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Manual Force Regulation in Children with Spastic Hemiplegia

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Kortom, laten we gaan spelen.

1

General introduction

Cerebral Palsy

Cerebral Palsy (CP) is the most common motor disability in childhood, with an incidence of 1-2 per 1000 in western countries.[1] CP is characterized by a persistent movement or posture deficit that results from a non-progressive disorder in the developing fetal or infant brain. Its clinical importance can be elucidated by that fact that half of the children undergoing treatment in Dutch pediatric rehabilitation centers have been diagnosed with CP.[2,3] Importantly, it is a not a homogenous condition, but has many clinical manifestations, which can be divided into several clinical types. Three types are mentioned in the classification of CP: spastic paresis, dyskinetic, and ataxic paresis.[3] From these spastic paresis has the highest frequency.[1,4] Spastic paresis has been defined as a posture and movement-dependent tone regulation disorder (SCPE).[1] A second classification criterion to describe the clinical presentation of CP is the division between unilateral or bilateral involvement of the limbs. In hemiplegia, the group under study in this thesis, one arm and leg on the same side of the body are involved (unilateral). In this thesis we focus is on manual performance in a specific group of CP, namely spastic hemiplegia.

Spasticity and muscle weakness

Spasticity is defined as a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflexes. Spasticity is considered to be one of the symptoms of the Upper Motor Neuron Syndrome (UMN).[5] This UMN is characterized by impairments at 2 levels, namely impairments of muscle activation and impairments in biomechanical properties of muscles and connective tissues. Impairment of muscle activation can lead to excessive and to reduced motor activity. Examples of excessive motor activity are spasticity, hyperreflexia, and clonus. They are called positive symptoms, whereas reduction of motor activity, such as weakness, fatigue, slowness and loss of selective motor control are called negative symptoms.[2,5] Of course the positive and negative symptoms interact. If agonist and antagonist muscles co-contract inappropriately, strength generation will be less effective and lead to weakness.[6]

Another possible cause of muscle weakness in children with CP can be disuse, secondary to the reduced output from the brain and damage to the pyramidal tract. [7] This will especially affect the distal muscles.[7] A next possibility for muscle weakness or reduced force production can be a structural change of the muscles involved.[8] In spastic muscles the cross-sectional area was found to be less than one third of normal, while spastic fibres showed decreased sacromere length at rest, selective atrophy of type 2b muscle fibres and increased elastic modulus of muscle fibres (stiffness) in subjects with chronic spasticity.[6,7,9-14]

Abnormal production of hand force is considered one of the primary sources for poor manual skills in CP. So far, most studies evaluating force control in children with CP used instrumented lift tasks in order to evaluate the coordination between lift force and grip force. Eliasson et al.,2000, and Valvano and Newell 1998 showed that children with hemiplegia have impaired grip-lift force synergies compared to control children.[15,16] Decreased grip force,[17] increased variability,[17,18] decreased ability for anticipatory control[17] in these tasks have also been reported. Furthermore decreased fine tuning in force accuracy tasks,[17,18] compared to the unaffected arm and to control children have

been described. If children with CP have problems with the fine tuning for accurate movements, the often reported slowness could be a strategy to comply with the required level of accuracy. There is a large volume of literature about the relation between moment speed and accuracy using their mathematical relationship as expressed in Fitts' law.[19] In children with spastic hemiplegia, however, this relationship has not been investigated and the results of the first study using this paradigm will be presented in this thesis.

Strength training

Whether muscle strength should be trained, especially when spasticity is involved, has been a debate for decades. However times have changed and muscle strength training is now more and more accepted as an important part of rehabilitation.[20-22] The focus of treatment of children with cerebral palsy has been changed from reducing spasticity and regaining range of motion to increasing strength and teaching functional skills.[23-25]

The reluctance to train strength was based on the thought that spastic muscles already were strong and that strength training would increase spasticity and cause deformities. However, muscle tissue studies in children with cerebral palsy showed weakness and paresis of the spastic muscles.[10-12] Importantly, recent research (Fowler et al.,2001, Dodd et al., 2002 showed that spasticity did not increase after strength training.[20,26]

If strength training does not increase spasticity, the next question is obvious, namely whether strength training improves performance in CP. Damiano et al.,1995, showed that strength training of the spastic leg muscles did increase quality of walking (stride length and speed).[27] In the upper limb only 2 studies, with small sample sizes, showed improvement on manual performance due to strength training. [28-29]

To measure the effect of upper limb training on muscle strength and manual performance, quantitative tests are needed that measure strength and force regulation in specific manual tasks. Therefore, the research on manual strength capacity in both isometric and dynamics tasks in the affected hands in children with spastic hemiplegia is the main focus of this manuscript.

Intervention

As mentioned, therapeutic interventions to increase manual performance in children with spastic hemiplegia have changed in the last decade. The aim is no longer focused on only decreasing spasticity and muscle tone. Instead strength training and specific skill training are nowadays more the primary focus of the therapy. In this thesis we studied the effect of an intervention in which reduction of spasticity (Botulinum Toxin- A), strength training and skill training are combined. One way to treat spasticity in the upper limb is the use of Botulinum Toxin-A (BTX). It has been suggested that the decrease of spasticity may increase the effect of physical and occupational therapy but this has not been tested rigorously.

BTX is a neurotoxin, produced by the anaerobic bacterium Clostridium Botulinum. If injected in a muscle, BTX causes a blocking of the release of acetylcholine at the neuromuscular junction.[30,31]This creates a dose-dependent temporal muscle relaxation of 2 tot 4 months. Recovery of the innervation takes place by re-innervation, by nerve sprouting, the formation of new synaptic contacts and

finally by reparation of the originally affected nerve-endings.[30,31]The application of BTX as a therapeutic tool is always followed by a period of intensive therapeutic – physical and occupational- intervention. Periods of 3-6 months are most commonly used in the Netherlands.
Many studies demonstrated the effect of BTX together with physiotherapy and occupational therapy. All of these studies did focus on functional and clinical effect measures.[32-35] Although a lot of studies reported effects of BTX , no positive or negative effect of BTX on manual function can be conclusively identified.[36-38] BTX decreases spasticity and muscle strength in the injected muscles and increases active range of motion of its antagonists.[36-38] No direct effect on passive range of motion has been described. Main goal of BTX is to reduce the muscle tone in the injected spastic muscles and if combined with intensive therapy, to improve the active range of motion (AROM) of the antagonistic muscles.[36-38] In studies reporting the direct effect of BTX within 2-3 weeks, increase of AROM of the antagonistic muscle was present, along with a decreased grip strength.[32-35] The effect of BTX and therapeutic intervention on muscle strength and muscle force regulation and control of dynamic movements have not been studied yet.

Standardization of therapeutic intervention
No standardized physical and occupational program is described in literature after BTX intervention. Therefore we developed a standardized task oriented therapy program, based on motor learning, strength training and treatment of mobility with splints. Motor learning was performed according to the learning principles of Fitts' and Posner.[39] Learning of skills and strength training embedded in task oriented training were performed during 6 months, 3 times a week (each 30 minutes of physiotherapy and 30 minutes of occupational therapy).

Thesis outline
The more specific aims of the present thesis are fourfold.
The first aim is to examine whether manual isometric muscle force generation and regulation, and manual dynamic force regulation in both affected and non affected hand of children with spastic hemiplegia differ from those seen in Typically Developing children (TD). The second aim is to investigate whether performance in the isometric task deteriorates, if spatial information about the target disappears, both for TD children and children with spastic hemiplegia in the affected hand. The third aim is to measure the direct effect (within 2 weeks) of BTX on isometric force control and dynamic manual force regulation. The last aim is to determine the effect of therapeutic intervention (comprehensive rehabilitation during 6 months) with and without BTX on the muscle force generation and regulation at long term (3 months after ending the therapy). These aims are taken up in the various chapters as outlined below.

Chapter 2 addresses the manual isometric force generation of children with spastic hemiplegia compared with controls. Both Maximum Force and generated force at 5 sub maximal force levels and the co-efficient of variation of force will be discussed in this chapter.
Chapter 3 presents the influence of spatial feedback on manual isometric force generation in children with spastic hemiplegia compared with controls.

In this chapter the hypothesis is tested if children with spastic hemiplegia rely more on externally guided visual feedback when trying to keep isometric force constant with their affected hand (AH) as compared to their non-affected hand (NAH) and as compared to controls. Absolute error and normalised force and power spectra analysis are used to test this hypothesis.
Chapter 4 describes the manual dynamic force regulation of children with spastic hemiplegia compared with controls. Primary question in this chapter is whether children with spastic hemiplegia obey Fitts' law, despite their motor difficulties. In a simple tapping task reaction time, movement time and accuracy were measured to compare the performance of children with spastic hemiplegia with theirs controls.
Chapter 5 addresses the direct effect of BTX on manual dynamic force regulation in a RCT. In this chapter, 2 kinematic aiming tasks (KAT) are used to test reliability and sensitivity of the KAT test and to quantify changes in arm movements (movement time, accuracy and spread of endpoints) within 2 weeks after Botulinum Toxine-A injections in children with spastic hemiplegia. Correlation with Ashworth scores, maximal force and range of motion are discussed.
Chapter 6 reports an RCT in which the additional effects of BTX on intensive therapy on manual isometric force regulation is presented over a 9 month follow up period. In this chapter the short- (2 weeks) and long-term (6 and 9 mo) effects were measured of a standardized functional training program with, versus without, the addition of chemodernervation of forearm and hand muscles. To quantify the changes isometric force (with over- and under-shoot as force production error), active and passive range of motion (measured by goniometry; ROM), stretch restricted angle (SRA) of joints; Ashworth scores at the elbow and wrist, and the Melbourne assessment of unilateral upper limb function are used.
Chapter 7 outlines the additional effect of BTX on dynamic force regulation. The direct (2 weeks) effect of therapy and follow up effect ((after 6 and 9 mo) of a standardized functional training program of two with, versus without, additive BTX are measured. Dynamic force control is measured by movement time, endpoint spread, proportion hits and performance in both lift and shift tasks.
Finally, in chapter 8, the results and the conclusions of the preceding papers are evaluated and discussed in the light of clinical, methodological and theoretical considerations. Some future directions for research are outlined.

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2

Muscle force generation and force control of finger movements in children with spastic hemiplegia during isometric tasks

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ABSTRACT

In this study the effects of force level on force control ability was investigated in 20 children, 5-15 years old, with spastic hemiplegia and mild and moderate hand dysfunction and an aged-matched control group. The expected outcome was that the effectiveness of force production would be decreased and relative force variability would be enhanced in the affected hand (AH). An isometric force production task at five different levels of their Maximum Voluntary Contraction (MVC) was performed. Results showed that MVC generated with the AH was only one third of the non affected hand (NAH), time to peak was almost two-fold at the highest force level and the coefficient of variation (CV) was twice as high. The NAH did not differ with the control children. Correlations between clinical and experimental variables were significant for the relation between the Ashworth score for the elbow flexors, MVC and variability at the highest force level. In conclusion, the finding of reduced MVC in AH suggests that strength training should be considered for agonist spastic muscles.

INTRODUCTION

Lesions of the corticospinal tract severely impair manipulative skills and isolated movements of the fingers.[1] Most studies for the hand have focused on the differences in the coordination of grip and lift force in normal children and children with hemiplegia.[2,3] Results showed that children with hemiplegia have impaired grip-lift force synergy compared to control children.[2,4] The ability to maintain force in a pinch task was clearly affected.[3] Abnormal production of hand force is considered a possible primary source for motor performance deficits in CP.[3] Based on these results, it is hypothesized that maximum force in the finger flexors will be less in children with spasticity and force variability may be increased.

The present study has implications for the clinic as well. Clinicians have long argued against strength training in children with CP since it was thought to exacerbate spasticity and the spastic muscles were estimated to be strong.[5-7] If any strength training was given at all, this was always to the muscles opposing (or antagonist to) those that were spastic. In this study we wanted to measure the capacity of one group of spastic muscles (the finger flexors) to exert force and to grade force. Because low correlations were found between between clinical spasticity scales, EMG activity[8] and functional measures[9,10] we also looked into the relationship between clinical measures and experimental force variables. It was hypothesized that the use of high forces could possibly reveal correlations, which until now went unnoticed.

In this study, we used a simple isometric task in which no trajectory planning or complex interlimb coordination was necessary. Moreover, since variability of force is related to absolute levels of force.[11] Force control is described in outcome variables relative to MVC and over a large range of force levels.

An isometric task was chosen, since an isometric contraction measures the force production ability of a muscle group without the change in overall length. Stretch responses characterizing spasticity will be minimized in this way and isometric testing has been shown to be reliable in CP children from about 4 to 5 years of age.[12,13] Force is measured over a large range of force levels (12- 60% of MVC). It is expected that with this paradigm we will selectively study muscle force gradation without much interference of trajectory planning, motor sequencing or intra -limb coordination.

In summary, the first question to be answered in this study concerns overall force generation in children with CP. The second aim is to compare the steadiness in maintaining a given amount of force between children with CP and typically developing children. Our third aim is to study the relation between clinical measures and instrumented force variables.

METHOD

Participants

Twenty children (10 female and 10 male, 10 right and 10 left side hemiplegia) with cerebral palsy participated in this study. They were aged 5 to 15 years (mean: 9.55). Based on clinical signs, the children were diagnosed with hemiplegia according to the Hagberg classification.[14]

All children were independent community walkers. Inclusion criteria were ability to co-operate with instruction, age between 5 and 16 years and hand function according to Zancolli with score I, IIA and IIB. (mild and moderate hand dysfunction).[15] See table 1. The group III was excluded in this study because of their inability to extend the fingers and wrist actively.

All children attended mainstream education in the special school belonging to the rehabilitation center and experienced no problems understanding the instructions. All children received physical therapy for more than one year. The parents gave informed consent and the Medical Ethic Committee of Stichting Revalidatiecentra Limburg (SRL) approved the study. Subject's characteristics are summarized in table 2.

Twenty age-matched children without known motor problems (confirmed by test scores above the 15th percentile of the MABC[16,17])participated in this study as control subjects.

Clinical assessment of hand function

Active and passive Range of Motion (ROM) of the elbow and wrist were measured manual standardized goniometry (Mie Goniometry).[18] Spasticity was measured using the Ashworth scale.[19]

Procedure and tasks

To perform the isometric force tasks, the subjects were seated on an adjustable chair, forearms resting on the table, in front of a PC monitor; on which a visual feedback was given. On the monitor a yellow cursor was displayed (figure 1a). The subject was asked to apply force with his/her index and middle finger positioned onto the end of a lever. The aluminium lever, a high-quality strain gauge (Sokki Kenkyujo; type CLS-20KA), transmitted the force onto a force transducer, placed in the middle of this lever. The pressure on the lever directly created a raising movement of the cursor on the monitor (See figure 1a en 1b). An amplifier (Burster; type 9154) delivered its output to a 12-bit AD-converter (DAS800). The computer sampled the signal at a rate of 1000 Hz.

First the Maximum Voluntary Contraction force (MVC) in this task was assessed.

In the experiment itself five different levels of constant force - ranging from 12 ,24, 36,48 to 60% of MVC-, duration 10 seconds per level, were recorded 5 times. A random design was used. An auditive start and stop signal was used. (For detailed description see Smits-Engelsman et al., 2003.[20]

Table 1: Classification according to Zancolli

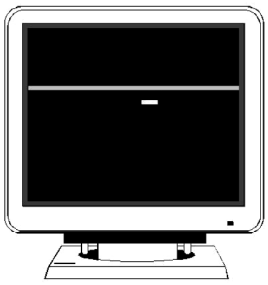
Classification according to Zancolli.	
Pattern I:	Active extension of the fingers is possible with less then 20 degrees palmar flexion of the wrist. Active extension of fingers en wrist is possible. Frequently light spasm of flexor carpi ulnaris muscle and extrinsic finger flexors. The position of the thumb will influence the function of grasping.
Pattern II:	Active extension of the fingers is possible with more then 20 degrees palmar flexion of the wrist. Active extension of fingers will be badly influenced by the spasm of wrist en finger flexors. The capacity of active dorsal flexion of the wrist leads to a further subdivision: IIA: Active dorsal flexion is possible with flexed fingers. IIB: No active dorsal flexion of the wrist is possible.
Pattern III:	No active finger extension possible, even when wrist has maximal palmar flexion

Table 2: Age, gender, affected side, Ashworth score, active and passive range of motion for all participants grouped by Zancolli classification.

