casting of unaffected hand[204].

On the contrary, the bimanual spontaneous use of the affected hand in self care activities is significantly improved by the intensive rehabilitation program (with and without restraint).

Even if some Authors suggested that learned non-use can be overcome more efficiently on the grip function, Steenbergen and colleagues sustain that is still to be demonstrated that the child will apply directly the gains while acting in spontaneous use during daily activities and play activities[205].

An interesting result that will need further attention in follow-up assessment phase is the quality of unaffected arm movements. Utilizing the QUEST items separately for affected and unaffected arm, results have shown that the unaffected limb shows a significant global improvement in movement in children treated with Intensive Rehabilitation Program (bimanual training) without restraint. On the contrary in the group treated with CIMT this has not been observed and apparently, neither amelioration due to growth nor an improvement due to intensive practice is observed. A similar effect has been observed in other research studies[206]. If this trend will be confirmed in the subsequent phases, it would confirm the hypothesis that *"two hands are better than one"*[207] and that bimanual training should be always considered as an intensive treatment option in improving bimanual skills development and longitudinal development of hand function[208].

All these results should be considered as preliminary and will be further explored while considering the secondary outcome and the persistence of gain in hand and global motor improvement[209].

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Tables & Figures

Table 7.1. Baseline participant characteristics

Characteristics	CIMT (n=39) N (%)	IRP (n=33) N (%)	ST (n=33) N (%)	p value
Age				0.2420
< 3	10 (*26*)	13 (*40*)	9 (*27*)	-
3-5	18 (*46*)	15 (*45*)	15 (*46*)	-
6-8	11 (*28*)	5 (*15*)	9 (*27*)	-
Female	20 (*51*)	16 (*48*)	16 (*48*)	-
Hemiplegia: side (right)	24 (*62*)	15 (*45*)	17 (*52*)	-
Hemiplegia: level of severity				0.6009
1	9 (*24*)	10 (*30*)	7 (*22*)	-
2	15 (*38*)	12 (*36*)	18 (*54*)	-
3	15 (*38*)	11 (*34*)	8 (*24*)	-
Gestational Age, months (SD)	36.3 (*5.2*)	35.4 (*8.5*)	36.9 (*4.5*)	-
Age of onset (months) (SD)	2.7 (*5.9*)	3.4 (*4.2*)	7.5 (*11.5*)	-
Cognitive disturbances (yes)				0.0738
normal	24 (*66*)	27 (*93*)	22 (*73*)	
clinical	12 (*33*)	2 (*7*)	8 (*26*)	
Stereognosis alterations (yes)	3 (*8*)	4 (*14*)	3 (*15*)	-
Speech/ language delay (yes)	9 (*24*)	6 (*21*)	7 (*29*)	-
Mood disturbances (yes)	5 (*13*)	6 (*21*)	5 (*23*)	-
Visual Impairment (yes)	10 (*26*)	0 (*0*)	2 (*10*)	-
Visual attention disorders (yes)	5 (*13*)	1 (*4*)	2 (*10*)	-
Hearing impairment (yes)	1 (*3*)	0 (*0*)	0 (*0*)	-
Associated malformations (yes)	6 (*16*)	1 (*4*)	0 (*0*)	-
Epilepsy (yes)	5 (*13*)	3 (*10*)	3 (*13*)	-
Other comorbidities (yes)	4 (*11*)	0 (*0*)	0 (*0*)	-

Abbreviations: CIMT Constraint Induced Movement Therapy; IRP Intensive Rehabilitation Program; ST Standard Treatment.

Table 7.2. Besta Scale assessment: effect of the 3 treatment approaches at post-treatment on primary outcomes

	Besta Scale					***QUEST***			
	Baseline	*Post-treatment*	*Δ*	*p value*		*Baseline*	*Post-treatment*	*Δ*	*p value*
CIMT									
Global score	2.39	2.62	0.23#	*0.0002*	Global score	70.9	78.1	7.12#	*<0.0001*
Grasp	2.87	3.15	0.30#	*0.0019*	Grasp	65.7	72.8	7.12#	*0.0003*
Bimanual spontaneous use	2.52	2.77	0.24**	*0.0079*	Dissociated movements	72.0	78.1	6.09#	*<0.0001*
ADL (younger)	1.88	2.09	0.22*	*0.0116*	Protective extension	61.6	70.2	8.58*	*0.0246*
ADL (older)	3.06	2.85	-0.19	*0.1250*	Weight bearing	84.6	91.2	6.63#	*0.0099*
Intensive Rehabilitation Program									
Global score	2.52	2.75	0.23#	*<0.0001*	Global score	72.5	76.9	4.43*	*0.0143*
Grasp	2.80	2.88	0.09	*0.2627*	Grasp	69.3	72.9	3.66	*0.1881*
Bimanual spontaneous use	2.66	2.95	0.28#	*0.0005*	Dissociated movements	77.3	80.4	3.08*	*0.0358*
ADL (younger)	2.34	2.55	0.25#	*0.0001*	Protective extension	69.3	71.6	2.28	*0.5710*
ADL (older)	4.00	3.25	-§	-§	Weight bearing	73.8	82.7	8.87**	*0.0012*
Standard Treatment									
Global score	2.63	2.69	0.06	*0.2112*	Global score	71.3	72.6	1.29	*0.0915*
Grasp	2.96	3.02	0.06	*0.4956*	Grasp	65.9	68.4	2.51	*0.1729*
Bimanual spontaneous use	2.87	3.01	0.16*	*0.0283*	Dissociated movements	72.7	75.4	2.74	*0.1786*
ADL (younger)	2.14	2.19	0.05	*0.5003*	Protective extension	66.4	64.9	-1.56	*0.4716*
ADL (older)	2.83	3.17	0.34	*0.1250*	Weight bearing	80.1	82.7	2.53	*0.2197*

Abbreviations: CIMT Constraint Induced Movement Therapy; IRP Intensive Rehabilitation Program; ST Standard Treatment.

Wilcoxon signed rank test - non parametric paired samples t-test * p<.05; ** p<.01; # p<.001; §due to the small number of cases the test was not performed

Table 7.3. Comparison among the 3 treatment approaches (CIMT vs IRP vs ST)

Besta Scale				**QUEST**				***Affected limb***				***Non Affected limb***			
		Δ%	***p value***			**Δ%**	***p value***	**baseline**	**Post-treatment**	**Δ%**	***p value***	**baseline**	**Post-treatment**	**Δ%**	***p value***
Global score	**CIMT**	13.2		Global score	**CIMT**	11.3		50.4	58.6	22.7		77.8	78.7	1.5	
	IRP	11.4	*0.1350*		**IRP**	6.5	*0.0049*	49.8	56.1	18.3	0.0730	77.7	81.2	5.1	0.2684
	ST	4.5			**ST**	2.0		51.4	54.5	6.3		75.7	77.7	3.2	
Grasp	**CIMT**	17.9		Grasp	**CIMT**	12.5		5.4	7.4	92.4		11.5	11.2	-2.4	
	IRP	5.7	*0.1581*		**IRP**	6.6	*0.4449*	6.0	6.7	34.2	*<0.0001*	11.8	12.3	5.7	0.0521
	ST	4.5			**ST**	6.6		6.3	6.2	2.5		12.1	11.8	-2.9	
Bimanual spontaneous use	**CIMT**	14.9		Dissociated movements	**CIMT**	10.0		14.3	16.6	22.8		26.4	27.1	4.1	
	IRP	15.6	*0.7886*		**IRP**	4.2	*0.4183*	16.4	17.2	4.7	0.3276	27.6	28.3	3.1	0.8854
	ST	10.5			**ST**	5.6		14.4	16.0	15.5		26.1	27.0	7.2	
ADL (younger)	**CIMT**	17.1		Protective extension	**CIMT**	21.6		11.6	13.9	120.2		17.8	17.8	1.7	
	IRP	12.8	*0.2876*		**IRP**	5.1	*0.0391*	12.1	14.4	139.0	0.9267	17.1	18.1	8.8	0.5589
	ST	6.7			**ST**	-2.6		12.3	14.2	79.6		16.7	16.5	1.0	
ADL (older)	**CIMT**	-6.9		Weight bearing	**CIMT**	11.1		22.1	23.7	18.3		25.1	25.7	3.9	
	IRP	**0.0**	*0.0365*		**IRP**	14.6	*0.8695*	18.4	20.7	15.8	0.0480	24.2	25.5	6.8	0.6282
	ST	7.0			**ST**	9.8		21.5	21.2	1.3		24.2	25.3	11.2	