Zancolli	**Number***	**Gender***	**Affected Side***	**Age****	**Rom active elbow****	**Rom passive elbow****	**Romactive wrist****	**Rom passive wrist****	**Tone elbow *****	**Tone wrist*****
Zancolli 1	6	3 Male 3 Female	2 Left 4 Right	9.4 (3.7)	169 (13.7)	174 (9.6)	27 (24)	79 (9.2)	0.33 (0.5)	0.17 (0.4)
Zancolli 2a	9	3 Male 6 Female	5 Left 4 Right	8.5 (2.9)	169 (7,5)	179 (1,65)	-1 (34.6)	70 (13)	1.00 (0.7)	0.33 (0.5)
Zancolli 2b	5	4 Male 1 Female	3 Left 2 Right	10.2 (4.0)	157 (18.7)	181 (4.7)	-42.2 (17.6)	66.8 (9.14)	1.00 (0.7)	0.80 (0.4)

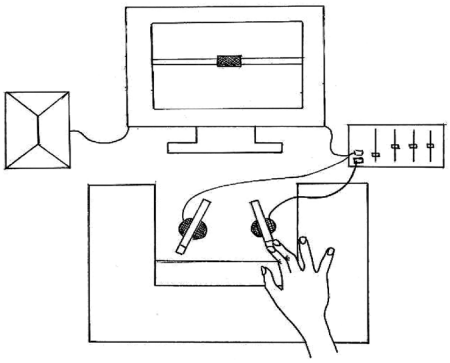
* frequencies ; ** mean and standard deviation; *** median and standard deviation.

1a



The cursor on the monitor, which moves upwards when the subject presses harder. It is the subject's task to keep the cursor on the grey bar.

1b



The subject is sitting behind a monitor with the index and middle finger on a lever, arm supported on the table.

Figure 1a and 1b. Apparatus and set up.

Signal and data analysis

The total force trace per trial was divided in three parts (figure 2a en b). The time to target force (time to peak), the hold phase (10 sec) and the time to release. Time to peak force is defined as the time from the starting signal till the moment the grey bar was reached. Time to release is the time needed after the 10 second hold end signal to reach the rest value again. Because our interest in the steadiness of the continuous force production and to filter out outliers in the raw signal the median force level per recording was calculated during the middle 7 seconds of the task (see figure 2a en 2b). To make a better comparison possible of the performance between groups and hands despite differences in MCV, we calculated normalized root mean square error (RMS), normalized force (generated force / MVC x 100) and normalized force variability. Normalized RMS error was calculated as index of the degree to which the participant's applied force deviated from the target force with respect to the mean force. To value normalized force variability the coefficient of variation (CV) was calculated (sd / mean force x 100). The normalized force, CV, time to peak and time to release were computed for each recording. The dependent variables were evaluated by means of General Linear Model, Repeated Measures design, with group (2) hand (2) percentage of MVC (5) and block of trials (5) as independent variables. Post hoc analysis was performed when appropriate. Spearman rank correlations were calculated to examine if the clinical measures (Zancolli, Ashworth Scale, active and passive ROM) could predict the quality of active force production. Linear regression model was used to find the strongest predictors of force generation and variability. We also

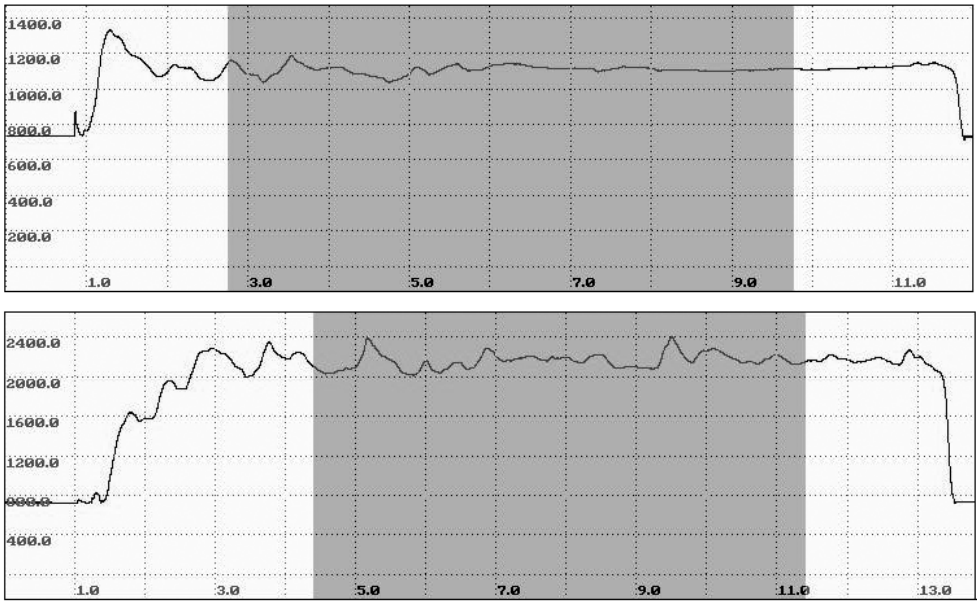


Figure 2a and 2b. example of a force trace of a control child (a) and a child with CP (b)

checked for gender differences, possible impact of side of the lesion and Zancolli classification. Alpha was set at 5% (two-tailed).

RESULTS

Force generation in CP and control group.

The force produced by the CP children with their NAH was comparable to that of the PH and NPH of the control group. However, overall the NAH produced almost three times as much MVC force as the AH (table 3). This was confirmed by a significant interaction effect on MVC between hand and group ($F(1,36)=62.10$, $p<0.001$).

For normalized force a significant main effect of force production level was found ($F(4,144)=2592.34$, $p<0.001$) along with a group by level of force interaction ($F(4,144)=4.98$, $p<0.01$). All the children were having more problems producing the higher force levels but the AH showed the largest problems at the higher force levels (see figure 3), but no differences in learning or fatigue effect during 5 blocks of trials between the PH, NPH, AH and NAH were found.

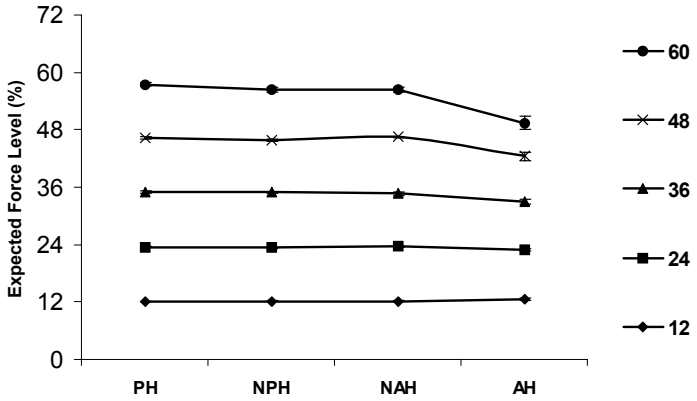


Figure 3. Normalized force for the preferred (PH) and non-preferred hand (NPH) of the control children and the non-affected (NAH) and affected hand (AH) of the children with CP at five force levels. Note the decrease at high force levels for the affected hand. Bars represent 1 standard error.

Table 3: Maximum Voluntary Contraction (MVC) for the preferred and non-preferred hand of the control children and the non-affected and affected hand of the children with CP.

Hand	MVC (N)	SE (N)
Preferred Hand	26.45	0.54
Non Preferred Hand	30.94	0.64
Non-affected Hand	27.70	0.53
Affected hand	10.15	0.24

Steadiness in maintaining force at all force levels in CP and control group.

Subjects performed 50 isometric trials each. Taken over all 2000 trials, on average no deviation was found between the absolute generated force (mean 8.240 N) and the absolute required target force (mean 8.245 N). The first important fact is that participants complied with the tasks well. Normalized RMS error values were also quite low 9.7, 3.9, 3.3 and 4.4% for AH, NAH, PH and NPH, respectively. For normalized RMS error a significant main effect of force production level was found ($F(4,144)=40.91$, $p<0.001$) along with a group by level of force by hand interaction ($F(4,144)=5.00$, $p=0.01$). All the children showed more deviations from the target at higher force levels and the AH showed the highest deviations.

For the coefficient of variation (CV) a main effect of force percentage emerged ($F[4, 144]=7.78$, $p<0.001$). This effect, however, was largely caused by a significant increase in CV in the AH at higher force levels ($F[1, 36]=17.35$, $p<0.001$). In figure 4 this interaction effect is depicted. The control children hardly showed any difference between the variability at different force levels. In the children with CP the CV of the NAH showed a comparable pattern to the controls. The mean CV for the NAH was 8.3% , PH 8.2%, NPH 11.3% and AH 17% of the generated force (increasing up to 22.2% at the highest force level).

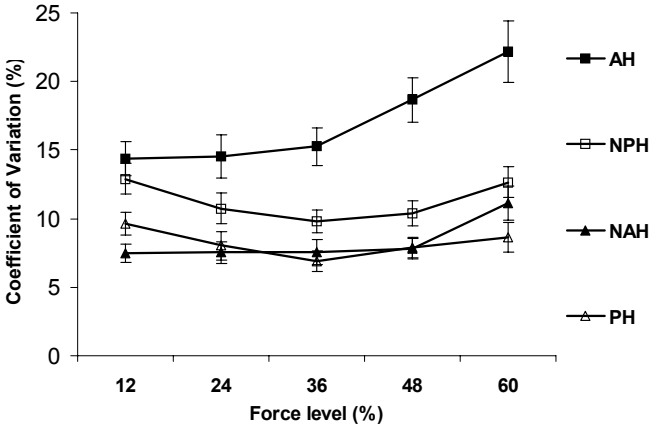


Figure 4. Coefficient of variation for the preferred (PH) and non preferred hand (NPH) of the control children and the non-affected (NAH) and affected hand (AH) of the children with CP at the five force levels. Bars represent 1 standard error.

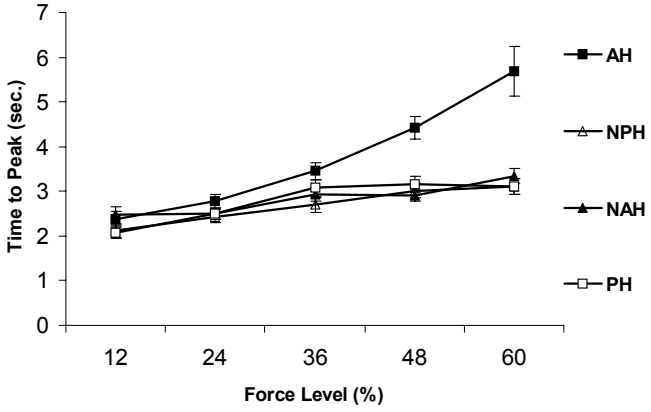


Figure 5.Time to peak force for the preferred (PH) and non-preferred hand (NPH) of the control children and the non-affected (NAH) and affected hand (AH) of the children with CP at the five force levels. Note the increase in the time for the affected hand at higher force levels, while no difference is seen between the hands of the control children and the non-affected hand of the children with CP. Bars represent 1 standard error.

Time to peak and to release.
For all hands it appeared to take more time to reach the highest force level (F [4, 144]=37.98, p<0.001) but this effect was larger for the AH (F [1, 36]=5.62, p=0.02). In figure 5 it is shown that at every force level the time to peak for the AH was higher than for the NAH, NPH and PH. Time to release showed a main effect of force level (F [4, 144]=9.71 p<0.001) but no other main or interaction effects yielded. All children needed more time to release the levers if they had to push harder.

Inter-correlation of clinical measures
Zancolli score showed an expected high negative correlations with active range of motion in the wrist (rho=-0.68).The wrist flexor Ashworth scores also correlated significantly to Zancolli scores (rho=0.46). Wrist and elbow flexor Ashworth scores showed only higher and significant negative correlations with the active ROM, and lower but not significant correlation with the passive ROM (Table IV). This shows that larger active range of motion co-occurs with less spasticity, which is to be expected. On the other hand it can be seen that neither spasticity or active range of motion were related to the passive joint motion indicating that tendinogen factors were not causing the primary functional limitation.

Comparison of experimental variables and clinical measures
Zancolli ratings showed no correlation to any of the force control variables. Correlation coefficient between elbow spasticity scores and MVC in the finger flexors was –0.80 (p<0.001). Elbow flexor tone also showed significant correlations with CV. Active ROM of the wrist correlated to CV from 48% and up, but not at the lower levels. (48%: rho=-0.44, p=0.050; 60%: rho=0.47, p=0.035). A stepwise regression analyzes showed that flexor tone and active ROM at the elbow were the strongest predictors of the generated force (MVC) (F [2, 17]=24.00, p<0.001). This combined model explained 73% of the variance in the MVC. Stepwise regression also showed that only one variable contributed significantly to the prediction of the variability of the force signal (CV), namely elbow flexor tone (F [1, 18]=8.15, p=0.011, $R^{2=}$31).

DISCUSSION

Force generation
The primary aim of this study was to assess force generation and its variability in the AH in children with hemiplegia. A first main finding of this study is that the MVC in the AH of children with CP is three times less than in the NAH or in the hands of the control children. The present data on the arm are in full agreement with other quantitative force data obtained in the legs of CP children.[21-23] The assumption that spastic muscles are strong and overactive has now been rejected for the finger flexors.

What is the cause of this loss of force?

A first possibility is that the impaired force generation in children with CP results from active or passive resistance from the opposing muscles, thereby leading to lower levels of net force. Passive resistance is unlikely since one would predict that the passive range of motion in the wrist or elbow would relate to the force variables, but this was not the case. Active resistance or spasticity is unlikely because in recent literature on the leg this explanation has been discouraged. Damiano et al. (2000) found no relation between co-contraction ratios or magnitudes to normalized strength of the knee flexor or extensors.[10]

A second possibility for the reduced force production is that the muscles involved are weaker and intrinsically stiffer themselves. Muscles in children with cerebral palsy undergo substantial remodeling. In spastic muscles the cross-sectional area was found to be less than one third of normal, spastic fibres showed decreased sacromere length at rest,[24] selective atrophy of type 2b muscle fibres and relative increased type 1 muscle fibres.[3,25,26] At higher levels of isometric force children with CP have to use type 2b muscle fibers. The problems to continue generating accurately power at higher force level we found could be due to this phenomenon.

A final explanation for the reduced force is a reduction in output from the brain. Damage to the pyramidal tract may lead to disuse, which then can lead to secondary loss of central output capabilities.[22] It has been shown that distal muscles are more affected in CP[28,29] and that direct cortical innervation is more pronounced to finger muscles motor units.[1]

Force variability

A second major result of the present study was that children with CP do not suffer from an inability to scale the size of contraction, but they do show a deficit with respect to the variability around the (rightly) chosen force level. The steadiness in NAH was comparable to the control children. Concerning the increased variability in the force signal of children with hemiplegia there are many possible sources. In healthy subjects, force variability increases linearly with force levels.[11] This led these authors to conclude that orderly recruitment by twitch amplitude was a necessary condition for producing linearly scaled variability.

Hence a possible factor involved in the increase in variability in CP is abnormal recruitment. It could be that motor unit reorganisation after early brain damage contributes to enhanced force fluctuations in muscle force. The changed or lacking influence from the upper motor cortex in the early stages of development alters the fibres type distribution,[26] which diminished fine motor control in the children with congenital hemiplegia.

Another possible explanation for increased variability is that feedback loops are abnormal in CP. There are no indications that visual feedback control of isometric tasks is affected in the children with CP. In the literature there are several examples showing that sensory input is not the primary cause of force variability.[4,30] The authors concluded that central factors rather than peripheral nervous system damage is associated with hemiplegia. Muscles spindles are known to be extremely sensitive.[31]

Consequently it is quite possible that the small corrective movements made during isometric force maintenance were sufficient to induce spindle stretch. An increased gain in the stretch

reflex pathway in CP has been demonstrated by many authors.[32,33] The failure to produce stable force may reflex cortical disuse. Hence, exaggerated stretch reflexes and cortical disuse could explain the excess variability and decreased accuracy on the affected side, especially at high force levels as found in our study. In that case one would also expect to find correlations between CV and Ashworth scores. Such significant correlations were indeed found at higher force levels.

In summary, the present findings emphasize that the neural control of the muscle activity by itself and not the spasticity or range of motion of the antagonist are the most critical factors in force generation and gradation. Results are in accordance with the idea that the deficit is primary caused by the inability of the agonist muscle to generate sufficient force.[34] As a result children with CP are not able to recruit their muscles to the extent at which typically developing children can.[35] It could be that motor unit reorganisation contributes to enhanced force fluctuations in muscle force and that all the fluctuations are amplified by the increased gain in the stretch reflex.