Abbreviations: CIMT Constraint Induced Movement Therapy; IRP Intensive Rehabilitation Program; ST Standard Treatment.
Kruskal-Wallis Test for non parametric version of ANOVA

Table 7.4. Comparison among the treatment approaches (CIMT vs IRP; IRP vs ST; CIMT vs ST)

Besta Scale	CIMT vs ST p value	CIMT vs IRP p value	IRP vs ST p value
Global score	0.0536*	0.3797	0.0336*
Grasp	0.0463*	0.0591*	0.4359
Bimanual spontaneous use	0.3860	0.3960	0.2195
ADL (younger)	0.1217	0.4772	0.0610*
ADL (older)	0.0073*	0.2944	0.2623
QUEST	**CIMT vs ST p value**	**CIMT vs IRP p value**	**IRP vs ST p value**
Global score	0.0014**	0.1628	0.0297*
Grasp	0.1401	0.2665	0.4223
Dissociated movements	0.0241*	0.1515	0.1417
Protective extension	0.0173*	0.1363	0.1340
Weight bearing	0.1722	0.2322	0.0317*

Abbreviations: CIMT Constraint Induced Movement Therapy; IRP Intensive Rehabilitation Program; ST Standard Treatment.
Mann-Whitney test for non parametric independent samples t-test

Figure 7.1. Booklet for parents' training entitled: *"Learning by playing. Suggestions for the development of manipulation ability for the hemiplegic child in play and daily living activities"*. Cover (A) and sample pages (B, C).

Annex 7.1 – Treatment groups

Group 1. Constraint Induced Movement Therapy (CIMT) (glove plus unimanual Intensive Rehabilitation Program). 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, and, thereby, prevents the ability to grasp (Figure 1). The thumb is kept in a fixed position tight against the index finger. The children could, however, use the hand for support or for breaking a fall. 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 or the therapist and/or parents and without removing the glove.

During the treatment period, children underwent an intensive rehabilitation program based on unimanual activities. They were treated for hand impairment according to a motor learning approach during play sessions and activity of daily living (ADL). Sessions were held 3 times weekly at the Rehabilitation Center: an individual therapist encouraged the child to solve tasks requiring the unilateral use of the paretic hand. Task goals referred to 4 main domains: (1) perceptual motor activities; (2) activities of reaching, grasping, holding and manipulating; (3) postural and balance activities; (4) self-care and daily living activities. The full description of treatment sessions with unimanual activities have been previously described[174].

Sessions lasted 3 hours: during the first part of the session (1 hour and ½) the therapist interacted with the child proposing unimanual activities of an appropriate

level of difficulty, in relation to age and motivation. In the second part of the session (1 hour and ½) parents, who cooperate during all the 3 hours sessions, were instructed to interact with their own children by proposing them unilateral tasks in play and daily living activities. Parents were trained to carry out similar 3-hour sessions at home on the remaining 4 days, as showed at the Rehabilitation Center (specific unilateral tasks during play and daily living activities).

Group 2. Bimanual Intensive Rehabilitation Program (IRP). Children were treated for hand impairment according to the same approach described above, and with the same schedule (3 hours a day, 3 times a week, half sessions with the therapist and half sessions 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. Parents were trained to carry out similar 3-hour sessions at home on the remaining 4 days, as showed at the Rehabilitation Center (specific bimanual tasks during play and daily living activities).

Task goals referred to the same 4 main developmental domains, but they implied a bimanual use in play and daily living activities. The full description of treatment sessions with bimanual activities have been previously described[174].

Group 3. Traditional treatment. This group includes children affected by cerebral palsy currently treated in territorial Rehabilitation Services. They usually undergo 1-hour standard rehabilitation sessions once or twice a week and the session

frequency differs in relation to child's age. Infants receive physiotherapy twice a week, while preschool and school-age children attend occupational therapy once a week (40-60 min).

Annex 7.2 - 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 bilia	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 form 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 form a big glass (>18 m)	0	1	2	3
Slice the bread (>18 m)	0	1	2	3
Fold a napkin (> 3 yrs)	0	1	2	3
Cut with fork and knife (> 6 yrs)	0	1	2	3
Wash hands (> 2 yrs)	0	1	2	3
Wash face (> 2 yrs)	0	1	2	3
Take off the shoes (> 2 yrs)	0	1	2	3
Take off the socks (>18 m)	0	1	2	3
Take off the sweater (> 3 yrs)	0	1	2	3
Take off the trousers (> 2 yrs)	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

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**
(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

CHAPTER 8. PRIMARY AND SECONDARY OUTCOME MEASURES IN THE FOLLOW-UP PHASE

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Title

Constraint Induced Movement Therapy in hemiplegic cerebral palsy: follow-up after 3 months from the end of treatment

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Background

The administration of Constraint Induced Movement Therapy (CIMT) in children with hemiplegic cerebral palsy is still object of a debate in the international literature[210] [211]. While in adults this new therapeutic approach has been demonstreated as being useful in ameliorating the upper limb function, its application in children still needs further exploration to be fully delivered to patients with hemiplegic cerebral palsy[212].

The basis for this approach originates from seminal studies by Taub of monkeys that had undergone deafferentation[213, 214]. Taub demonstrated that animals forced to use the affected upper extremity through immobilization of the intact limb for short periods could soon learn to use the insensate limb even when the use of both limbs was possible. Training of the monkeys that had undergone deafferentation during the forced-use period was achieved through successive approximations as the basis for shaping intended movement. The animals would be rewarded as they progressively reached toward and subsequently grasped objects. Taub proposed that the animals had undergone "learned nonuse" of the affected limb and, given the appropriate behavioral training, could relearn to use it indefinitely. Although the duration of the effect of deafferentation was never assessed, Taub proposed that this approach be used for patients with hemiparesis and presumed that the diaschisis after stroke led to a learned suppression of movement comparable to the suppression of the spontaneous limb use in monkeys that had undergone cervical deafferentation.

Although great expectations are posed on this novel approach, there are still many aspect that need thoroughly exploration and research. The question arisen form researchers regard its real efficacy on function, cortical reorganization and plasticity[215], and also the persistence of the observed effect in time[216].

According to recent publications in fact, this therapy result effective in amelioration the upper limb motor performance, particularly in the grasp function on request, but it is still unclear if this new abilities acquired could be directly engaged in performing complex activities such as the common ADL[217].

If this therapy would be confirmed as effective additional questions will need an answer: one of the most interesting regards the possibility to predict which children would benefit most, which characteristics of the child will orient the professionals in proposing to the child and the family this therapeutic approach. It is still unclear in fact which is the best age at which the cost-benefit balance of CIMT is advantageous for the patient, or again which disability profile and which level of impairment can benefit from affected harm casting. For example, in adults one of the predictors of CIMT successful application has been demonstrated to be the ability of the patient to initiate finger extension[218].