Clinical implications

The variability in controlling force followed an approximate linear trend of increased variability at force levels from 36% MVC and upwards. This means that in every day life the AH can be rather accurate if the force required is low. These low force levels plus their unpredictability may explain why these children prefer to use mainly their unaffected upper limb to perform motor tasks, thereby inducing "learned disuse" in the affected arm.

In conclusion, spasticity in the upper extremity is predominantly localized in the flexor muscles, which do not only have weakened antagonists but are weak themselves. This weakness should be considered an important contributor to the motor dysfunction in CP. It follows that strength training should not be limited to extensor muscles but that flexors muscles should be strengthened as well. Strength training will not restore normal motor function. However, with intensive training in the AH, and associated increased strength, the children could use their affected arm in daily tasks at lower levels of their MVC. This would imply that, they would work with less variability in the AH and thus improve functional use. Strength training will cause a reduction in spasticity and an increase in range of motion.[9,10,36,37] In conclusion, children with coordination problems like CP can especially benefit from strength training in their affected upper limb when it is given as close as possible to the functional task for which it is needed.

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3

Children with spastic hemiplegia are equally able as controls in maintaining a precise percentage of maximum force without visually monitoringtheir performance

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ABSTRACT

In this study the hypothesis was tested that children with spastic hemiplegia rely more on externally guided visual feedback when trying to keep force constant with their affected hand (AH) as compared to their non-affected hand (NAH) and as compared to controls. An isometric force task in which a cursor had to be moved to a visually specified target that disappeared half way the task, was performed by 19 children with Cerebral Palsy (CP), spastic hemiplegia, aged between 5-16 years and an aged matched control group. It was found that the absolute deterioration of performance after withdrawal of target visualization did differ between AH, NAH and controls. The absolute error was smaller and the variability was larger in the hemiplegic hand. However, the normalized force error and co-efficient of variation increased similarly between groups. Furthermore, power spectrum density analysis of the force signal showed that both hands in both groups had a similar loss in the energy in the 2-3 Hz range when target visualization was removed. These results suggest that CP children are equally able to produce stable force without visually monitoring their performance than children without CP, provided they are allowed to operate within their own force range.

INTRODUCTION

Isometric contractions with visual force representation are frequently used to investigate force control. Performance in this kind of task relies heavily on haptic and proprioceptive feedback. In isometric tasks direct visual feedback is limited since there is virtually no movement. However one can provide externally guided visual feedback about the produced force as an "augmented" cue on a display and this allows one to study how subjects integrate this augmented feedback in a task of precise force control. These various sources of information have to be integrated through feedback processes to correct the motor output if errors in the force level are detected.[1-7] The reliance on feedback in static grip force tasks shows changes during development in children. At a young age (3 years and younger), grip force is predominantly controlled with internal proprioceptive control mechanisms. However, after the age of 6 years this changes to more reliance on visual feedback.[1,2] Information from the cutaneous receptors in the fingertips is also essential for adjusting and correcting movements in force regulation.[4,6,8] In pathology, selective dependency of visual information can be enlarged as has been shown in Parkinson disease and other central nervous system diseases as Cerebral Palsy.[9-11]

This study investigates the influence of withdrawal of visual target display on force regulation in children with the diagnosis spastic hemiplegia using an isometric task.

We chose isometric force production since this has been shown to be reliable in CP children 4 to 5 years of age.[12,13] This way muscle force production can be studied without much interference of trajectory planning, motor sequencing or interlimb coordination, which are all elements known to be disturbed in children with CP. Several types of feedback can be used during the isometric task performance. Firstly, there is somatosensory feedback (especially from muscle receptors and from mechanoreceptors of the fingertips). Secondly, there is internal information about the muscular effort. Last but not least there is the augmented visual feedback about the applied force (a computer screen with a cursor, representing the momentarily generated force, and a target bar, in which the cursor had to be placed and held). The presence of the cursor in the target bar gave the child the possibility to use external visual information to monitor if the required force level was reached. Although these external types of feedback differ from the more direct visual feedback present in some reaching, grasping or pointing tasks, it nevertheless provides a powerful means of feedback about the accuracy of the generated force.

In children with spastic hemiplegic Cerebral Palsy (CP), force scaling of fine motor skills is disturbed, due to damage of various cortical sensorimotor areas, thalamus and basal ganglia.[9,10,12-16] These damaged areas of the brain lead to several possible constraints on force scaling. In previous studies[12,13,17]children with hemiplegia showed a much higher variability in the force signal of the affected hand when performing an isometric manual force task. One of the possible reasons for this is a deficit in visual, cutaneous and proprioceptive feedback regulation. It has been argued that CP children suffer from tactile and proprioceptive disturbances leading to more variability in force scaling and increased dependence on visual

feedback.[3,9,10,13,16] However, these arguments have not been tested directly. A method to distinguish between the impact of externally guided forms of visual feedback versus other types of feedback is to eliminate the former. To achieve this, a task was used in which participants had to maintain a constant force at a target level over an extended period of time (10s.). They could always see the cursor but the target bar was removed after 5 seconds. After withdrawal of the target bar, the children were no longer able to monitor the accuracy of their performance. No knowledge of results was given after the end of a trial.

MATERIALS AND METHODS

Subjects

Nineteen children (10 female and 9 male) aged 5 to 16 years (mean: 10.9) with CP, spastic hemiplegia according to the definition of Hagberg[18] participated in this experiment. Hand function was rated according to Zancolli (pattern 1, 2a, 2b).[19] Informed consent was given and the Medical Ethic Committee of Stichting Revalidatiecentra Limburg (SRL) approved the study. Nineteen age-matched control children without known motor problems also participated in this study.

Apparatus and procedures

In the isometric force task the subjects had to apply force, with their index and middle finger positioned onto the end of a high quality strain lever (Strain gauge (Sokki Kenkyujo; type CLS-20KA; resolution 64 steps per Newton, 0.5% RO). The forces were transmitted onto a force transducer (sampling rate 1000 Hz), Amplifier (Burster: type 9154), 12-bit AD converter (DAS800), causing a cursor to move vertically upwards on the monitor. To perform the isometric force tasks, the children were seated on an adjustable chair in front of a 17" monitor, which was placed at eye level. On the monitor a yellow cursor was displayed, either on the right or on the left side (figure1). Participants could control the vertical position of the cursor by applying force with their index finger onto the end of a lever. The harder they pressed, the higher the cursor moved on the monitor. The subjects were only allowed to use the flexor muscle of their index finger and middle finger and had to leave their arm on the table so they could not use the weight of their entire arm. The thumb was slightly in opposition and placed on the table.

First the Maximum Voluntary Contraction force (MVC) in this task was assessed. In the experiment itself five different levels of constant force were recorded, at 12, 24, 36, 48 and 60% of the MVC (for detailed description, see Smits-Engelsman et al, 2003)[17].The tasks levels are calculated relative to MVC, because variability of force is related to absolute levels of force.[20] A target bar represented each specific force level and a cursor represented the force generated by the child. Each force level was measured in a random order for 10 seconds and the target bar was removed after 5 seconds. Each hand, the affected (AH), non affected hand (NAH), pre-

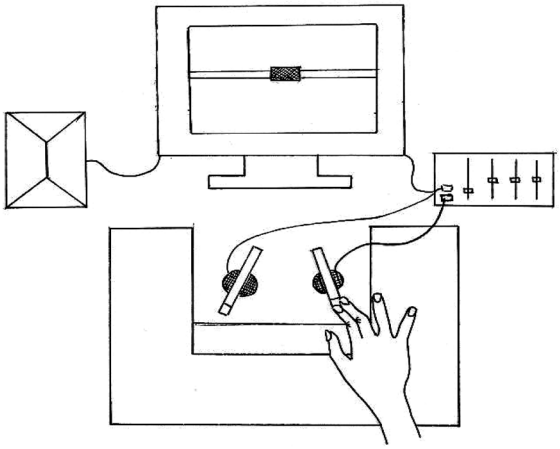

Figure 1. Experimental set up of subject, levers, wires to transducers, monitor and hand position. Thumb is slightly in opposition

ferred (PH) and non preferred hand (NPH) was measured 25 times (5 times per 5 force level). The experiment focussed on the steadiness of the continuous force production with and without the availability of the target bar as a reference value for visual monitoring of the required force level. Median force level per recording was calculated over two "steady" periods, one with and one without the visual target. During the first 5 seconds with visual target bar the first 1500 ms were discarded for analysis because we were interested in the steady state part only. From the second period (5 seconds without visual target bar) the first 1000 ms were discarded as well (hence the period just after the disappearance of the target bar). In addition, the last remaining 500 ms were removed because the auditory stop signal induced some irregularities in some subjects. For the whole 10 seconds epoch, the remaining 2 periods taken for analysis thus corresponded to 1500-5000 ms and 6000-9500 ms. See figure 2.

Analysis

The absolute root mean square error (RMS error) was calculated before and after withdrawal of the target bar. To compare the performance between groups and hands despite differences in MVC, we calculated for each recording the normalized RMS error and normalized force variability as coefficient of variation (CV). Normalized RMS error was calculated as an index to the degree of which the mean generated force deviated from the mean target force.[21,22] To correct for signal dependent variability, the CV was calculated as the standard deviation per trial divided by the mean force multiplied by 100.

In order to obtain more insight in the motor control strategies, a power spectral density analysis (PSDA) was performed before and after withdrawal of the target bar. A grand average of the resulting spectra over all trials and subjects in both periods was calculated to form an overall spectrum with thirty-two bands of 2 Hz per band. Relative spectra were calculated by

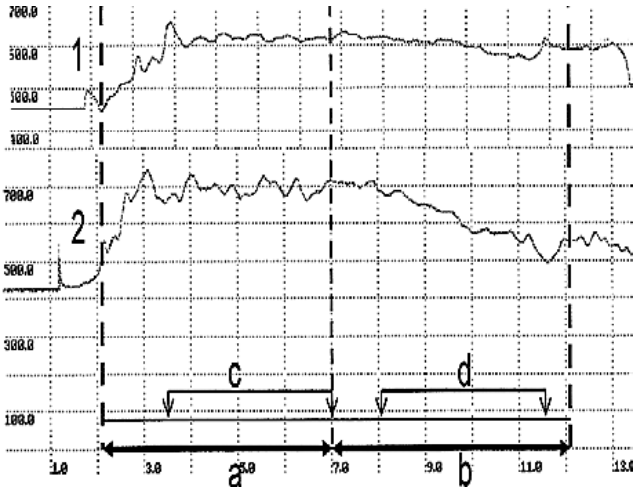

Figure 2. Task performance during the 10 seconds isometric task. Number 1 is performance of Preferred Hand (PH), number 2 is performance of Affected Hand (AH). Letter a represents 5 seconds period with visual feedback and in which Power Spectrum Density Analysis (PSDA) for that period has been done. Letter b represents 5 seconds period without visual feedback and in which PSDA for that period has been done. Letter c represents 3.5 seconds period in which Root Mean Square Error (RMS Error) and Coefficient of Variation (CV) has been calculated. Letter d represents 3.5 seconds period in which RMS error and CV has been calculated.

dividing the summed energy per band by the total power. Due to our interest in the long loop feedback frequencies we analyzed the 0-13 Hz band of the power spectrum.[17,22]
These dependent variables were evaluated by means of a General Linear Model (Polynomial) Repeated Measures design, with group (2), feedback condition (2), hand (2), percentage of MVC (5) and repetitions (5) as independent variables. Alpha was set at 5%.

RESULTS

Maximal Voluntary Contraction and generated force

Overall, MVC of the PH and NPH in the controls was comparable with the NAH of the children with CP (33.53 N, 36.55 N and 41.72 N). The AH produced one third of the MVC force of the NAH (13.86 N). This was confirmed by a significant group by hand effect ($F(1, 36)=71,285$, $p<0.001$). The range of absolute MVC was 4.40-30.15N (AH), 27.80-53.75N (NAH), 21.35-47.90N (NPH) and 25.9-47.71N (PH). These results are comparable with earlier studies.[13,17] In figure 3A these differences in absolute generated forces in AH, NAH, NPH and PH are reflected in relation to MVC. The children performed the tasks at comparable percentages of their MVC. figure 3B shows that after this normalizing procedure the differences in absolute generated forces were still present at all force levels and that these were enlarged at higher force levels. The differences between the required target force (mean 11.3 N) and the mean generated force with

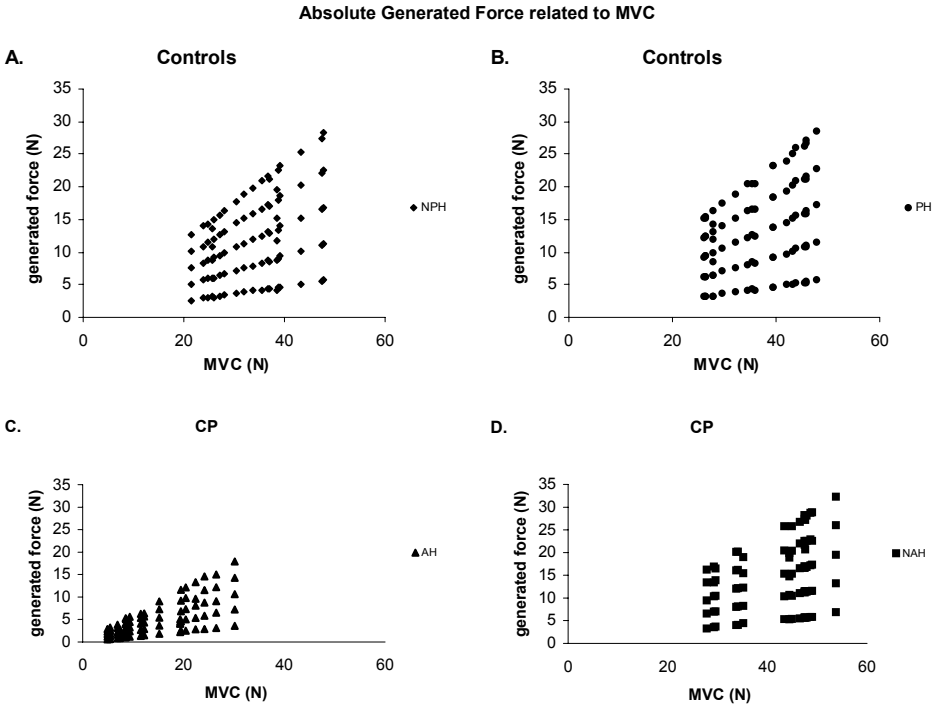

Figure 3A. Absolute generated force per individual related to Maximal Voluntary Contraction (MVC). In A. controls Non Preferred Hand (NPH), in B. controls Preferred Hand (PH), in C. children with CP Affected Hand (AH) and in D. children with CP Non Affected Hand (NAH). All are tested in the condition with visual target bar. Each point represents a mean value of 5 trials.

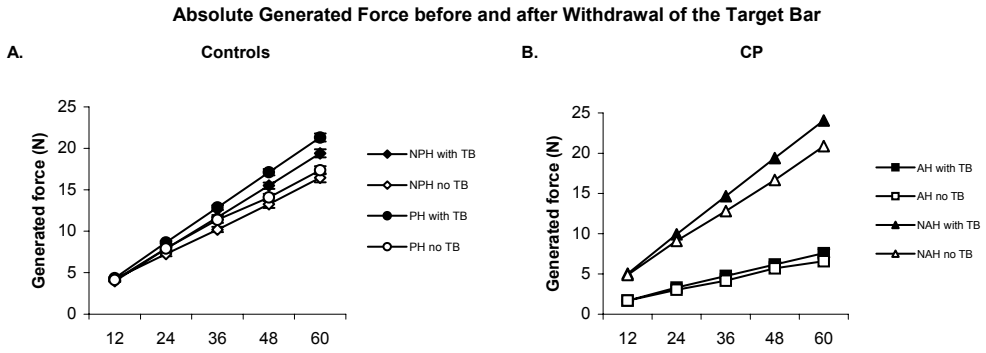

Figure 3B. Absolute generated force. In A. controls and in B. children with CP at all force levels for the affected (AH), Non Affected (NAH), preferred (PH) and Non Preferred hand (NPH) in condition before (with TB) and after withdrawal of the target bar (no TB). Error bars are +/- 1S.E.M.

target visualization was small (0.3 N) and more than two times larger for the tasks without visible target bar (0.7 N). This indicates the high degree of difficulty to perform the task when the reference value was removed.

Absolute and normalized root mean square error

Figure 4A and 4B shows the difference in absolute RMS error before and after the target bar was removed. The AH showed the smallest absolute RMS error indicating that the performance was least affected in that hand as compared to the others. However, because of the large differences in the MVC between AH and NAH, NPH and PH, normalized RMS error was calculated, to correct for signal dependent variability. After normalization a clear main effect of feedback condition on RMS error was shown ($F(1, 36)=177{,}78$, $p<0.001$). Furthermore, a main effect of force level ($F(4,144)=83{,}66$, $p<0.001$) emerged along with a feedback condition by level of force interaction ($F(4,144)=75{,}24$, $p<0.001$). The increase in normalized RMS error after withdrawal of the target bar was larger at higher force levels (see figure 4C and 4D). An important finding was that there was no main effect of normalized RMS error for group, repetitions and hand. To evaluate this result it is important to consider the possible impact of learning in the present task. Inter-trial learning effects can be discarded since performance did not change over repetitions. Hence the only "learning" during this task occurred during a single trial. The data then showed that the acquired skill to maintain a given force level using an artificial source of force feedback, was preserved equally well in CP as in control children after removal of this source of information. The lack of significant interaction for group and hand, or for hand and feedback condition, indicated that all hands in both groups of children were not different in controlling their force when the target bar was removed. These results showed that this group of children with spastic hemiplegia could successfully rely on remaining sensory and memory resources to accomplish the task at an equivalent level as seen in normal children. The mean difference on normalized RMS error between both conditions was 7.3%, 6.4%, 5.1% 5.4% for the PH, NPH, NAH and AH respectively. Therefore, the difference on normalized RMS error for the children with CP still was actually slightly lower than for the control children

Coefficient of variation

After removal of the target bar the subjects had to rely more on cutaneous and proprioceptive feedback to regulate their force constancy. If this type of feedback is deficient one would expect to find more irregularity in force in CP as compared to controls. This was not the case as shown in figure 5A and 5B. The average difference in the coefficient of variation (CV) between both conditions for the PH, NPH, NAH and AH was respectively 4%, 4.8%, 3% and 3.2%. The PH and NAH showed smaller difference in CV compared with AH and NPH. For the CV a main effect of hand ($F(1, 36)=22.80$, $p<0.001$ and feedback condition was found ($F(1, 36)=41.48$, $p<0.001$). No main effect of group and repetitions was found, again showing that learning did not significantly affect the results. Moreover an interaction of force level by feedback condition ($F(4, 144)=2.96$, $p=0.022$) was detected, showing an increase of CV in the condition with-

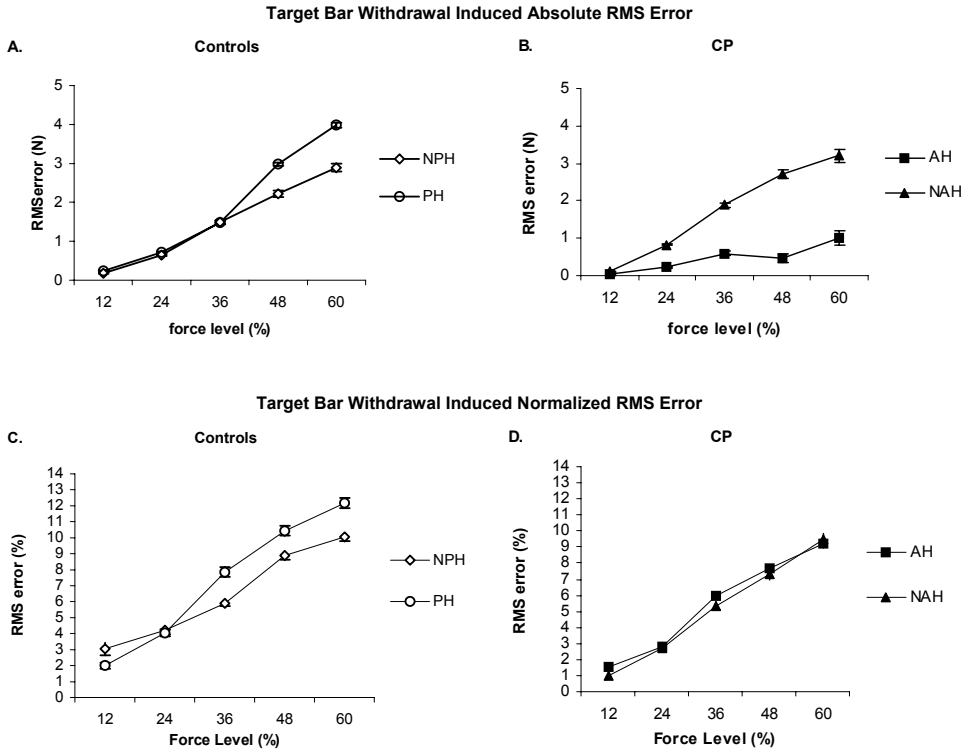

Figure 4. Force level related increase of absolute Root Mean Square (RMS) error caused by withdrawal of the target bar in Controls (A) and in CP (B). The normalized RMS error in Controls (C) and CP (D), at all force levels for the affected (AH), non-affected (NAH), preferred (PH) and non-preferred hand (NPH) show that children with CP did not differ from controls when forces are scaled. Error bars are +/- 1 S.E.M.

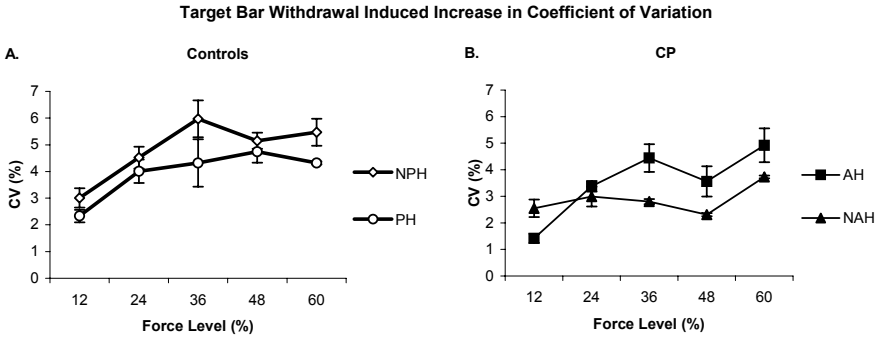

Figure 5. Increase of Coefficient of Variation caused by withdrawal of the target bar in Controls (A) and in CP (B), at all force levels for the affected (AH), non-affected (NAH), preferred (PH) and non-preferred hand (NPH). Error bars are +/- 1 S.E.M.

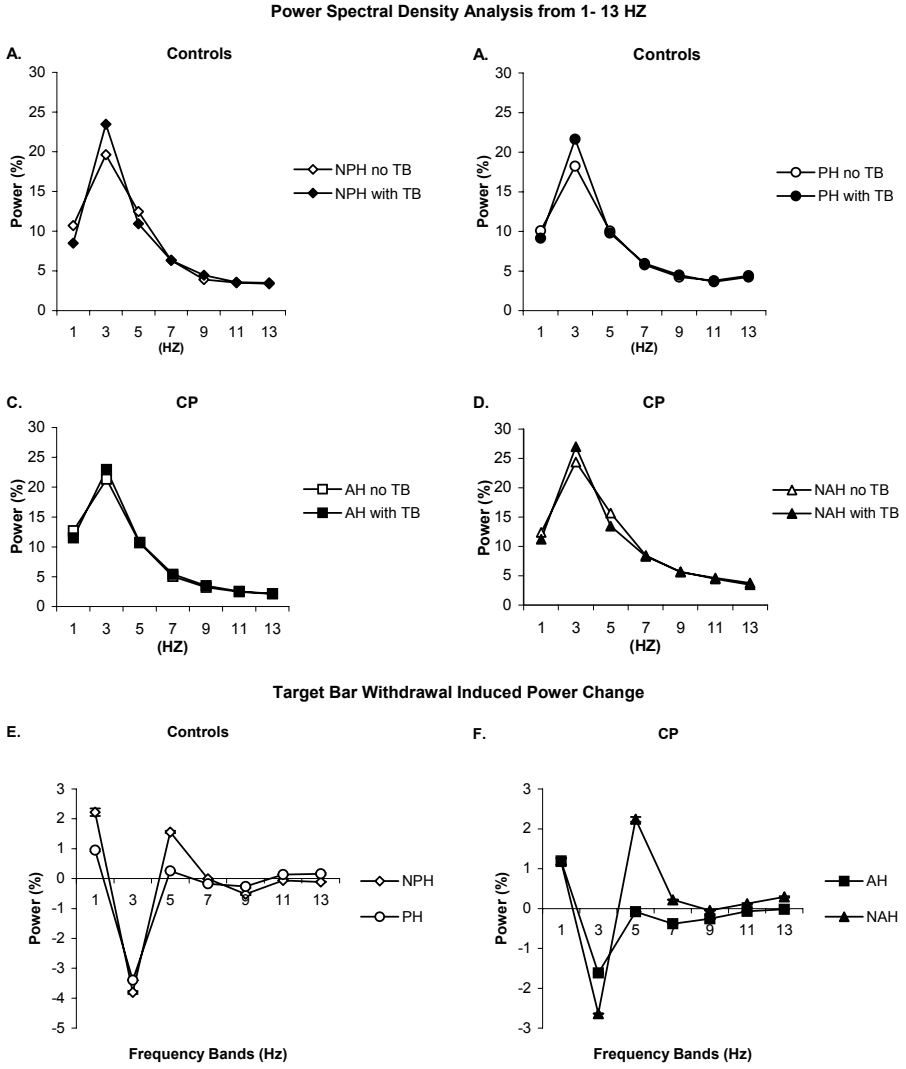

Figure 6. Power over frequency bands 1 to 13 Hz in condition before (with TB) and after withdrawal of the target bar (no TB) for Controls and CP. In A. for the non-preferred hand (NPH), in B. the preferred hand (PH), in C. the affected hand (AH) and in D. the non-affected hand (NPH). Changes in power over frequency bands 1 to 13 Hz caused by withdrawal of the target bar in Controls (E) and in CP (F) for the affected (AH), non-affected (NAH), preferred (PH) and non-preferred hand (NPH). Error bars in (E) en (F) are +/- 1 S.E.M. As seen in (E) and (F) an increase of power after withdrawal of the target bar was seen in 0-1 Hz band for all hands while in 2-3 Hz there was a decrease seen for all hands. In the frequency bands 4-5, 6-7, 8-9 and 10-11 Hz the main effect for hand was present ($F(1,36)=4,68$, $p=0.03$, $F(1,36)=18,55$, $p<0.001$, $F(1,36)=19,00$, $P<0.001$, $F(1,36)=23,07$, $P<0.001$ respectively). This was caused by the difference of energy shift for the AH compared to the NAH, NPH and PH.

out visual target bar at different force levels (see figure 5A and 5B). No significant interactions of hand and feedback condition or hand and group were observed. This indicates that there was no difference in CV between both hands and groups when the target bar was removed.

Power spectrum density analysis

At first view there was not much difference between children with CP and controls when performance was scaled with MVC. Still the possibility exists that this apparent output consistency relied on quite different mechanisms in CP and controls. To further scrutinize this question a spectral analysis was made of the force traces since it is known that the use of feedback strategies is reflected in changes in energy content in certain frequency bands (depending on feedback loop times).[11,17,22] As seen in figure 6A, 6B, 6C and 6D, most peak power was generated in the frequency band of 2 -3 Hz in both feedback conditions for all hands. The energy in these bands represents the use of visual feedback loops.[11,17,22] After removal of the target bar the power percentage in this 2-3 Hz band changed from 21.6% to 18.2% for PH, from 23.4% to 19.6% for NPH, from 27% to 24.4% for NAH and from 23% to 21.4% for AH. In the 4-5 Hz band there was usually a selective increase after the withdrawal of the target bar (PH from 9.8% to 10%, NPH from 10.9% to 12.5%, NAH from 13.4% to 15.7%), but for the AH only a very slight decrease was found (from 10.7% to 10.6%). The energy of the 4-5 Hz band represents the cutaneous and proprioceptive feedback loops.[11.17.22] This different behaviour of the AH was confirmed by an interaction of hand by group by feedback condition for the 4-5 HZ band ($F(1,36)=14,51$, $p=0.001$). The differences in the spectra are plotted in figure 6E and 6F.

DISCUSSION

The main results of the present study are an equal increase of both normalized force error (RMS error) and force variability (CV) for CP and for controls if the reference value (target bar) is no longer available to assist in maintaining force constant. The reference value (target bar) in this task represents an augmented form of visual feedback. This equal relative increase is also seen when error was not scaled for force. It was a surprising finding that AH and NAH did not differ in this respect. Overall the AH had a MVC which was only 30% of the MVC of the NAH and 25 % of the PH and NPH respectively. The increase in error after withdrawal of the visual reference value was 5.4 % and 5.1% for the AH and the NAH, as compared to 7.3% and 6.4% for the PH and NPH. This equal increase of RMS error and CV for CP and controls was present when they were considered over their own operating range. It is a well-know fact that error and variability scale with force (Jones et al., 2002). Hence, the relative low increase in these parameters in CP after removal of the target bar is an effect of operating at low force levels. Such explanation is further supported by the present finding that these parameters indeed increase with force levels in all hands examined. The increase of variability (CV) is less steep than for error but a tendency is present for all hands measured. If absolute force levels are considered then the difference in RMS error and CV between CP and controls is much larger.

For example, the 36% level of MVC of the CP children corresponds roughly to the 12 % MVC level of the controls. Removal of the target bar results in an average increase in absolute error of 0.8N at 36% force level for AH, 0.12N at 12% level for NAH, 0.2 N at 12 % force level for NPH and 0.27N at 12% force level for the PH. Hence for the same absolute force levels the increase is almost fourfold. In other words, in absolute force levels the CP performance deteriorates much more than the one of controls, but if performance is judged within the operating range of the CP children there is no difference between CP and controls. Therefore, the present data do not support the idea that CP children rely more on external visual monitoring of results than controls.

A second important result is that the visual loops are apparently equally important for both CP and controls in these tasks since removal of the target bar yields a large decrease in the 2-3 Hz band in the force power spectrum of both groups. CP children are known to have deficits related to vision, such as loss in visual acuity,[23] deficits in visuomotor control [24] and difficulties in mapping between vision and proprioception.[5] Therefore, it is conceivable that they would relatively rely more on cutaneous and proprioceptive loops (represented by higher frequency bands). This is not borne out by the present data since CP children have a large amount of energy in these higher frequency bands but they do not differ from controls in this respect.

Why was there no difference between CP and control children after removal of the external visual feedback? One possibility is that both groups could use a memory trace equally well. This could have played a role, especially just after the removal of feedback, but it is unlikely that this was the main source of information used. It is assumed that under this type of conditions the subjects try to use remaining sources of feedback to successfully accomplish the task. In this case the main source of remaining feedback comes from the pressure receptors in the fingers and from muscle proprioceptors, indicating changes in muscle force and length. If both groups made use of these cues then an interesting conclusion can be made, namely that CP children are not necessarily worse in using the latter type of feedback. It is commonly thought that CP children lack proprioceptive abilities making them extremely dependent on various types of visual feedback. We showed that the withdrawal of one type of visual feedback used in the current study had little effect on precision of force control in these children. This allows us to state that children with CP have equal problems to rely on remaining sensory and memory resources to accomplish the task as normal children provided one takes into account their smaller MVC.

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Children with congenital spastic hemiplegia obey to Fitts' Law in a visually guided tapping task

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ABSTRACT

Fitts' law is commonly found to apply to motor tasks involving precise aiming movements. Children with cerebral palsy have severe difficulties in such tasks and it is unknown whether they obey Fitts' Law despite their motor difficulties. If Fitts' law still does apply to these children, this would indicate that it is extremely robust and that even performance of children with damaged central nervous systems can adhere to it. The integrity of motor control processes in spastic cerebral palsy is usually tested in complex motor tasks, making it difficult to determine whether poor performance is due to a motor output deficit or to problems related to cognitive processes since both affect movement precision. In the present study a simple task was designed to evaluate Fitts' Law. Tapping movements were evaluated in 22 children with congenital spastic hemiplegia (CSH) and 22 typically developing children. Targets (2.5 and 5 cm in width) were placed at distances of 10 and 20 cm from each other in order to provide Indices of Difficulty (ID) of 2 to 4 bits. Using this Fitts' aiming task, prolonged reaction and movement time were found in the affected hand under all conditions in children with CSH as compared to controls. Like in the control group, movement time in children with CSH was related to ID. The intercept "*a*", corresponding to the time required to realize a tapping movement, was higher in the affected hand of the children in the CSH group. Although, the slope b (which reflects the sensitivity of the motor system to a change in difficulty of the task) and the reciprocal of slope (that represents the cognitive information processing capacity, expressed in bits/s) were similar in both groups. In conclusion, children with CSH obey Fitts' law despite very obvious limitations in fine motor control.