Finally, according to recent advances in the understanding of neuronal plasticity and influence to cortical reorganization processes, CIMT seems to play a major role in influencing this process. Looking more deeply into structural modifications, it is still object of researches how the process of cortical reorganization (contralateral vs ipsilateral) can modify the CIMT effect and translate it differently into function[219]. Recent studies have explored the

interhemispheric influences on movement initiation or control, the intracortical inhibition of the contralateral (affected) motor cortex[220, 221, 222]. Severe impairment might result from hyperactive cortical inhibitory interneurons rather than direct disruption of descending motor system[223].

Aim of this study is to measure the persistence of the effect of CIMT on patients with hemiplegic CP 3 months after the end of 10-weeks intensive treatment practice. The result are to be compared with two comparison groups of patients: in one children are treated with an Intensive Rehabilitation Program of bimanual training and in the other with a traditional treatment.

Method

Study design

The study has been designed as a multicenter, prospective, cluster-randomized controlled clinical trial. The effect of CIMT (intended as restraint of unaffected limb combined with unimanual intensive rehabilitation program, *group 1*), is compared with a comparison group undergoing bimanual Intensive Rehabilitation Program (bimanual IRP, *group 2*), and a second comparison group receiving a traditional rehabilitation program (standard treatment ST, *group 3*). The comprehensive description of study design and methodology of the trial has been previously published[224]. The comparisons between group 1 vs 2 may highlight the effect of restraint and the comparisons between group 1 vs 3 and group 2 vs 3 may show the effect of intensive practice of movements and exercises. The traditional rehabilitation treatment has been considered as the baseline treatment.

Due to possible organizational difficulties within the rehabilitation services and the subsequent impossibility to randomize patients by treatment group for 3 different treatment approaches in every single clinical center, the Authors have chosen a cluster randomization design[225, 226 227, 228].

21 clinical sites located in 8 Italian regions took part in the research project. At least 2 clinicians per center were involved in the research project, a physician (neuro-pediatrician or physiatrist) and a physiotherapist. All the centers involved in the research study belong to the Italian Group of Cerebral Palsy (G.I.P.C.I.). 2 supervisors of outcome measures examined videotapes of all evaluations of patients from each treatment group and they were blinded to treatment allocation.

Sample Size and Power

A sample of 111 participants has been recruited (with an estimated 10% drop out), with a delta value set at 30%, ($1-\beta = 0.80$, $\alpha = 0.05$, $\pi_i = 0.15$). 37 cases have been enrolled in 7 centers for CIMT, 37 cases in 7 centers for IRP and 37 case in 7 centers for traditional treatment.

Inclusion and Exclusion Criteria

Patient inclusion criteria were: age range between 2 and 8 years, diagnosis of hemiplegic cerebral palsy (anamnestic, clinical and neuroimaging documentation to be collected) according to Hagberg's classification[229]. To avoid the confounding effects of other intervention studies, potential participants have been excluded from the study if they have previously undergone restraint therapy or have received injections of anti-spasticity drugs into UE musculature (e.g., botox). Differing clinical severity and/or comorbidity with other diseases (e.g. epilepsy,

mental retardation) do not constitute exclusion criteria, but have been used to describe clinical variability.

Participants' motor criteria were divided into 3 groups: 1) mild, 2) moderate, and 3) severe motor impairment, based on and modified from criteria set by Beckung et al[230] and Eliasson et al[231].

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.

Treatment groups: main characteristics

Group 1. Constraint Induced Movement Therapy (CIMT) (glove plus unimanual Intensive Rehabilitation Program). 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, and prevents the ability to grasp.

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 or the therapist and/or parents and without removing the glove. During the treatment period, children underwent an intensive rehabilitation program based on unimanual activities. Sessions were held 3 times weekly (lasted 3 hours divided in 1 hour and ½ with the therapist and 1 hour and ½ with parents) at the Rehabilitation Center: an individual therapist encouraged the child to solve tasks requiring the unilateral use of the paretic hand.

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

Group 2. Bimanual Intensive Rehabilitation Program (IRP). Children were treated for hand impairment according to the same approach described above, and with the same schedule (3 hours a day, 3 times a week, half sessions with the therapist and half sessions 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. Parents were trained to carry out similar 3-hour sessions at home on the remaining 4 days, as showed at the Rehabilitation Center (specific bimanual tasks during play and daily living activities).

Group 3. Standard treatment (ST). This group includes children affected by cerebral palsy currently treated in territorial Rehabilitation Services. They usually undergo 1-hour standard rehabilitation sessions once or twice a week and the session frequency differs in relation to child's age. Infants receive physiotherapy twice a week, while preschool and school-age children attend occupational therapy once a week (40-60 min).

The full description of treatment sessions for each group has been previously and published[174] and are fully illustrated in previous chapters.

Primary Outcome Measurements

Primary outcomes were assessed in 2 major domains: UE motor ability (QUEST[232]) and hand function assessment evaluating both grip function and the spontaneous use of the affected side (Besta Scale).

QUEST (Quality of Upper Extremity Skills Test) explores four main domains: dissociated movements, grasp, protective extension and weight bearing. All items were scored for both arms using a dichotomous scale and percentage scores were calculated[233]. This characteristic allowed us to assess separately the function of each hand (affected and unaffected).

The Besta Scale was developed in 1985 to assess quality of grip (hand function on request) and spontaneous hand use (bilateral manipulation), and their changes in relation to age and degree of impairment. Several studies have been perform to test validity, reliability and inter-observer agreement[234, 235, 236].

In the scale, grip assessment is performed in a standardized setting, asking the child to pick up different sized cubes on request. The quality of grip is videotaped and scored in a hierarchical way (from 0 to 3). Spontaneous use is assessed during structured activities and activities of daily living (ADL) requiring both hands and being standardized according to age. The scoring system for the quality of manipulation is based on variability and stereotypy of movement pattern according to Touwen[237].

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

Secondary Outcome Measurements

Besides the general assessment (anamnesis, objective and neurologic exams), in order to assess the child's overall development and if it is influenced by the treatment assigned, the evaluation sessions before and after treatment included additional tests assessing: a) the patients' cognitive level (Wechsler/ Griffiths scales, according to patient age), b) general motor development (Gross Motor Function Measure), c) the level of familial stress (Parenting Stress Index[238]), d) parents evaluation of the child's autonomy in daily living activities (Parents Besta Scale), e) the child behavioral changes (Child Behavior Checklist[239]), f) and treatment satisfaction and compliance perceived by parents (ad hoc questionnaire).

Training, standardization and agreement

Before starting the controlled trial, a specific training program was provided to familiarize professionals (both principal investigator and therapist) with testing and training procedures in order to develop a homogeneous administration and videotaping of the QUEST and Besta Scale tests[174]. A specific training at the Rehabilitation Center and a dedicated booklet with a DVD (Figure 1) was provided to parents of recruited children in order to standardize the activities at home during play and daily living.

Statistical analysis

The analysis regarding the primary outcome measures has been carried out considering the differences on the global score of both Besta Scale and QUEST right after the end of treatment and 3 months later for each treatment group. Moreover, the subscales have been studied separately in order to verify the effect

on specific skills and patterns of movement (e.g. fine grasp or weight bearing for QUEST and spontaneous use in ADL for Besta Scale). Wilcoxon signed-rank test for non parametric paired samples t-test was utilized to test statistical significance. For the comparison among treatment groups (1 vs 2 vs 3; 1 vs 2, 2 vs 3 and 1 vs 3) percentualized differences on the global and subscale scored have been calculated. Respectively, Kruskal-Wallis Test for non parametric version of ANOVA was utilized to test statistical significance for 3-groups comparison (1 vs 2 vs 3) and Mann-Whitney test for non parametric independent samples t-test for paired groups comparisons (1 vs 2, 2 vs 3 and 1 vs 3).