INTRODUCTION

Cerebral palsy (CP) is a heterogeneous group of syndromes involving various kinds and degrees of motor, sensory and cognitive problems. A consistent finding however is the devastating effect of early cortical lesions on manual dexterity.[1] The corticospinal pathway, often damaged in congenital spastic hemiplegia (CSH)[2] is the principal constituent of the motor system underlying skilled motor performance. Progress in understanding the basis of the multifaceted symptoms of the disease is required for treatment and rehabilitation.

Several recent functional magnetic resonance imaging (fMRI) studies have shown that a large network, including several contra- and ipsilateral cortical areas, are involved in precise movement planning and execution.[1,3,4] Goal-oriented behaviors, like picking up an object and releasing it on a target, rely on multiple neural interactions within a distributed and context-dependent cerebral network.[5] In particular, an emerging view is that preparatory activity evoked in different cerebral regions might reflect different combinations of motor preparatory processes. For example, motor planning might dominate premotor signals, whereas encoding potential targets of movement might be the main drive behind parietal responses. Finally, posterior temporal cortices might be involved in the extraction of contextual and intentional cues.[6,7]

It has been well established that children with hemiplegia have great difficulties with both movement speed and accuracy of goal directed behavior on their affected side. Therefore, it is surprising that the formalized relationship between the speed-accuracy trade off, expressed in Fitts' law has not yet been studied in children with spastic hemiplegia.[8] Fitts' Law states the log-linear relationship between the amplitude (A) of the movement, the target width (W) and the average movement time (MT) and is defined by the following equation:

$$MT = a + b * \log_2(2A/W) \quad (1)$$

where MT is movement time, A is movement amplitude, W is target width, and a and b are coefficients. In spatially constrained movements where both A and W are given, 2A/W is related to the number of possible movements, and the $\log_2$ (2A/W) is the information required (in bits) to resolve the uncertainty among them. The difficulty of the movement is represented by the value $\log_2$ (2A/W) and is called the Index of Difficulty (ID) (bits).

Furthermore Fitts' Law can be used to equate the processing ability or performance of the motor system by the Index of Performance (IP):

$$\text{Index of Performance (IP)} = \log_2(2A/W)/\text{Movement Time.} \quad (2)$$

Fitts' law was found to be valid for a wide range of environments and tasks.[9] Paradigms to test Fitts' Law are frequently used in motor control research. Many adaptations have been made to Fitts' original formula and various explanations have been given for the possible underlying principles that account for the speed accuracy trade off, since Fitts' original publication

in 1954 (e.g. Crossman and Goodeve 1983; Van Galen and De Jong 1995; Smits-Engelsman et al. 2002).[10-12] However, no research has been conducted in determining whether goal directed movements in children with spastic cerebral palsy obey Fitts' Law. Amongst the more than 200 studies that have used some kind of Fitts' task, none involved children with spastic hemiplegia (for review see Plamondon and Alimi 1997).[13] Sanger et al. (2005), studied cyclic aiming movements in children with dystonia owing to several different causes, and found a consistent relationship between movement time and target size in the dystonic children.[14] In that study keys of different sizes needed to be pressed and it was shown that the children with dystonia were more sensitive to accuracy requirements than the control group. Two other studies were performed on aiming movements with adults with cerebral palsy but both used only a small number (n=6 and n=8) of subjects (LeGare et al. 1994; Gump et al. 2002).[15,16] Gump and co-authors studied adult CSH subjects on a wide range of Indices of difficulty (2.19-6 bits/s). They found high error rates in subjects with CSH, which they assumed might be caused by oculomotor difficulties. Their most important conclusion was that subjects with CSH did not adhere to Fitts' law but only to square root of the amplitude of the equation (see equation 3). A possible explanation proposed by the authors was that severely affected subjects were not using their visual input properly to guide their movements. If this were the case, motor performance in subjects with CSH would better adhere to the ballistic factor (Gan and Hoffmann 1988):[17]

$$MT=K\sqrt{A} \quad (3)$$

where MT is the movement time, K is constant and $\sqrt{A}$ is the square root of the distance to the target.

One of the possible reasons the Fitts' paradigm has not been tested in children with spastic cerebral palsy is that they have poor motor abilities and that one cannot apply the commonly used tests to this group. Due to limited range of motion and poor motor coordination, children with CSH may have difficulties in planning and executing precise movements as required in a Fitts' task.[18]

According to the definition of spasticity, the faster the movements the higher the velocity dependent resistance will be.[19] As a result of their poor coordination, children with CSH may have problems converting the spatial position seen on a computer screen, typically used in a Fitts' task, into arm coordinates and to move their hand in the actual workspace. Together this would lead to a high error rate and leave only little experimental data to analyze.

It was crucial therefore to design a simple task which could be applied to children with CSH. Instead of using an experimental setting with a computer screen to show both the targets and a moving cursor on a vertical screen, as in our former studies (Smits-Engelsman et al. 2004 and 2006),[20,21]we used a horizontal LCD screen to display targets. We chose tapping tasks for this study because they were closest to the original Fitts' set-up and did not require precise braking at the end of the movement. In addition, spatial accuracy remained very important in these tasks since a special puppet designed for this experiment had to land on the target

Figure 1. The experimental set up with a digitizer as color LCD monitor. The XY-tablet is placed in flat position directly in front of the participant. Adaptations in equipment were made if the impairment was so severe that the children could otherwise not hold the puppet.

to succeed in the trial (see figure 1). Another advantage of these tasks was that movements did not have to be made by the fingers, which are usually most constrained in hemiplegic patients. If children were too severely disabled to hold the puppet between thumb and fingers, a ball shape was put on top so they were able to hold it in an easy grip with few requirements on supination of the fore arm (see figure 1). Thus, the tasks were made simple enough to be performed by the participants with CSH.

The aim of the present study was to examine the impact of congenital brain damage on goal directed movement control in children with hemiplegia.

Predictions

1. Increased processing time in CSH will be reflected by longer reaction time (RT). Higher levels of antagonist activity will lead to prolonged activation times before the movement starts (mechanical delay) and both RT and movement time (MT) will be longer. Furthermore less agonistic muscle force is expected due to strength loss in CSH and this will also lead to increased movement time.[19] Together this will lead to a higher Y-intercept *a* in the Fitts' equation.
2. It is hypothesized that decreased coordination in CSH will lead to a decrease in the accuracy of the movement. This will be measured by a larger spread of the end points of the movement. Because accurate movements are extraordinarily difficult for the children with CSH the regression coefficient or slope *b* is expected to be steeper than in controls with increasing task difficulty.
3. Based on studies in adults with CSH one might expect the control of amplitude to be more affected in children with CSH as a result of the increased stiffness and velocity dependent resistance. Performance in the tasks with the same ID is then expected to be poorer in the large amplitude condition. Furthermore, if deficits in amplitude control primarily underlie the increased movement time then children with CSH will show better adherence to Gan and Hoffmann's ballistic factor than to Fitts' Law.

4. Moreover if velocity dependent resistance and restricted range of motion are important underlying features for poor performance in goal directed movements, significant correlations between the kinematic variables and the clinical measured are to be expected.

METHOD

Tasks and procedure

In this experiment, the children had a real object, a custom made puppet, in their hand and they could directly see their hand movements and the targets. An LCD screen was placed in flat position on a table in front of the child and was used to record the XY coordinates of the moving object. To test if children with spastic hemiplegia obeyed Fitts' law, a discrete visually-guided tapping task was developed. Oasis software[22] was used to program four Fitts' tasks with 3 Indices of Difficulty (ID) that were expected to be easy enough for children with CSH to perform. The tasks were first tested on typically developing 3-year-old children and adapted until all of them were able to accomplish 85% of the trials.[22] To differentiate whether amplitude or target size had more of an impact on their performance, movements were made over 10 or 20 cm distance and to a small (2.5 cm) or large (5.0 cm) target. Thus, we had two conditions that had the same ID (3 bits) but differed in amplitude and target size (large amplitude with small target, and vice versa). According to Fitts' Law they should have the same outcome unless amplitude or target size proves to have a larger impact.

The goal for the children in this experiment was to get the puppet in the target circle while performing an arm movement on the digitizer (Wacom, type Cintiq 18sx, sample rate 206 Hz). This digitizer also functioned as a SXGA full 24-bit color LCD monitor and was placed directly in front of the participant (see figure 1). After the children picked up the puppet and put it in the starting circle on the left side of the digitizer the investigator pressed the start button. After a random period (between 0.5 -1.5 s) a tone sounded and a target appeared on the right side of the digitizer. This was the 'go' signal for the child who was then required to move as fast and as accurately as possible to this target by lifting the puppet and letting it land on the target that had appeared. If the puppet was held still on this target after it landed, a next target would appear on the other side of the digitizer etc.

The four task conditions were presented to the children with increasing difficulty, in the following order: (a) 10 cm movements to a 5 cm target; (b) 10 cm movements to 2.5 cm target; (c) 20 cm movements to a 5 cm target; and (d) 20 cm movements to a 2.5 cm target. The indexes of difficulty were 2, 3, 3 and 4 bits, respectively. The tasks consisted of 4 trials of 10 movements each. All tasks were performed with the preferred (or non-affected) and the non-preferred (or affected hand). One practice session per task was given to see if the child understood the task. Sufficient rest was given to the children after every task to avoid fatigue.

Table 1: Characteristics of the participants with CSH.

Age	Male Female	Affected Side	Zancolli	Tone Elbow	Tone Wrist	ROM Active extension Elbow	ROM Passive extension Elbow	ROM Active dorsifexion Wrist	ROM Passive dorsiflexion Wrist
5.5	Male	L	1	0	0	180	180	45	90
5.6	Female	R	2a	0	0	160	175	-45	65
6.1	Female	R	2b	1	1	140	180	-40	70
6.2	Male	L	1	0	0	180	180	30	90
6.6	Female	R	1	0	0	180	180	30	80
6.10	Male	L	1	0	0	180	180	30	90
7.11	Male	R	2a	1	0	170	180	40	95
8.4	Male	R	2a	1	0	180	180	-20	80
8.5	Female	L	2a	0	0	180	180	10	60
11.0	Female	R	1	1	0	150	158	-20	70
11.5	Female	L	2a	2	1	160	180	0	50
11.5	Male	R	2b	1	1	170	170	-50	64
11.11	Female	R	2a	1	1	175	180	-15	70
12.2	Female	L	2a	2	0	165	175	-60	65
12.5	Male	L	2b	1	1	180	190	-50	80
13.0	Male	R	1	0	1	154	166	40	70
14.0	Female	R	1	1	0	170	180	40	75
15.0	Male	L	2a	1	0	170	179	40	65
15.0	Male	L	2b	0	0	162	180	-10	55
16.0	Female	R	2a	2	2	135	150	-30	70
16.0	Male	L	1	1	2	170	175	55	60
16.0	Male	L	2b	1	2	180	180	40	60

Participants

The experimental group consisted of twenty-two children (aged 5-16 years) with a diagnosis of congenital spastic hemiplegia according to the Hagberg classification.[23] All children were independent community walkers. All of them attended a mainstream school curriculum at a special school for motor-disabled children at the rehabilitation centre. Participants were required to be able to co-operate with instruction and to have a hand function according to Zancolli with score I, IIA and IIB (mild and moderate hand dysfunction).[25] The group III was excluded in this study because of their inability to extend the fingers and wrist actively. Eleven children had a right sided lesion and eleven children a left sided lesion. None of them had known visual field or sensory deficits. Twenty-two age-matched, typically developing children were measured as controls. The study was conducted with informed consent obtained from the participants and their care providers. It complied with the requirements of the declaration of Helsinki and was approved by the local ethics committee (Stichting Revalidatie Limburg).

Clinical evaluation of hand function

Active and passive Range of Motion (ROM) of the elbow and wrist of affected arm in the children with CSH were measured using manual standardized goniometry (Mie Goniometry).[26] All the children could easily move their affected arm up to 90 degrees abduction and elevation in the shoulder. Spasticity was measured in supine position using the Ashworth scale.[27] (Ashworth 1964).

The participants' information is summarized in table 1.

SIGNAL AND DATA ANALYSIS

Data analysis

Spatial accuracy was calculated in two ways: first using the dichotomy between the correct and incorrect responses (Percentage Successful Movements), second, as the distance of the centre of the puppet to the centre of the target (Endpoint spread, mm). RT (s) and MT (s) were calculated as temporal variables. The delay between the start tone and the beginning of the movement was the RT. The MT started when the puppet moved out of the starting area. In order for the children to not simply slide the puppet through the target, the MT ended only when the puppet stopped within the boundaries of the target and the tangential velocity dropped below 0.2 cm/s. The IP (bits/s) was evaluated as a measure of performance.

The stability of the kinematic outcome variables was calculated by randomly re-testing half of the children with CSH 4 weeks later on the same set of tasks. The ICC for all variables (Endpoint, MT and IP) was 0.80 or higher.

Different analyses were performed to test the various hypotheses. First, an overall multivariate analysis was performed for all dependent variables, with group (2) as between subject variable and hand (2) amplitude (2) and target size (2) as within subject variables. We also

added a post hoc (bonferroni) test to determine if task performance deteriorated in the affected hand with the task order.
Effect sizes, as measured by Eta Squared (η^2) values, were calculated in two separate multivariate analyses with either Index of Difficulty (Fitts' Law) or Root Amplitude (Gan and Hoffmann's factor) as the within factor. Two dependent variables were used, namely RT and MT, to check if children with CSH and control children responded differently to these factors. According to Wolff et al. (1984), only η^2 of ≥ 0.14 obtained from multivariate analyses are considered sufficiently large to be of any importance. Lastly, Spearman correlations between kinematic and clinical measures were calculated. Alpha level was set at 1%.

RESULTS

Overall results of amplitude and target size

Accuracy

The first important result was that the tasks were easy enough for the children to perform with their affected hand. Moreover, no significant differences emerged in the Percentage of Successful Movements between groups or hands. The movements with the affected hand of children with CSH succeeded in 78.7% of all trials. Percentages for the control children were 89.1 and 89.7 % for the preferred and non-preferred hand respectively. The non-affected hand came very close to these values with a success rate of 88.7 % and this was also not significantly different from the control group. Although the movements of the two groups of children ended comparably often in the target, the spread of the endpoints was larger for the affected hand. This was confirmed by a group by hand interaction ($F(1,45)=24.78$, $p=0.000$). However, this finding was not dependent on target size (figure 2a), movement amplitude (figure 2b) or index of difficulty (figure 2c). One interaction effect was found for amplitude by group ($F(1,45)=4.24$, $p=0.045$) but this was caused by the more accurate performance of the preferred hand of the control children and not (as predicted) by more difficulties in moving over the larger amplitude by the affected hand of the children with CSH.
To control for possible fatigue or decreased attention during the tasks, post hoc analysis compared the Endpoint spread in the 4 consecutive conditions. As can be seen in figure 3, no indication of decreased performance was seen in the course of the experiment and this was confirmed by the statistics.

Speed

Both RT and MT were much longer (approximately 60 and 80%, respectively) for movements made by the children with CSH as compared to controls ($F(1,45)=9.51$, $p=0.003$ and $F(1,45)=18.14$, $p=0.000$). MT was longer for the non-preferred hand in all the children ($F(1,45)=4.70$, $p=0.035$). This effect tended to be stronger in the affected hand as compared to the non affected hand for both RT and MT ($F(1,45)=3.57$, $P=0.065$; $F(1,45)=2.90$, $p=0.095$,

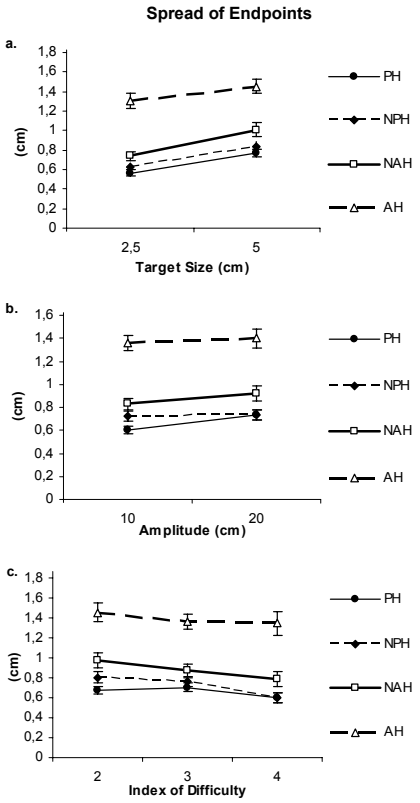

Figure 2a,b,c. Changes in Endpoints as a function of Target Size (a) Amplitude (b), Index of Difficulty (c). Data are for all subjects for preferred hand (PH) and non preferred hand (NPH) of the control children, and the non affected hand (NAH) and affected hand (AH) and the children with CSH. Error bars are +/- 1 S.E.M.