For secondary outcome measures a preliminary descriptive analysis was carried out.

Results

Between march 2006 and January 2009, 105 patients were recruited and assigned to the treatment groups Constraint Induced Movement Therapy (n=39), bimanual Intensive Rehabilitation Program (n=33) and Standard Treatment (n=33). One patient recruited in the IRP group withdrew the program because the family moved and did not undergo the post-treatment and follow-up assessment.

Effect persistence of 3 treatment approaches on primary outcomes at follow-up

Comparing the evaluation after the end of treatment to 3-months follow-up evaluation, for all the treatment approaches mild changes were observed in the primary upper-extremity outcome variables (Table 8.1). The changes are much more relevant for the children undergoing an intensive rehabilitation program –

mostly for bimanual IRP – if compared with the ST group (Table 8.1). The changes are not statistically significant.

3 treatment approaches: comparison analysis (1 vs 2 vs 3)

Comparing the 3 treatment groups of children at Besta scale, the statistical analysis shows no significant differences in any of the domains, but on grasp function an apparent worsening is observed compared to IRP and ST both improving (Table 8.2). At QUEST, no statistically significan differences are observed (Table 8.8).

3 treatment approaches: comparison analysis (1 vs 2; 2 vs 3; 1 vs 3)

CIMT vs Standard Treatment. In this analysis, tthe CIMT group shows a significant improvement in ADL in older children compared to Standard treatment (Table 8.3).

IRP vs Standard Treatment. No statistically significan differences were observed. (Table 8.3).

CIMT vs IRP. This comparison demonstrated that IRP result more effective in improving grasp function in Besta scale (Table 8.3), while in QUEST scale CIMT results improving the protective extension (Table 8.9).

Discrete improvements

In tables 8.4, 8.5 e 8.6 the Besta scale was analyzed as discrete improvements or worsening. Previous results are confirmed.

Secondary outcome measures

- Familial stress result reduced in CIMT and IRP groups, while it is similar in standard treatment;

- CBCL scoring after treatment and 3 months later show no clinical or borderline profiles for IRP group, 3% bordeline profiles and no clinical profiles for CIMT. The standard groupshowed 5% of clinical profiles, 14% of borderline profiles and the remaining normal.

Discussion

Given the scarce evidences on the efficacy of CIMT, there is a clear need of valid and reliable research studies on this issue that could be able to anwer to the numerous questions arisen from clinical studies and from animal models and experimental research.

The persistence of the effect derived from a period of CIMT combined with an intensive rehabilitation program is one of the most burning questions because if confirmed, it would change the indications on this treatment approach and would open the way to other hypothesis regarding neural plasticity.

The results outlined in this paper demonstrate that the persistence of the effect previously demonstrated is not constant. Namely, CIMT seem to reduce rapidly its effect 3 months later on what attains grasp funcion. To our knowledge this result has never been reported before.

On the contrary the intensive rehabilitation program continues to improve the upper limb function. The increase in primary outcome measures is much higher than the one determined by standard rehabilitation program and this difference is significant.

The preliminary analysis on secondary outcome measures seems to sustain the hypothesis that, although requiring an important effort for the child and his/her

family, the intense treatment shows a decrease in the levels of stress within the family and positive consequences on child's behaviour with no observation of clinical patterns. On the contrary, standard treatment has the highest levels of stress and child's behavioural disturbances.

If confirmed, these results will be useful to sustain the proposed model of CIMT influence on limb function, giving evidence for the additional factors (motivational, behavioural, stress-related, …) involved in promoting or suppressing CIMT effect on impaired limb function and learned non use[240].

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Tables & Figures

Table 8.1. Besta Scale: 3 months follow-up after the end of treatment

	CIMT			***IRP***			***ST***		
	mean t_1	**mean t_2**	***p****	**mean t_1**	**mean t_2**	***p****	**mean t_1**	**mean t_2**	***p****
Global score	2.60	2.65	0.0567	2.74	2.81	0.3275	2.45	2.51	0.2732
Grasp	3.15	3.13	0.9375	2.83	2.94	0.0947	2.88	3.03	0.5117
Spontaneous use	2.74	2.70	0.7852	2.94	2.91	0.6937	2.79	2.84	0.5018
ADL (younger)	2.05	2.16	0.0850	2.55	2.65	0.7169	2.13	2.17	0.4884
ADL (older)	2.85	3.00	0.1250	3.25	3.25	1.0000	2.58	2.45	1.0000

** Wilcoxon signed ranck test - non paremetric paired samples t-test*

Table 8.2. Besta Scale: 3 groups comparison

		Δ %	***p****
Global score	**CIMT**	1.40%	
	IRP	2.81%	0.8005
	ST	3.24%	
Grasp	**CIMT**	-0.58%	
	IRP	4.87%	0.2026
	ST	3.23%	
Spontaneous use	**CIMT**	-0.46%	
	IRP	-0.41%	0.6729
	ST	1.82%	
ADL (younger)	**CIMT**	4.69%	
	IRP	3.57%	0.7608
	ST	5.11%	
ADL (older)	**CIMT**	4.96%	
	IRP	5.00%	0.1952
	ST	-4.76%	

** Kruskal Wallis test – non-parametric version of ANOVA*

Table 8.3. Besta Scale: 1 vs 2; 2 vs 3; 1 vs 3 comparison

	CIMT vs ST	**CIMT vs IRP**	**IRP vs ST**
Global score	0.4058	0.2949	0.2880
Grasp	0.2684	0.0280	0.2100
Spontaneous use	0.2477	0.4353	0.1937
ADL (younger)	0.4316	0.2205	0.3534
ADL (older)	0.0504	0.4522	0.1665

** Mann-Whitney test - non parametric independent samples t-test*

Table 8.4. Besta Scale: N of items with a positive improvement (+ 1 or +2 or +3) or no-improvement/worsening (0 or -1. -2, -3)

		Positive	p*	Negative	p*
Global score	**CIMT**	3.8		13.7	
	IRP	2.7	0.1015	11.7	0.1135
	ST	4.1		15.1	
Grasp	**CIMT**	0.4		4.0	
	IRP	1.3	0.0337	3.9	0.7176
	ST	1.3		4.0	
Spontaneous use	**CIMT**	1.5		4.2	
	IRP	0.7	0.0399	3.6	0.5244
	ST	1.2		3.8	
ADL (younger)	**CIMT**	3.7		9.0	
	IRP	1.8	0.1316	5.9	0.0136
	ST	2.8		8.8	
ADL (older)	**CIMT**	1.3		2.9	
	IRP	0.5	0.3653	3.0	0.5172
	ST	1.0		4.0	

** Kruskal Wallis test - non-parametric version of ANOVA*

Table 8.5. Besta Scale: two by two comparison for positive improvements (+ 1 or +2 or +3)

	CIMT vs ST	CIMT vs IRP	IRP vs ST
Global score	0.3519	0.0456	0.0227
Grasp	0.0266	0.0071	0.4876
Spontaneous use	0.2252	0.0100	0.0324
ADL (younger)	0.3126	0.0257	0.0819
ADL (older)	0.2919	0.1450	0.3085

** Mann-Whitney test - non parametric independent samples t-test*

Table 8.6. Besta Scale: two by two comparison for no-improvement/worsening (0 or -1. -2, -3)

	CIMT vs ST	CIMT vs IRP	IRP vs ST
Global score	0.1379	0.1112	0.0204
Grasp	0.4584	0.2115	0.2935
Spontaneous use	0.3568	0.1396	0.2295
ADL (younger)	0.3683	0.0043	0.0076
ADL (older)	0.1673	0.5000	0.3187

** Mann-Whitney test - non parametric independent samples t-test*

Table 8.7. QUEST: 3-months follow-up

		Overall			***Affected limb***			***Unaffected limb***		
		mean t_1	**mean t_2**	***p****	**mean t_1**	**mean t_2**	***p****	**mean t_1**	**mean t_2**	***p****
	Global score	77.0	75.4	0.2201	57.6	55.0	0.3295	78.2	78.1	0.0615
	Dissociated movements	77.2	76.1	0.6905	16.2	16.0	0.7369	26.9	27.0	0.5781
CIMT	Grasp	71.5	72.0	0.8680	7.2	6.8	0.1923	11.1	11.8	0.4375
n=34	Weight bearing	90.2	88.0	0.6794	23.5	22.8	0.5121	25.5	25.2	0.3438
	Protective extension	69.3	66.5	0.3302	13.7	12.5	0.1758	17.8	17.1	0.5000
		mean t_1	mean t_2	*p**	mean t_1	mean t_2	*p**	mean t_1	mean t_2	*p**
	Global score	73.9	74.6	0.6409	53.1	52.7	0.4939	80.2	77.2	0.9827
	Dissociated movements	76.8	76.7	0.7136	15.7	16.8	0.9085	28.0	26.6	0.8801
IRP	Grasp	70.1	68.8	0.6980	6.1	5.9	0.0127	11.8	11.4	0.7588
n=20	Weight bearing	80.2	79.2	0.9312	21.2	20.0	0.8750	25.6	25.0	0.4063
	Protective extension	68.4	73.5	0.0510	13.2	13.0	0.5313	17.8	17.2	1.0000
		mean t_1	mean t_2	*p**	mean t_1	mean t_2	*p**	mean t_1	mean t_2	*p**
	Global score	66.1	66.0	0.8422	47.5	47.9	0.7718	75.1	75.2	0.7180
	Dissociated movements	68.6	69.8	0.4398	12.8	12.7	0.2126	26.4	26.8	0.4768
ST	Grasp	61.3	60.1	0.4136	5.1	5.2	0.8481	11.2	11.2	0.9453
n=17	Weight bearing	79.1	77.6	0.2925	19.9	20.7	0.3320	25.0	24.3	0.6250
	Protective extension	56.4	57.1	0.8945	12.6	12.3	1.0000	15.5	15.8	1.0000

** Wilcoxon signed rank test - non paremetric paired samples t-test*

Table 8.8. QUEST: 3 groups comparison

		Overall		*Affected limb*		*Unaffected limb*	
		Mean %	*p**	Mean %	*p**	Mean %	*p**
Global score	**CIMT**	-1.9%		-4.1%		0.1%	
	IRP	1.0%	0.5024	15.4%	0.7471	-3.9%	0.23
	ST	0.4%		73.1%		0.5%	
Dissociated movements	**CIMT**	-1.3%		5.0%		2.3%	
	IRP	-0.6%	0.4423	18.1%	0.6085	-5.2%	0.784
	ST	2.9%		26.8%		2.2%	
Grasp	**CIMT**	3.2%		-0.1%		8.2%	
	IRP	-0.2%	0.5162	11.6%	0.4876	-2.5%	0.1774
	ST	3.8%		8.8%		4.7%	
Weight bearing	**CIMT**	-0.8%		1.8%		-0.6%	
	IRP	-1.2%	0.7601	22.7%	0.4369	-2.4%	0.3571
	ST	-2.3%		36.6%		-3.2%	
Protective extension	**CIMT**	0.0%		10.5%		-2.9%	
	IRP	11.0%	0.0603	34.5%	0.9406	-3.2%	0.7691
	ST	8.7%		-3.3%		9.1%	

** Kruskal Wallis test - non-parametric version of ANOVA*

Table 8.9. QUEST: 1 vs 2; 2 vs 3; 1 vs 3 comparison

	CIMT vs ST	**CIMT vs IRP**	**IRP vs ST**
Global score	0.3337	0.1353	0.2276
Dissociated movements	0.1091	0.3799	0.1840
Grasp	0.1606	0.5000	0.1459
Weight bearing	0.3059	0.4240	0.2191
Protective extension	0.1467	0.0094	0.1632

** Mann-Whitney test - non parametric independent samples t-test*

CHAPTER 9. REHABILITATION AND RESEARCH:

THE OPINION OF PROFESSIONALS

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Title

Clinical research in rehabilitation: results of a cross-sectional survey on attitudes of professionals of the Italian Paediatric Rehabilitation Services

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Abstract

Background. In the last decades, the world of rehabilitation has been more and more calling for clear evidence to support intervention and numerous research programs have been developed. At stake, relatively little research on opinions and attitude of rehabilitation personnel involved in research conducted in real clinical settings has been carried out.

Methods. Among all professional participating to a multi-centre clinical trial on the effects of Constraint Induced Movement Therapy on children with hemiplegic cerebral palsy, a cross-sectional study was conducted to explore their opinion on conducting research in clinical rehabilitation. A 15-questions questionnaire was utilized.

Results. Among those working in one of the 19 rehabilitation centres part of the multi-centric study, 76 professionals were asked to fill in the questionnarie. 68 professionals answered (89.4% of response rate). More than 75% of the sample think that their rehabilitation centre is suited to develop clinical research. Research results useful for the development of their daily activities (new tools for the assessment of children, demonstrate the efficacy of a new treatment option and to learn a new way of working, and strengthen the ties within the working team). Research is costly in terms of personal time and effort, but it can modify the rehabilitation praxis (assessment tools, the relationship with colleagues/patients). 98% of of the interviewed declared to will to participate to other research projects.

Conclusions. This survey highlights the importance of conducting research in local rehabilitation services, besides the generation of new evidences, also in terms of building networks, sharing experiences and knowledge, connecting with centers of excellence and providing a specific training for research conduction.

Key-words:
Research; clinical trials, rehabilitation, paediatric services; attitude of health personnel

Background

In the last decades, more and more the world of rehabilitation has been calling for clear evidence to support intervention. At stake, relatively little research in rehabilitation recruits patients as subjects and is conducted in real clinical settings.

The American Physical Therapy Association (APTA) has recently developed its Clinical Research Agenda (CRA): this tool aims to support and promote research that is useful to clinicians, and it suggests that research has to be carried out on patients in real clinical settings such as outpatient clinics, hospitals and facilities[241, 242]. The aims are to verify the effectiveness of interventions as well as identifying prognostic indicators and validate tools to classify and diagnose.

If research is conducted in real-world settings, authors suggested that retooling may be needed for researchers, through upgrading, updating and acquiring new knowledge and skills[243, 244].

Facilities or institutional resources, management of patients, adequate availability of target population and support from collaborating professionals (therapists, psychologists, physicians, nurses) result as key elements to complete successfully research projects within real clinical settings[245, 246, 247, 248].

Institutional resources include adequate access to targeted patients' populations and effective mechanisms for identifying and recruiting potential subjects, a network of professionals from other disciplines, institutional review boards and medical-legal support. In general, academic clinical centers are characterised by the coexistence of these resources in a single institution due to their institutional role of research developers. Therefore any clinical research project is by far more

easily carried out in this environment. In a different setting, such as a local health service, several burdens to research development are found, for example the lack of specific professional figures or facilities and tools[242].

Another key issue is represented by the involvement of physical therapist. According to Fitzgerald and Delitto[242] *"…the quality of data and the ability to successfully complete a clinical trial will largely depend on the willingness of physical therapists to participate…and therapists may be less likely to participate in a clinical trial if they believe that an investigator views them simply as a convenient work force to collect data"*. Moreover the Authors highlight that physical therapists*"…may be more likely to participate if they view the investigator as an important member of their clinical team, whose research may have a direct impact on their practice environment…and if they believe that the investigators views them as important members of the research team"*[242].