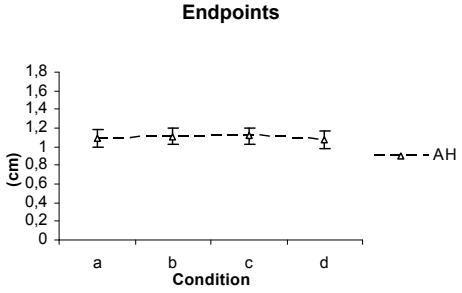

Figure 3. Changes in Endpoints as a function of Condition. There was no significant change in Endpoint spread for AH over the consecutive task conditions with increasing difficultly. Data are for affected hand (AH). Error bars are +/- 1 S.E.M

respectively). However no interaction with task emerged, meaning that the children with CSH responded similarly to the task conditions as control children. As is shown in figure 4 the movements with the affected hand had a higher Y-intercept *a* (as predicted). However, contrary to our expectations, the betas of the regression lines were not statistically different between groups or hands. All children needed relatively more time to move to smaller targets (figure 4a), to cover larger distances (figure 4b), and to perform tasks which had a higher index of difficulty (figure 4c).

Results of effect sizes for Index of Difficulty or Root amplitude

To test whether amplitude was the only explaining factor for the increased MT, the effect size (Eta squared) of the interaction of group by Root Amplitude (Gan and Hoffmann's ballistic

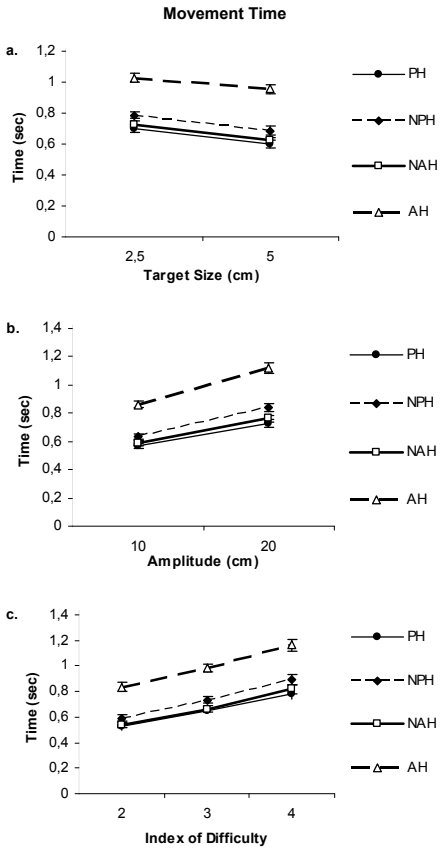

Figure 4a,b,c. Changes in Movement Time as a function of Target Size (a) Amplitude (b) and Index of Difficulty (c). Data are for all subjects for preferred hand (PH), non preferred hand (NPH), non affected hand (NAH) and affected hand (AH). Error bars are +/- 1 S.E.M.

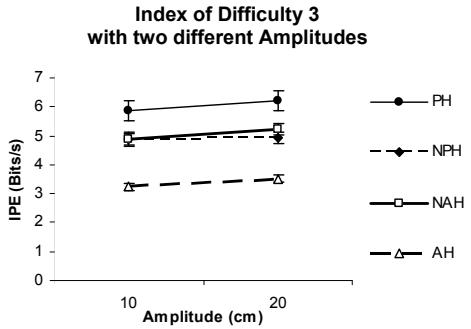

Figure 5. The Index of Performance Effective of the two tasks with the same Index of difficulty but different amplitudes for preferred hand (PH), non preferred hand (NPH), non affected hand (NAH) and affected hand (AH). Error bars are +/- 1 S.E.M.

factor) was compared to that of the Index of Difficulty (Fitts' Law). As can be seen in Table 2 children with CSH did not adhere better than controls to Gan and Hoffmann's ballistic factor, .since the effect size for the Root Amplitude by group interaction was found to be smaller than for interaction with the Index of Difficulty. However, this difference was not significant.

To further test if children with CSH acted in accordance with Fitts' Law we compared their Indices of Performance over the tasks with the same ID. As can by seen in figure 4 all groups showed similar patterns for tasks with the same ID, although the target width or amplitude was different. No group by task interactions occurred, indicating the both groups responded similarly to the task constraints. The small, non-significant differences seen in figure 5, pointed in the opposite direction than hypothesized; the IP over the larger amplitude was slightly higher for all children.

Table 2. Main effects on the variables RT, MT and the interactions of group by Root Amplitude (Gan and Hoffmann's ballistic factor) and by Index of Difficulty (Fitts Law). Notice that ID and Root have the largest effect sizes (Eta squared) and that the effect sizes of the interactions with group are very similar.

Effect on RT and MT	p-value	Eta squared
Group	0.000	.443
Hand	0.000	.658
Hand x group	0.000	.416
ID	0.000	.726
ID x group	0.05	.201
Root	0.000	.816
Root by group	0.009	.194

Table 3. Spearman correlation between the clinical measures and kinematic outcome variables

Spearman	Tone Elbow	Tone Wrist	Active Elbow	Passive Elbow	Active Wrist	Passive Wrist
RT	-0.03	-0.14	0.04	0.23	*-0.30	-0.06
MT	0.18	0.17	-0.01	0.06	*-0.45	-0.07
IP	-0.16	-.017	0.01	-0.05	* 0.43	0.08
Endpoints	0.09	0.21	-0.08	0.05	*-0.60	-0.07

If * : correlation is significant at the 0.01 level

Correlation between clinical evaluation of hand function and the experimental data

Table 3 shows that active range of motion of the wrist, rather than the level of spasticity, was the most important factor in predicting the outcome in the Fitts' tasks used in the present study. In particular the MT and IP were partly predicted by this measure.

DISCUSSION

The present study confirms that children with spastic hemiplegia have great difficulties with both movement speed and accuracy of goal directed arm movements on their affected side. This study was the first to test the formalized relationship between speed and accuracy as expressed in Fitts' law in children with CSH. There were three major findings.

First, it is clear that movements made with the hemiplegic hand have longer reaction and movement time which led to a higher Y-intercept *a* in the Fitts' equation. These deficits can be ascribed to a loss in force generation. In earlier studies, it was determined that children with CSH were deficient in force recruitment. Eliason and Gordon have shown that children with hemiplegia have a distinct deficit in force scaling while lifting an object between their thumb and index finger.[28,29] We have previously provided direct evidence of increased force variability in the force output signals of children with CSH within 12-60% range of their MVC.[30] Furthermore these children produced only 1/3 of the force compared to their healthy age-

matched controls. Hence it is clear that the force they can generate is reduced. Moreover it also takes longer for the force to be recruited. Taken together these factors indicate a problem of reduced motor output.

The second important finding is that the children with CSH did not respond differently than controls to increasing indexes of difficulty in tapping tasks, as measured by a similar regression coefficient as compared to controls (see figure 4). The log-linear relationship between the amplitude (A) of the movement and target width (W) also held for both hands of children with CSH, indicating that children with CSH adhered to Fitts' Law in easy tapping tasks. Current models of motor problems in CSH emphasize the abnormal development of motor control processes (e.g., perceptual processes and reflex activity responsible for adapting an appropriate motor response). However, the integrity of motor control processes in CSH is often inferred from tasks that require complex motor programming. Therefore, it has been difficult to determine whether poor performance on such tasks purely reflects a deficit either of the motor output or of cognitive control processes, since both functions may compromise the precision with which movements are made. In the present study, based on a very simple motor task, it was found that the slope of the speed-accuracy trade-off, which is supposed to reflect the efficiency of the motor system to deal with tasks of increasing difficulty,[8,21] was not different between controls and children with CSH. Thus, it appears that the children with CSH have comparable capabilities to control their affected and non affected hand and compared to the control children. The only difference is in their off-set values. Their prolonged reaction and movement time are independent of task complexity and thus information processes.

A third finding of this study was that the impact of amplitude in the range tested (up to 20 cm) was not larger for children with CSH compared to controls. In other words, the data did not show better adherence with Gan and Hoffmann's ballistic factor than with Fitts' Law. This was confirmed by the comparable outcome of the two tasks with the same Index of difficulty, but different in amplitudes. Furthermore, spasticity does not seem to be an important explanatory factor for movement speed or accuracy, since no significant correlations emerged between the spasticity measures and any of the kinematic variables (see table 3). The only significant correlation between clinical and kinematic variables indicated that if the active wrist excursion is more constrained, children with CSH need more time to make a goal directed movement.

Finally, the non-affected hand showed no decrease in performance compared to the controls in the Fitts' tasks (see figure 4 and 5). For the young children in this group the present results are in line with our earlier finding.[20] In that study it was found that the non-affected hand of children with CSH fewer than ten years of age produced equal muscle power relative to their typically developing peers. A difference in strength (Maximum Voluntary Contraction) became apparent in children with CSH over 10 years of age. The present results do not permit a conclusion of whether the satisfactory performance in Fitts' tasks in the non-affected hand in CSH will decrease with age. Further research will have to determine if the failure of the non-affected hand to improve with age, as found in the previously published study,[20] is a more general concept that applies to different movements. Such future studies should unravel the

issue of whether children with CSH fail to improve due to disuse of the non-affected hand or because of the contribution of ipsilateral motor areas on manipulative tasks.[31,32] Moreover, experiments using fMRI can reveal whether the applicability of Fitts' law in children with CSH is due to the use of cortical areas that are distict from those used by control subjects.

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5

Kinematic aiming task: a way to assess functional changes in the hand and arm movements after Botulinum Toxine-A injections in children with spastic hemiplegia

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ABSTRACT

Objective: To describe different aspects of a kinematic aiming task (KAT) as a quantitative way to assess changes in arm movements within 2 weeks after Botulinum Toxine-A (BTX) injections in children with spastic hemiplegia.

Design: Intervention study randomised clinical trial, follow-up within 4 weeks after baseline measurement.

Results: The KAT gave a high Intra Class Correlation on Movement Time, Spread of Endpoints and Index of performance effective. After BTX a significant increase of END and IP-E was shown if precision demand in the KAT was high, while the inverse occurred when speed was more important. These functional changes coincided with a significant decrease of the Maximum Voluntary Contraction of the flexor muscles of the forearm. Muscle tone measured with the Ashworth scale did show a non-significant decrease of muscle tone as did the Stretch Restricted Angle and the Active and Passive Range of Motion of the elbow and the wrist.

Conclusions:

Muscle force decreased immediately after BTX, showing the direct effect of BTX. The KAT is an adequate and reproducible way to quantify functional changes after BTX in the upper limb. BTX has an inverse effect in the precision task when accuracy is important but a positive effect when speed prevails.

INTRODUCTION

Children with congenital spastic hemiplegia show poorer manual skills with their affected side.[1] The most frequently mentioned causes for this loss of function are related to degrees of spasticity and increased muscle tone,[2] decreased muscle power,[3] decreased muscle length[4] and probably low capability to learn skills.[5] A lot of research has been directed to the functional relation between spasticity and manual skills in children with CP.[2,5-7] The level of spasticity is most often graded by the Ashworth Scale (AS) and Tardieu test (TT).[8,9] Reduction of spasticity however, is not automatically related to improvement in manual skills.[10] Indeed, low correlations have been found between levels of spasticity and outcome measures of skilled motor control.[11-13] Several explanations for this low correlation have been put forward. Both AS and TT score the increased resistance against a fast velocity stretch. The TT uses the difference between the joint angle at the moment of the fast velocity resistance (stretch restricted angle) (SRA) and the slow velocity angle (passive restricted angle) (PRA) as a measure of the dynamic component of muscle tone abnormality.[14] However, this increased resistance is probably not just a measure of spasticity. It also relates to myogen and collagen stiffness.[4,15,16] Scholtes et al, 2006 even stated that the solitary use of the SRA for evaluation of treatment of spasticity is probably better because of the interest in fast velocity stretch as measurement of velocity dependent resistance.[14] Damiano et al, 2006 showed that the TT seems to be somewhat task dependent. TT was measured by resistance torque at 3 velocities, during passive knee flexion and extension, combined with EMG. TT showed weak to moderate relationships with knee motion during gait.[17] This underlines the need to have performance tasks that are close to daily life behaviour. Related to the leg, such studies are performed using gait parameters to quantify change in walking performance.[12] In accordance with the walking performance we developed a visual guided aiming task with quantitative parameters as speed and accuracy to measure if differences in the parameters of the arm movements can be reliably reproduced over time and if the task is sensitive enough to measure change after intervention. This task has been called the Kinematic Aiming Task (KAT), using two simple visual guided aiming movements, with low memory and cognitive load.[18,19]

Because in many ADL tasks the reaching, grasping and pointing of objects are represented, this task focus on grasping and holding an object as well as transferring it with one hand to a new target position and adapting the movement to the task requirements. In this study we developed two differentiations -discrete and continuous- of the KAT in which an object (puppet of 7 cm height, 2.5 cm width) had to be shifted over a smooth surface between two targets. One task was called “discrete task”, focused on precision in performance. This task is expected to be sensitive to adaptations in force recruitment. In this task every movement started after a signal and ended in a target. The second task was called “continuous task”, focused on movement speed because it requires the subjects to move the puppet continuously between the two targets. It was expected that rapid reciprocal movements would be conducted at a faster rate if spasticity levels were lower.[20] Especially at high speed the influence of velocity on SRA should be important.

Table 1. Baseline characteristics and scores of all 20 children with CP.22

Baseline median scores/ degrees (°) (min - max), Newton (N) or Frequencies (Freq)		Treatment group (n=10)	Non Treatment group (n=10)
Side paresis (Freq)		9 R 1 L	3 R 7 L
Mean age (years)		9.4 (5-16)	9.7 (4-16)
Sex (Freq)	♀	5	6
	♂	5	4
Zancolli (Freq)	I	4	5
	IIA	4	1
	IIB	2	4
Ashworth wrist (Freq)	0	7	5
	1	2	4
	2	1	1
Ashworth elbow (Freq)	0	3	3
	1	6	5
	2	1	2
Stretch Restricted Angle wrist (°)		60 (30-90)	52.5 (15-90)
Stretch Restricted Angle elbow (°)		160 (100-180)	127.5 (50-180)
Active dorsal flexion wrist (°)		-18 (-51 – 45)	-6 (-55 – 55)
Active extension elbow (°)		170 (135 – 180)	170 (140 – 180)
Passive dorsal flexion wrist (°)		70 (65 – 90)	67 (50 – 90)
Passive extension elbow (°)		180 (150 – 180)	180(160 – 190)
MVC flexors wrist/fingers (N)		9,9 (2.1 – 23)	8.9 (2 – 19.5)

In the present study we are specifically interested in subtle quantitative changes after Botulinum Toxin-A (BTX) injections because of the ascribed effect in reducing spasticity and muscle force.[21] To test our KAT we measured changes in the performance of children with spastic hemiplegia with the affected hand, before and after BTX injection in the muscles of the wrist and elbow compared to a non treatment group.

This leads to the following research questions.

1. How reproducible is the current KAT in the non treatment group of CP children?
2. Are the main outcome measures of the present KAT related with spasticity measured with AS and SRA, the range of motion and Maximum Voluntary Contraction (MVC)?
3. Does MVC of the finger flexors decrease in the injected arm?
4. Do the KAT detect changes after treatment (BTX)?

METHODS

Participants

For this study the same children were enrolled as in the study of Speth et al 2005.[22] Namely, twenty children, aged 4-16 years (mean 9.5) with CP, with a diagnosis of hemiplegia according to Hagberg classification[23] and the hand function according to Zancolli classification (pattern I, IIa, IIb)[24] excluded, because their incapability to extend their wrist and actively grasp and hold an object with their affected hand. In table 1 an overview of the baseline characteristics of the participants are given. The parents gave informed consent and the Medical Ethics Committee of the Rehabilitation Foundation Limburg approved the study.

Design

Matching according to age and Zancolli level resulted in ten pairs of children. One child of every pair was randomly allocated to either the treatment or the non treatment group.[22] Baseline measurement was performed about 14 days before the treatment group received BTX. To examine the short-term effect of BTX we tested the children 14 days after BTX was given. The non treatment group was tested with the same time interval as the treatment group. The examination consisted of spasticity assessment (AS and SRA), passive and active range of motion (PROM and AROM), MVC and the visually guided aiming task (KAT).