Another major challenge is how to incorporate research evidence into clinical practice (Evidence Based Practice, EBP) within human service agencies. The major implications emerging from the analysis of Johnson and colleagues[249] are: services-university partnerships to identify the data to support EBP, staff training that features problem-based learning approaches to support the introduction and utilization of EBP, and the modification of services cultures to support and sustain EBP[250, 251, 252, 253].

Furthermore, the productivity demands that therapists are required to satisfy in their daily practice can affect clinical research conduction. The daily patients visit quota is a main due for many therapists and services. The burden of testing and

document the results of a clinical trial may influence or limit the therapist's patient management and clinical responsibilities, and favour incomplete data collection and therapist's withdrawing from the study.

Reviewing the international literature on perception and attitudes to research, it emerges clearly that much attention is paid to how patients involved in research projects perceive the meaning of research conduction and how they feel in being involved in such studies, while little interest is devoted to professional's point of view.

In Italy, experimental research in the field of paediatric rehabilitation has begun very recently and the studies on scientific evidences are very rare, mainly data on botulinum toxin and intratecal Baclofen have been published[254, 255, 256]. To our knowledge, neither reports on therapeutic trials conducted in local rehabilitation services nor perception of professionals involved in research projects have been published to date.

The aim of this study is to present the perceptions and attitudes of different professionals involved in a multisite clinical trial on the efficacy of a new rehabilitation approach[257], exploring their attitude towards the usefulness of clinical research, the difficulties to be faced in conducting an experimental project in a local rehabilitation service and the translation of the results into clinical daily practice.

Materials and Methods

Study design and sample

To explore the opinions on conducting research in clinical rehabilitation, a cross-sectional study was conducted among 76 professional working in 19 Italian rehabilitation services (4 research institutes, 15 local rehabilitation services).

All the professionals interviewed are currently inolved in a multi-centre clinical trial on the effects of Constraint Induced Movement Therapy (CIMT) on children with hemiplegic cerebral palsy[257] and they all belong to the Italian Group of Cerebral Palsy (G.I.P.C.I.), an association founded in 1994 and composed by physiotherapists, physicians and psychologists. The group has worked for 15 years in defining the decision-making process and clinical management of children with cerebral palsy.

The questionnarie

The pilot survey was conducted utilizing an ad hoc questionnaire (see annex 1) composed by 15 questions. The questionnaire explored several areas dealing with feasibility, usefulness, products, costs, judgement and perceptions about clinical research in rehabilitation.

In detail, the questions explore the opinions on the usefulness of clinical research in general and in daily practice, on which are the main difficulties to be faced in conducting experimental projects in a rehabilitation service (either within a local health service or in a hospital/research institute), the personal experience in terms of time and efforts spent, the influences and changes in the organization of daily

practice needed in developing the project and, finally, the possibility to translate the results in clinical daily practice.

One question was organized with a 5 point scale (1 = few resources → 5 = a lot of resources), seven questions with a 4 point scale (totally agree/partially agree/do not agree at all/don't know) and the remaining seven consisting of open questions with several proposed answers.

The participants answered voluntarily to the questionnaire, that was distributed at each of the 19 rehabilitation centres or hospitals currently involved in the multicentric clinical trial.

The validity of the questionnaire has not been explicitly tested but it's content validity was explored and confirmed. The instrument was developed in three phases.

In the first phase, the items were developed via an extensive literature review, which was analysed by content analysis. This review was conducted using the MEDLINE and PsycINFO databases from the years 1990 to 2008 and the following key words: rehabilitation research, professionals attitude, rehabilitation services, professionals perception, clinical research.

To estimate and evaluated the face validity, the first draft of the instrument was examined and critiqued and experts in rehabilitation, in physical therapy, in social research, epidemiology and biostatistics (*n*= 15). The purpose of the expert evaluation was to ensure that the items would represent critical attributes as well as to gather more relevant items from the experts' point of view. In addition, they

were also asked to write their comments and to add items if they considered them relevant to the phenomenon. One item was removed on the basis of the expert evaluation because of its redundance, two were added and four were slightly modified.

Results

68 out of 76 professionals working in one of the 19 rehabilitation centres participating to the research project answered the questionnaire (response rate of 89.4%): responders' main characteristics are summarized in Table 9.1. Responders are mainly women, with a proportion of 5:1, a mean age of 42 years (median 43, mode 53, age range 22-61).

69% of professionals were rehabilitation therapists (physical therapists and occupational therapist), 28% were physicians (25% child psychiatrists or child neurologists and 3% physiatrists) and 3% psychologists.

More than 50% of professionals works in the actual rehabilitation service since 10 years ago: on average, the responders have been working since 13,7 years ago (range 1-35 years) (Table 9.1).

The professionals who refused to answer the questionnaire did not differ significantly from the responders according to the main variables considered (age, sex, background, professional experience, type of rehabilitation service).

Feasibility

More than 75% of the sample think that their rehabilitation centre is suited to develop clinical research, while the remaining 25% thinks that research trials have to be carried out in other centers (11%) or in centres of excellence (14%).

Thinking to case to be recruited in research projects, professionals think that any kind of case is suitable for being enrolled (51%), regardless severity of impairment, age and compliance to treatment, while the remaining 49% thinks that cases with too severe motor impairment (17%), too young (< 2-4 years of age) (24%) and those in which a small change is expected (3%), should not be included.

Usefulness

Nearly all the interviewees think that clinical research in rehabilitation is very useful both in general and for the development of their daily activities. In particular, the research project carried out was fruitful to acquire new tools for the assessment of children (48%), demonstrate the efficacy of a new treatment option and to learn a new way of working (26% each) and strengthen the ties within the working team (12%) (Figure 9.1).

Costs' perception

Clinical research is considered very costly in terms of personal time and effort in more than 50% of the sample, while it is less costly in terms of service time, organization and resources (nearly 40%) (Figure 9.2).

Products

According to professionals, research can modify the rehabilitation praxis, mostly on what attains the ability to utilize and apply assessment tools (60%), the relationship with colleagues and other professionals (50%), the relationship with children and their families (25%). In a single case, the relationship with the child has worsened.

Extendibility

According to most of the interviewees, a research trial experience should be proposed and conducted also in other rehabilitation services, and a similar experience should be planned also for other new treatment options.

Overall judgement

70% of the sample thinks to have a flair for research activity, although in 60% of cases declares that research is not on of his/her service's duty (Table 9.2).

Research is considered a positive experience because of the gaining of competence and new technical skills (63%), collaboration with other centers/services (62%), amelioration of the organization, cooperation and working within each service. On the contrary, research is considered as negative due to the difficulties in organizing the new treatment/intervention according to a shared protocol (often requiring a modification is usual organizational procedures), and those related to the complex and time-consuming assessment phase, required in the research program.

In general, 98% of professional declared to be disposed to participate to other research projects and clinical trials.

Discussion

There is a widespread agreement on the need of creating a culture of research to keep pace with the increasing need for developing and testing new approaches for diseases management[258]. This statement is particularly true and urgent in the field of paediatric rehabilitation, since too often in the past, a low-quality research or no research at all has allowed the diffusion of rehabilitation treatments and praxis not based on scientific evidence and whose efficacy and safety was not tested and demonstrated [259, 260].

However, the several problems encountered in conducting research in pediatric rehabilitation are a matter of fact and are usually related to the health-care delivery systems and to professionals attitudes and role, as well as to the their different cultural background.

Research and care are often seen as conflicting activities. In the literature, conducting research in clinical setting includes two sets of relationships: researcher-subject and clinician-patient, usually performed by the same individuals and therefore potentially generating conflicting and confusing professionals roles[261].

The struggle to reconcile care and research often depends upon professionals perception that certain types of care were inseparable from the research and that research is a *way of taking care of patients*[261], and therefore, clinicians must be

encouraged to consider research as their own responsibility, not only academic institutions' and research organizations' duty.

The results of our investigation on the clinicians perception of research is in accordance with these remarks on research.

In our sample, the results show that most of the professionals interviewed consider worthwhile the research experience conducted and, besides the efforts taken and the difficulties, nearly all responders express the will to repeat the experience.

According to professionals, the conducted research has improved and enriched their rehabilitation practice and their systematic utilization of validated assessment tools. This issue is reported by other Authors that underline that scientific research offers many other satisfactions in addition to the excitement of a new approach validation[242].

Another relevant result regards the opportunity to associate with colleagues involved in the same project study, as other Authors emphasized. Clinicians working as researchers with peers who think deeply and care passionately about subjects of common interest, besides the primary outcomes of research, have many chances to work with different people in areas where disciplines overlap, explore new fields, and broaden their expertise[262].

In Italy, the rehabilitation services are mainly located in territorial and community health centers which are inhomogeneous due to different aspects, i.e. different departments of affiliation (social, medical, psychological, psychiatric services), professionals' training and background, resources availability, being or not

involved in an updating and collaborative network or working in structures of rural areas, with the result that very often professional suffer from “working isolation”. In this context, research can create the opportunity to promote networking and experience sharing. Support and networking should be considered in research projects planning in real-world clinical settings[263].

The most relevant negative aspect of research development regards the conflicting interest between care organization and delivery and research conduction, mainly on the assessment phase.

In general, this problem needs to be encompassed by a commitment of resources and a respect of clinicians practice burdens and environments. This is usually very difficult in a primary care setting where the main duty is respect a daily patient visit quota.

Furthermore, an adequate study design tailored on therapists’ interests and questions and providing information that the therapists perceive as relevant to their clinical practice is clearly needed. Researchers often have considerable freedom both in choosing what to investigate and in deciding how to organize their professional and personal lives. For future research project involving rehabilitation professionals, the dialogue between investigators and therapists is urgently needed, especially on problems and hypothesis arising from clinical practice[264, 265].

Conclusions

This pilot survey highlighted the importance and the meaning of conducting research in local rehabilitation services in terms of building networks, sharing experiences and knowledge, connecting with centers of excellence.

In the professionals' opinion, in fact, the most relevant outcome deals with the personal benefits deriving from research conduction in terms of new knowledge, skills and attitudes, rather than the generation of new and good evidence for an innovative rehabilitation praxis.

In conclusion, two main needs arise. On one side, professionals working in the field of rehabilitation seem to look forward for a new professional identity, which has been confused and modified by the isolation and fragmentation of the local rehabilitation service. The currently available tools for professionals updating and continuing education seem to be inadequate to meet the real need of those who work in local contexts, far from research and teaching centers. An efficient network is urgently needed linking all the services, allowing the peer discussion, the experiences exchange, the acknowledgement of one's professionals role and of the quality of the work developed, and requiring the continuous review of competences and relationship with patients and families.

Moreover, the second need deals with the education system for rehabilitation. The agencies in charge to train professionals that will work in the rehabilitation services need to include specific training modules to shape the attitudes of future professionals towards research and to give tools to conduct and translate research intro daily practice[266].

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Tables & Figures

Table 9.1. Responders: main characteristics

Variables		
Sex	Male	16%
	Female	84%
Age	Mean	42 yrs
	Range	22-61 yrs
Background	Neurologist	25%
	Physiatrist	3%
	Psychologist	3%
	Physical therapist	54%
	Occupational therapist	15%
Employed since		
	70s	16 (24%)
	80s	19 (28%)
	90s	13 (19%)
	2000	17 (25%)
No information provided		3 (4%)
Working in	Teaching Hospital	(29) 42%
	Local Rehab Services	(39) 58%
Professional experience	Mean	13, 7 yrs
(years)	Range	1-35 yrs
Employed in the same Service since		
	< 5 years	19 (27,9 %)
	5-10 years	17 (25,0 %)
	10-20	13 (19,1 %)
	> 20	19 (27,9 %)
Clinical Research Institute		17 (25 %)
Local Territorial Rehab Service		51 (75 %)

Table 9.2. Research and daily practice: professional's opinion

	Totally agree (%)	Partially agree (%)	Do not agree (%)	Do not know (%)
Research in rehabilitation is useful	99	0	0	1
Research is a duty of my Service	42	39	18	1
Research is useful to my personal daily practice	94	6	0	0
I have a flair for reaserch	69	23	2	6
Research experience should be extended to other Services	88	12	0	0
The research I am involved in should be applied for other treatment options	58	15	4	23

	Better	Worse	No change	Do not know
How my practice changed after conducting the research	71*	1**	1	27

* The answers indicated an amelioration in the (A) clinical relationship with patients, parents, collegues or other professionals, and (B) in the utilization of new assessment tools

** The answers indicated a worsening in the (A) clinical relationship with patients

	Yes	No
I wish to participate to other research projects in the future	88	12

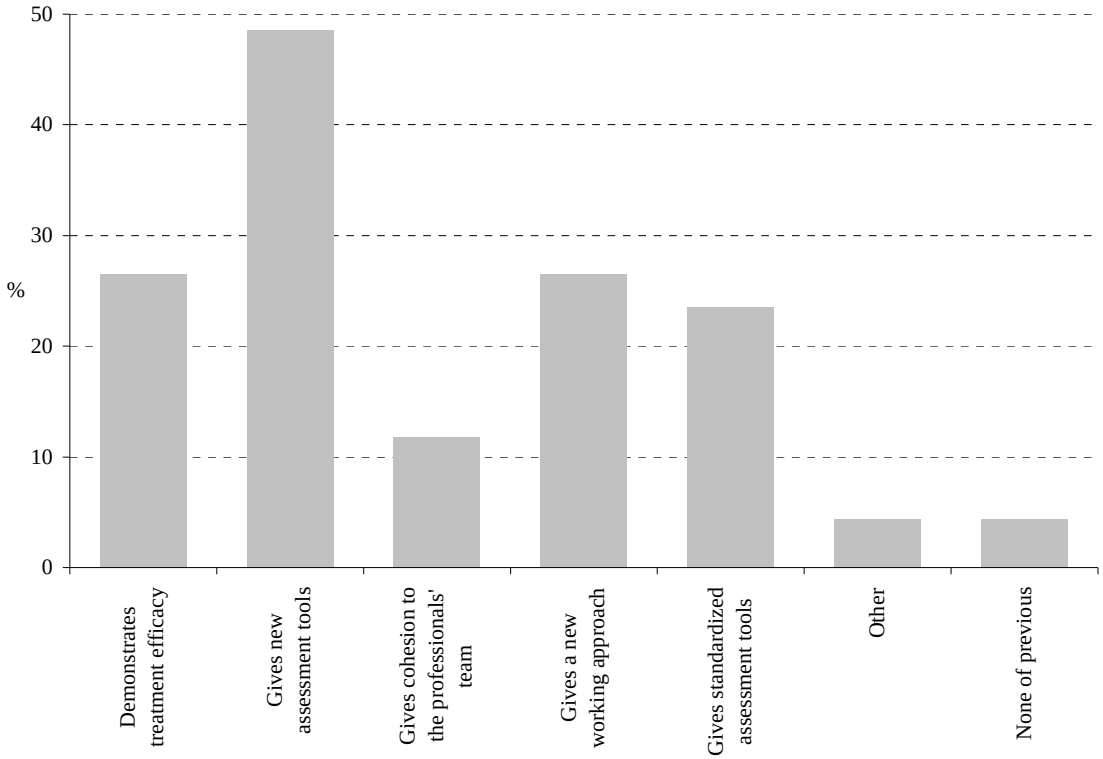

Figure 9.1. *Is research useful in your daily practice? Why?* The professionals' opinion (more that one answer allowed).