Injection technique and dosage

Botox® from Allergan was used (dilution 5 U/0.1 ml). Dosage was 2-3 U/kg bodyweight in the upper arm, 1-2 U/kg in the fore arm, with a maximum of 50 units at any one site, with an overall maximum dose of 400 U/Kg total bodyweight.[25] For more detailed description of dose and localisation see Speth et al.[22]

Outcome measures

Outcome measures are divided in measures of the level of function and the level of activity, according to the International classification of functioning, Disability and Health.[26]

Function level

Muscle tone

Spasticity was measured in supine position using the AS and SRA.
The muscle tone of wrist and elbow was measured with the original 5-point Ashworth Scale.[8] The SRA was assessed by moving wrist and elbow as fast as possible (within one second) through the whole range of motion.[27] SRA was measured with manual standardized goniometry (Mie).[28]

Range of motion
AROM and PROM of the elbow and wrist were measured in sitting position using the same goniometry.

Muscle force
Muscle force was evaluated using a method as described in earlier work.[29] The maximum voluntary contraction (MVC) of the finger and wrist flexors was measured (in Newton) in a task in which subjects had to apply maximum pressure onto the end of a high quality strain lever. The pressure was transmitted onto a force transducer.

Activity level

Kinematic aiming tasks (KAT).

Procedure
The KAT consisted of 2 different kinds of tasks, the discrete and the continuous task.
In the discrete task the children had a custom made puppet in their spastic hand and could directly see their movements. A LCD screen could record the XY coordinates of the moving object and was placed in horizontal position in front of the child. Oasis software30 was used to program four conditions, which were expected to be easy enough for children with spastic hemiplegia to perform. The conditions were (a) movement over 10 cm to a 5 cm target (condition 1); (b) movement over 10 cm 2.5 cm target (condition 2); (c) movement over 20 cm to a 5 cm target (condition 3); and (d) movement over 20 cm to a 2.5 cm target (condition 4).
The goal for the children was to get the puppet (2.5 cm diameter) exactly in the target circle (2.5 or 5 cm diameter) while performing a substantial arm movement (10 or 20 cm) on a digitizer (Wacom, type Cintiq 18sx, sample rate 206 Hz). This digitizer served as a SXGA full 24-bit color LCD monitor. The surface of the digitizer was made of glass, which made the sliding movement very easy to perform. This is illustrated in figure 1. After putting the puppet on the digitizer in the starting circle the investigator pressed the start button. After a random period (between 0.5 -1.5 s) a tone sounded and the target appeared on the digitizer. This was the 'go' signal for the child who was then required to move as fast and as accurately as possible to the target by shifting the puppet to the target that had appeared on the other side. After placing the puppet in the target, the child had to stop and wait for a new auditory 'go' signal. Ten movements were made in each condition. The four conditions were presented in a block design with increasing difficulty. After a practice session the experiment started.
In the continuous task as many movements within 20 seconds as possible had to be made between the presented targets in the same four conditions. After putting the puppet on the left side of the digitizer in the starting target area the investigator pressed the start button. After a random period (between 0.5 -1.5 s) a tone sounded and the right target appeared on the digitizer. This was the 'go' signal for a series of back and forth movements between 2 positions. Since the starting position was still visible it was possible to come back to the start position

Figure 1. The experimental set up with a digitizer as colour LCD monitor. The tablet is placed horizontally directly in front of the participant. Adaptations in equipment have been made if disablement was too severe to hold the puppet.

after reaching the target. After 20 seconds an automated auditive stop signal was given. Block design for the four conditions was also used in this task. Discrete and continuous tasks were randomly performed and after each task at least 2 minutes rest was included.

Signal analysis

In the KAT, both movement speed and accuracy are combined. The relationship between movement speed and accuracy in goal directed movements is expressed in the speed accuracy trade off.[31] This can be used to equate the processing ability or performance of the motor system by the Index of Performance Effective (IP-E). In formula format the definition is:

$IP\text{-}E=a+b*Log_2 (2A/ ETW) /MT$

(a and b are empirical constants, A=distance between targets, ETW=effective target width, MT=movement time). The ETW is calculated as target size plus the distance between the centre of the target and the centre of the puppet.[32]

Movement Time (s) per segment was computed from the moment the puppet left the start area till it entered the target area. Spatial accuracy was calculated in two ways: first as a clear dichotomy between the correct (hit) and incorrect (no hit) ending of the movement within the target area (Percentage Successful Movements) (PSM). Secondly, the distance of the centre of the puppet to the centre of the target area was calculated. This distance was taken as a measure for Endpoint Spread (END). The index of performance effective (IP-E) (bits/s) was calculated.

Statistics

Reproducibility of both KAT and MVC measurement were measured with Intraclass Correlation (ICC) for the non treatment group within 1 month time difference.

The dependent variables PSM, END, MT and IP-E were evaluated by means of the General Linear Model (Polynomial), Repeated Measures design, with group (2) and session (2) as between, task (2), amplitude (2) and target size (2) as within subject variables. Alpha level was set at 0.05. Post hoc analysis was done when appropriate.

The changes between the two measurements of the baseline values of MVC, SRA, AROM, PROM of elbow and wrist were also calculated. Because of the non Gaussian distribution of the data the Mann-Whitney U test was used to assess the differences in the changes from baseline to the second measurement between the two groups.
Spearman rank correlation was used to examine if clinical measures (AS, SRA, AROM, PROM and MVC) at baseline correlated with the PSM, END, MT and IP-E in both KAT. Statistical significance was set at 0.01 to account for the use of multiple comparisons.

RESULTS

Reproducibility (Test retest reliability)

An overview of (ICC) of the PSM, END, MT and IP-E in both KAT and of MVC in the MVC task is given in table 2. High ICC is found for all outcome measures in both KAT and in MVC task, indicating a high reproducibility.

Correlation between clinical measures and functional outcome measures

At baseline, the outcome measures of the KAT were correlated with the AS, SRA, AROM, PROM and MVC. The only significant correlation was seen in AROM of the wrist with PSM and END in both tasks (See for p-values table 3). No significant correlation was found with any of the tests to score spasticity, illustrating the lack of correlation between KAT outcome measures and function measures.

Effect of BTX

As seen in table 4 no significant changes in differences were measured after BTX between treatment and non treatment group on SRA, AROM and PROM. However, a significant median decrease of MVC of 4N (min. -0.9, max. 8.5) ($p<0.001$) occurred in the treatment group, while no change was observed in the non treatment group.

Percentage Successful Movements and Endpoint Spread

The first important property of the KAT was that both different tasks were easy enough for the children to perform successfully with their affected hand. General children in both tasks reached the target in 70% (sd 29) of the movements. The treatment group succeeded at baseline in 71.7% (sd 29) of the movements and post-BTX 69.3% (sd 28), the non treatment group (69.7% (sd 28) and 69.4% (sd 29). The treatment group showed a non-significant decrease after BTX, namely 2.4%. This was mainly caused by the most difficult condition (2.5 cm target –20 cm distance) in both tasks. A main effect for task was found ($F(1,36)=40.69$, $p<0.001$), indicating that the tasks differed in accuracy. For the treatment group the PSM changed in discrete tasks from 82.9% (sd 24) to 79% (sd 23), in continuous tasks from 60.6% (sd 31) to

Table 2. Intraclass Correlation of Percentage of Successful Movements, Endpoint Spread, Movement Time and Index of Performance Effective for Non Treatment Group in Discrete and Continuous tasks, and of maximum voluntary contraction measurement in the MVC task.

Intraclass Correlation (ICC) for Non Treatment Group	**Discrete task**	**Continuous task**
KAT task	ICC	ICC
PSM	0.89	0.95
END	0.87	0.78
MT	0.81	0.90
IP-E	0.95	0.89
MVC task	ICC	
MVC	0.99	

Table 3. Correlation between AS,SRA, AROM AND PROM of wrist and elbow, MVC and PSM, MT, END, IP-E in discrete and continuous tasks. Only significant correlations are presented.

Spearman correlation	**PSM Discrete**	**PSM Continuous**	**END Discrete**	**END Continuous**
AROM Wrist	.78 0.000	.649 0.002	-.616 0.004	-.77 0.000

Table 4. Changes in median scores of SRA, AROM and PROM in wrist and elbow and MVC in the Treatment and Non Treatment Group. P-values are based on comparisons between Treatment and the Non Treatment Group for change from baseline. Between brackets minimum and maximum scores are represented.[22]

Changes in Median scores in degrees (°) (min - max) for SRA, AROM, PROM and in Newton for MVC (N).	**Treatment group (n=11)**	**Non Treatment Group (n=11)**	**P value**
SRA wrist (°)	0 (-10-30)	0 (-10-30)	0.9
SRA elbow (°)	5 (-30-70)	0 (-35-50)	0.9
AROM dorsal flexion wrist (°)	12.5 (-4 – 82)	3 (-31 – 71)	0.2
AROM extension elbow (°)	5 (-20 – 20)	0 (-20 – 30)	0.4
PROM dorsal flexion wrist (°)	0 (-10 – 10)	0 (-25 – 15)	0.9
PROM extension elbow (°)	0 (-10 – 20)	0 (-5 – 10)	0.6
MVC (N)	4 (-0.9 – 8.5)	0 (-0.6 – 0.6)	0.005

59.6% (sd 30). In the non treatment group these values were 75.7% (sd 27) and 76.8% (sd 26) in discrete tasks, and 63.7% (sd 28) and 62.1% (sd 32) in the continuous tasks, respectively. When examining END, again a main effect for task was found ($F(1,36)=5.15$, $p<0.03$) along with an interaction with group, session, target size and target width ($F(1,36)=4.95$, $p<0.04$), indicating that both groups had different spread of the end points in different conditions after BTX, but approximately equal END in the discrete task (1.5 cm,(sd 0.8)) and in the continuous task (1.8 cm, (sd 0.9)).

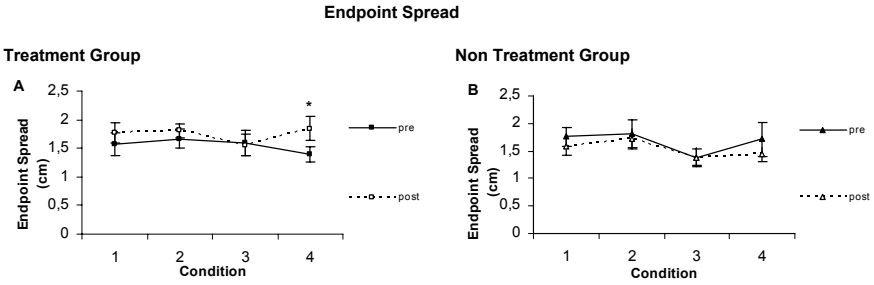

Figure 2. Endpoint spread for both Treatment Group (A) as Non Treatment Group (B) for both tasks combined (discrete and continuous), pre (baseline) and post (post BTX or second measurement). Condition 1=(target width 5 cm, target distance 10 cm), condition 2=(target width 5 cm, target distance 20 cm), condition 3=(target width 2,5 cm, target distance 10 cm) and condition 4=(target width 2,5 cm, target distance 20 cm). Bars represent 1 standard error.*=significant at 0,05 level.

Post hoc analysis of combined tasks did show a significant interaction with group, session, target size and target width ($F(1,76)=5.334$, $p<0.03$). As shown in figure 2 an increase in endpoint spread occurred after BTX especially for the large movements, indicating that larger amplitudes led to poorer accuracy after BTX.

Movement Time

A main effect for task ($F(1,36)=80.49$, $p<0.001$), target width ($F(1,36)=68.95$, $p<0.001$) and target size ($F(1,36)=22.38$,$P<0.001$) was found for this parameter. A trend for differences with session, group, target size and width and task occurred ($F(1,36)=3.01$, $P=0.09$). As seen in figure 3 after BTX the treatment group moved slightly slower in the discrete task and faster in the continuous task except for the most difficult condition (target 25 cm, distance 20 cm).

Index of performance effective

A significant interaction for IP-E between task, target size, distance, group and session was found. ($F(1,36)=6.09$, $p<0.03$), indicating that performance was different for both groups, tasks and session.

As can be seen in figure 4, controls had similar performance in both tasks in all conditions. Treatment group however showed a slight decrease in performance in the discrete task, which focussed on accuracy, in all conditions. In the continuous task, which is targeted on speed, a slight increase in performance was shown in the treatment group after BTX, except for the most difficult (target 2.5 cm distance 20 cm) condition. After BTX the treatment group showed in that condition a specific decrease of IP-E (0.5 bits/s). Post hoc analysis did show that only in the continuous task an interaction with session, group, target width and size was reliable ($F(1,36)=9.58$, $p<0.005$).

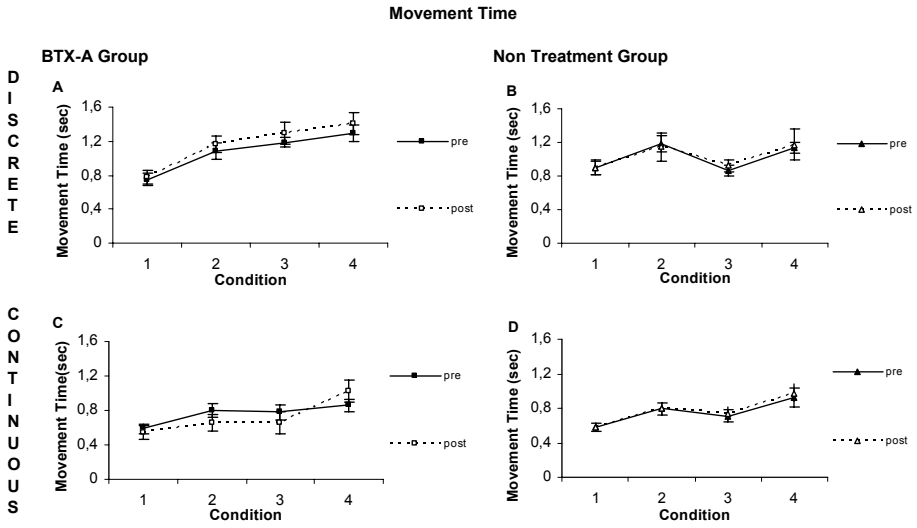

Figure 3. Movement Time for both Treatment Group (A and C) as Non Treatment Group (B and D) in discrete and continuous task, pre (baseline) and post (post BTX or second measurement). Condition 1=(target width 5 cm, target distance 10 cm), condition 2=(target width 5 cm, target distance 20 cm), condition 3=(target width 2,5 cm, target distance 10 cm) and condition 4=(target width 2,5 cm, target distance 20 cm). Bars represent 1 standard error. As can seen in B and D the reproducibility of this task is high.

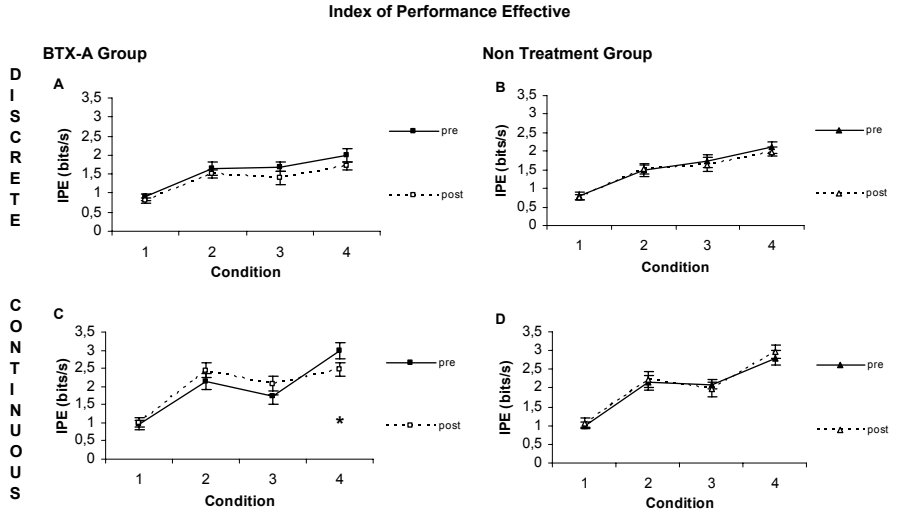

Figure 4. Index of performance effective (IPE) for both Treatment Group (A and C) as Non Treatment Group (B and D) in discrete and continuous task, pre (baseline) and post (post BTX or second measurement). Condition 1=(target width 5 cm, target distance 10 cm), condition 2=(target width 5 cm, target distance 20 cm), condition 3=(target width 2,5 cm, target distance 10 cm) and condition 4=(target width 2,5 cm, target distance 20 cm). Bars represent 1 standard error. As can be seen for controls the reproducibility of this task is high.*=significant at 0.05 level.