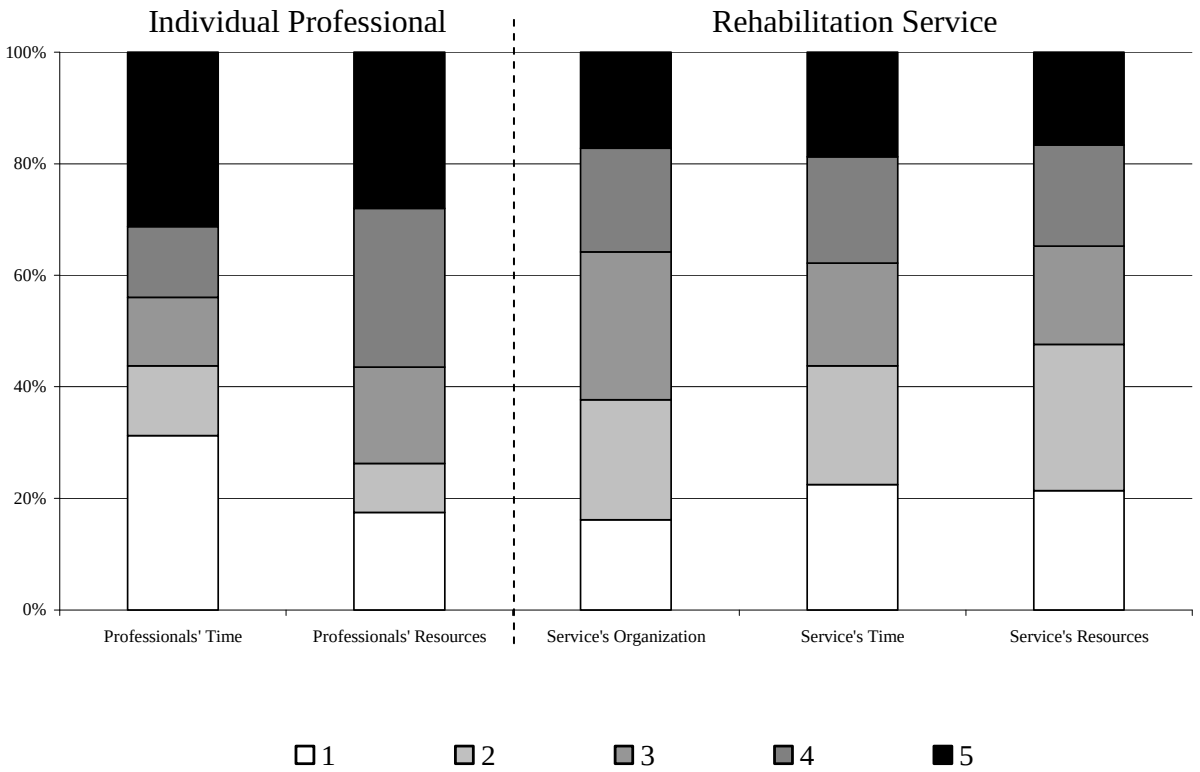

Figure 9.2. *How many resources where spent during the research project? In terms of what?* The professionals' opinion (1 = few resources → 5 = a lot of resources)

Annex 9.1 Re.Pro.At.T.Res.
REHABILITATION PROFESSIONALS ATTITUDES TOWARD RESEARCH

Service _____
Sex _____
Age _____
Professional role _____
Employment year _____
Employment year in this service _____

1. I think the research project I'm working on could also be developed:
- |_| in my Service
- |_| in other services
- |_| in centers of excellence
- |_| other _____
- |_| none

2. Such research project requires to be developed:
- |_| 3 years
- |_| less than 6 months
- |_| at least 1 year
- |_| other _____
- |_| none

3. Such research project requires to be developed:
- |_| extremely severe cases
- |_| mildly severe cases
- |_| any kind of case
- |_| other _____
- |_| none

4. The research project developed was useful because:
- |_| has demonstrated the efficacy of a new treatment option
- |_| learned to utilize new tools for children assessment
- |_| has contribute to build the team
- |_| has introduced a new working methodology
- |_| learned to utilize standardized tools for children assessment
- |_| other _____
- |_| none

5. Resources spent

	1	**2**	**3**	**4**	**5**
Personal time	☐	☐	☐	☐	☐
Personal effort	☐	☐	☐	☐	☐
Service organization	☐	☐	☐	☐	☐
Service time	☐	☐	☐	☐	☐
Service resources	☐	☐	☐	☐	☐

6. This experience could be reproduced for other types of treatment
- |_| totally agree |_| partially agree
- |_| do not agree at all |_| don't know

7. This experience should involve other services
- |_|yes |_|no

8. Is Research useful in Rehabilitation?
- |_| totally agree |_| partially agree
- |_| do not agree at all |_| don't know

9. Is Research part of the duties of your Service?
- |_| totally agree |_| partially agree
- |_| do not agree at all |_| don't know

10. Is Research useful for your personal work?
- |_| totally agree |_| partially agree
- |_| do not agree at all |_| don't know

11. Do you feel inclined for Research?
- |_| totally agree |_| partially agree
- |_| do not agree at all |_| don't know

12. Has this research experienced changed something?
- |_| yes (better) |_| yes (worse)
- |_| no |_| don't know

If yes, main changes:
- |_| relationship with patients
- |_| relationship with relatives of patients
- |_| relationship with colleagues
- |_| relationship with other professionals
- |_| tools that I am able to utilize

13. What I have appreciated most
- |_| competence
- |_| organization
- |_| kindness
- |_| collaboration with other Services
- |_| a different way of working
- |_| collaboration within my Services
- |_| none
- |_ |other _____

14. What weighed most
- |_| scarce collaboration among professionals
- |_| difficulties in making/organizing treatment
- |_| not enough time spent
- |_| too much time spent
- |_| too much involvement of the family
- |_| not enough involvement of the family
- |_| no results
- |_| scarce information
- |_| being isolated
- |_| economic burden
- |_| other _____
- |_| none

15. Would you participate to a new research project?
- |_| yes |_| no

ANNEXES

Annex 1

Facchin P., Ranzato C., Rosa Rizzotto M. Constraint therapy nella forma emiplegica di paralisi cerebrale infantile: Sperimentazione sulla efficacia e sicurezza del trattamento. In: *La Clinica Della Riabilitazione Nel Bambino Con Emiplegia. Conoscenze teoriche ed esperienze rieducative*. A cura di: GIPCI – Gruppo Italiano Paralisi Cerebrale Infantile (con DVD). Milano, FrancoAngeli, 2007. ISSN 9 “788846”487957” ISBN 978-88-464-8795-7.

Annex 2

Facchin P., Rosa Rizzotto M., Ranzato C. *Constraint therapy nella forma emiplegica di paralisi cerebrale infantile: sperimentazione sulla efficacia e sicurezza del trattamento.* XXX Congresso AIE Associazione Italiana di Epidemiologia. Palermo 4-6 ottobre 2006, 245.

Annex 3

Rosa Rizzotto M, Visonà Dalla Pozza L, Ranzato C, Facchin P. La validazione degli strumenti: la gestione dello studio multicentrico. In: *La riabilitazione precoce nel bambino con danno cerebrale. Dalle conoscenze neurobiologiche alla prassi terapeutica*. A cura di: Gipci-Gruppo italiano paralisi cerebrale infantile (con DVD). Milano, FrancoAngeli, 2009. ISBN 13: 9788856811520.

Annex 4

Rosa Rizzotto M, Facchin P, Visonà dalla Pozza L, Fedrizzi E, GIPCI. La ricerca clinica nei Servizi di riabilitazione: cosa ne pensano gli operatori? *Riabilitazione oggi*. 2008; 25(7):46-47.