DISCUSSION

Our study describes two different tasks of the KAT to assess functional changes in the hand and arm movements in a quantitative way within two weeks after BTX in children with spastic hemiplegia.

The first aim of the study was whether the KAT was reproducible. As seen in table 5 the ICC's for the KAT are high for the non treatment group, when tested within 1 month interval. The high reproducibility indicates that the KAT is an adequate instrument to measure quantitative changes in manual ability of the spastic arm. Furthermore, the high percentage of correct trials showed that both tasks are not too complex for children with spastic hemiparesis.

No significant correlations were found between spasticity scores at baseline (AS and SRA) and kinematic outcomes in the KAT. One possible reason for this lack of correlation is embedded in the fact that the measured resistance is composed of several factors such as spasticity, muscle stiffness and contractures.[15] Furthermore, one may expect that scores obtained by passive tests, such as AS and PRA, are not comparable and therefore not fully predictive of measures obtained during active motor control tasks[2, 17] or that AS and SRA are no usable tests.

However, significant correlations were found between AROM of the wrist with the percentage successful movements and the endpoint spread in the KAT, suggesting that AROM of the wrist is probably more predictive for manual task performance than muscle tone. If a greater AROM of the wrist was present, a higher percentage of successful movements and a lower spread of endpoints was seen. This indicates that the AROM of the wrist might be more important to select patients for treatment then AS or SRA.

With respect to the questions about the direct effect of BTX, significant reducing effect was confirmed by the significant decrease of MVC of the fore arm flexors within 2 weeks after BTX injections. The reason of this decrease of MVC is caused by the decreased M-reflex and the blocking of a large number of motor units after BTX in the injected muscles and therefore introducing "paresis".[19, 33]

Clinical relevant but a not statistical significant effect on reducing muscle tone and increasing AROM was already shown in the study of Speth et al 2005.[22] One possible reason for the lack of significance could be that the treatment group was too small in this study. In other placebo controlled studies significant short term effects on muscle tone and AROM of wrist after BTX (2 weeks till 6 weeks) were shown for spasticity.[34, 35]

The most important question was whether there is a detectable effect of BTX on the KAT outcome measures. The PSM did change slightly in the treatment group (small decrease of 2.9% after injections) in both tasks and the non treatment group maintained the same percentage of PSM. Overall the treatment group showed increase of END after BTX injections and this effect was significant in the most difficult condition. No changes were seen in the non treatment group. If more accuracy was asked and more distance had to be covered spread of endpoints enlarged after BTX. Overall MT showed no significant change. MT increased in the discrete task, but in the continuous task a decrease was seen, except for the most difficult condition. This difference in MT between the two tasks levelled out the effect over all conditions.

Due to BTX a lower speed induced muscle hypertonia and a increase of AROM and PROM was expected, creating the possibility to make movements faster, especially in an ongoing movement task as the continuous task. This was indeed found in all conditions, except the most difficult condition, in which the opposite occurred. Probably the specific demand of accuracy in the most difficult condition was so high that MT had to increase.[31] In the discrete task the movement time increased in all conditions, indicating that the accuracy demand and the exact braking within the target area slowed down the movement. The increase of movement time in the discrete task could also be explained by a decrease of muscle power after BTX. When less muscle activity can be generated and discrete movements are required, then MT can possibly increase if accuracy demand is high and more force is needed to control the movement.[36, 37] In the continuous task in contrast, accuracy demands are not high and then the effect of a decrease of muscle tone seemed to be more beneficial than the negative impact caused by loss of force.
With respect to the IP-E in the continuous task an expected increase occurred after BTX, because the children were able to move faster. Only in the most complex condition a decrease in IP-E occurred, if accuracy demand was very high. In general the performance after BTX decreased in the discrete task. Again an increased accuracy demand results in decreased performance after BTX.

Limitations of the KAT
A block design was chosen because randomisation made the test to confusing for the children and they had difficulty complying with the demands. Possibly fatigue at the moment of the last most complex condition could occur. However, the results on END and MT showed no clear indication for fatigue. If fatigue would occur more END would be expected in the last test condition and MT would increase. This was not observed. In fact the END was less for the most difficult condition 1.3 (sd 0.6) than for the most easy condition 1.5 (sd 0.9). MT did increase slightly from 0.7 (sd 0.2) to 1 (sd 0.3) in the most difficult condition.

CONCLUSION

The KAT seems to be an adequate and reproducible way to quantify functional changes after BTX in the upper limb, especially in the most complex condition and in the continuous task. The KAT is very easy to perform for the children and applicable in clinical settings.
Only AROM of the wrist did show a positive correlation with the KAT outcome measures.
BTX seems to have a direct inverse effect on MT, END and IP-E in the discrete tasks, when a high appeal is made on accuracy and control of braking movements. On the other hand, there is a positive effect on MT and IP-E in continuous tasks, when speed is important and less accuracy is demanded.
Muscle force decreased immediately after BTX, showing the direct effect of BTX.

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6

Botulinum Toxin-A in children with congenital spastic hemiplegia does not improve upper extremity motor-related function over rehabilitation alone: a randomized controlled trial

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ABSTRACT

Background: Rehabilitation of the upper extremity in children with hemiplegic cerebral palsy has not been compared to the same intensity of therapy combined with injected Botulinum Toxin.

Objective: To measure the short- (2 weeks) and long-term (6 and 9 mo) effects of a standardized functional training program with versus without the addition of chemodenervation of forearm and hand muscles.

Methods: Twenty children with spastic hemiplegia, aged 4-16 years, were matched for baseline characteristics and then randomized to standardized functional physical and occupational therapy for 6 mo (PT/OT group) or to the same therapies plus multi-muscle BTX (BTX+ group). Main outcome measures were isometric generated force and over- and under-shoot (force production error), active and passive range of motion by goniometry (ROM), stretch restricted angle (SRA) of joints, Ashworth scores at the elbow and wrist, and the Melbourne assessment of unilateral upper limb function. All measures were performed at baseline, 2 weeks after BTX and 6 months (end of therapy), then 3 months after termination of the therapy.

Results: Clinical measures (muscle tone, active ROM of wrist and elbow) showed improvement in both groups. However no significant differences emerged between groups on functional measures. Generated force decreased directly after the BTX injection, but increased during the therapy period. The PT/OT group, however, showed a significantly higher increase in force and accuracy with therapy compared to the BTX+ therapy group.

Conclusions: Functional rehabilitation therapies for the upper extremity increase manual isometric flexor force at the wrist and ROM, but Botulinum Toxin injections cause weakness and do not lead to better outcomes than therapy alone.

INTRODUCTION

Cerebral palsy impairs motor performance due to increased muscle co-activation,, reduced muscle strength, fatigability, and in association with spasticity. In upper motor neuron syndromes, agonist and antagonist muscles may co-contract inappropriately and therefore, strength generation may be less effective.[1-4] This has been reported both in leg muscles, [2,5 -7] and in wrist flexor and extensor muscles.[4,8-11]

Training to increase muscle force in children with CP has been shown to increase strength in the upper[12,13] and lower extremities[1,6,14-16] of both the spastic muscles and their antagonists. When functional strength training was used, both strength and the specific skills that were practiced improved.[15-17] An important question is whether further improvement in addition to skill training can be obtained with Botulinum Toxin–A (BTX). The main goal of BTX is to reduce the muscle tone in the injected spastic muscles. When combined with intensive therapy, these interventions may improve the active range of motion (AROM) of the antagonistic muscles and functional use of the hand and arm in activities of daily life.[13,18]

In a previous study we looked at the short-term effect of BTX in the upper extremity and showed that isometric wrist flexor force decreased when measured 2 weeks after administration. Moreover, in a dynamic goal-directed task the movement accuracy decreased while movement velocity increased.[19] However, it was postulated that beneficial effects may need more time to be revealed and therefore a long-term evaluation was needed.

No strong evidence supports or refutes the efficacy of BTX as an adjunct to manage the upper limb in children with spastic cerebral palsy.[18 20] One possible reason for the lack of positive effects could be that the manual skills used in motor tests require more gain of dexterity than is feasible in children with central nervous system damage. Another cause could be the subjectivity and crudeness inherent in the scoring of these tests, based as they are upon observation of the child, lead to large standard errors and low reproducibility. This compromises the outcomes when used to measure change. A third problem could be the methodology, e.g., small effect size and short follow up. Thus, we investigated this question in a small randomized clinical trial using simple but quantitative measures of motor skill and long term follow up.

In earlier studies we successfully used a simple isometric force task for the wrist flexors, which must be used for daily manual tasks, such as lifting a book, cup or bucket. We measured both the maximal generated muscle force (MGF) of the wrist flexors and the accuracy and steadiness of generated force (GF) at different levels of the maximum force (12-60%), comparable to levels required in daily activities. With this task we were able to measure small changes in the capability of force generation in a reproducible way in children with CP.[19,21] An advantage of this isometric task is that the chance to elicit stretch reflexes is low and that it avoids complex cognitive processes. Furthermore a benefit of this wrist flexor task was the directly measurable effect of BTX in the forearm flexor muscles. In grip force tasks, in which finger and wrist flexors were charged with force generation, maximum muscle force recovered 3 months after BTX.[18] In the present trial, we compared BTX combined with intensive physical and occupational therapy (BTX+) to the same intensive therapy only (PT/OT).

Our aims were:

- To evaluate the effect of intensive physical and occupational therapy on manual skills, isometric wrist flexor force regulation and clinical measures.
- To evaluate the additive effect of BTX on manual skills, isometric wrist flexor force regulation and clinical measures.
- To evaluate the duration of any effects last by comparing outcomes at the end of treatment (at 6 months) to the ones 3 months later (no-treatment follow-up).
- To investigate if isometric force regulation of the wrist flexor muscles is related to manual function and skills.

METHODS

Participants

Twenty children, aged 4-16 years (mean 9.5) with hemiplegic CP according to the Hagberg classification[22] participated in this study. The severity of the hand function impairment was graded according to the Zancolli classification (pattern I, IIa, IIb).[23] Children were excluded if they had contractures in elbow extension or wrist extension of 30° or more, inability to open the hand for finger extension, cognitive level below 3 year or sensory loss. A standardized PT/OT program was developed and adapted to each Zancolli level. These data were collected in accordance with the study of Speth et al.[24] The parents gave informed consent and the Medical Ethics Committee of the Rehabilitation Foundation Limburg approved the study.

Design

Matching according to age and Zancolli level (I and II) resulted in ten pairs of children (figure 1). One child of every pair was randomly allocated to either the BTX+ group or the PT/OT group. Only one pair of children had different Zancolli levels (I and II).
Outcome measures were collected at baseline (about 2 weeks before BTX), 2 weeks after BTX injections and at 3, 6 and 9 months after the start of the therapy. At 6 months the therapy program ended, followed by a period of 3 months without therapy. The PT/OT group was tested at the same intervals.

Physical and occupational therapy program

The standardized task-specific therapy program for all the children included 30 min of physical therapy and 30 minutes of occupational therapy supervised by experienced therapists, three times a week for 6 months. Functional strength training was performed within task specific activities and skills, and not in more isolated resistance training. Based on individual goal setting, weights or body weight was used which were adapted to the force and performance level of the child.[2,5] All children wore a thermoplastic night splint with the elbow extended, the forearm in neutral position, and the wrist in 20° extension with the thumb in abduction to improve passive range of motion (PROM). A specific wrist splint (wrist in 20° extension) was

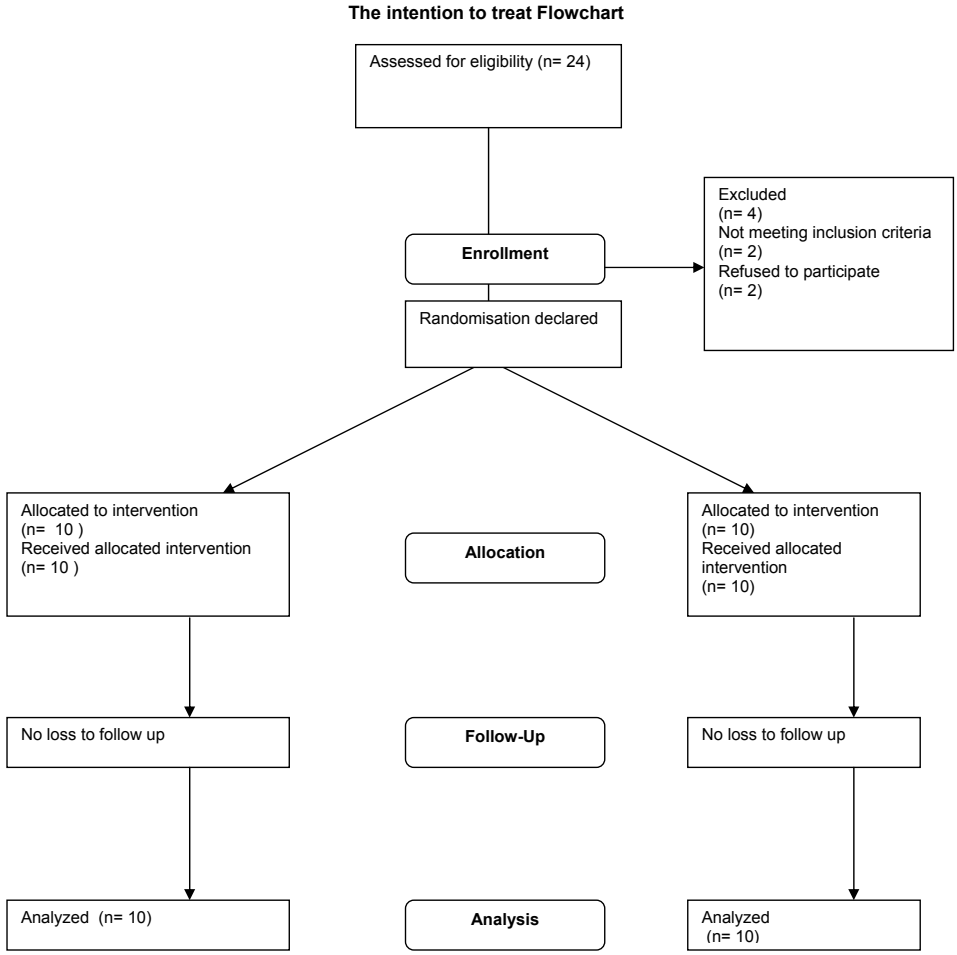


Figure 1. Intention to treat flow chart

worn during the day by the children graded Zancolli IIB, as a usual element of the therapy after BTX.

Injection technique and dosage

Botox® from Allergan was used (dilution 5 U/0.1 ml). Dosage was 2-3 U/kg body weight per muscle in the upper arm, 1-2 U/kg body weight per muscle in the fore arm, with a maximum of 50 units at any one injection site and an overall maximum dose of 400 U per total body weight.[25] The most common muscles treated were the adductor pollicis (10 U), flexor carpi ulnaris (2 x 20U -2x 40U) and pronator teres (30-50U). Others that were less often injected

Table 1. Injected muscles and participant characteristics in the BTX-+ group

Number	Age	side paresis	Zancolli 0 wk	m. add. poll.	m. fl. poll br.	m .fl. carpi uln.	m. fl.carpi rad.	m. pron. Teres	m. brachio-rad.	m. biceps	Body weight kg	U/kg body-weight
1	5	R	IIB	10 U	5 U	30 U	20 U	35 U			18,6	5.38 U
2	12	R	I	10 U		2 x 35 U				2 x 50 U	48,6	3.7 U
3	11	R	IIB	10 U	5 U	2 x 30 U	30 U	40 U	40 U		32,5	5.7 U
4	12	R	I	10 U		2 x 40 U	40 U	50 U			38,6	4.7 U
5	12	R	I	10 U		2 x 40 U		50 U			49	2.9 U
6	16	R	IIA	10 U		2 x 40 U	2 x 30 U	50 U	2 x 40 U		58,6	4.9 U
7	8	R	IIA	10 U		2 x 25 U	30 U	35 U			22	5.7 U
8	5	R	IIA	10 U		2 x 20 U		30 U		2 x 20 U	21,5	5.6 U
9	8	R	IIA	10 U		2 x 25 U		35 U		2 x 25 U	25,2	5.8 U
10	5	L	I	10 U							19	<1 U
11	16	L	IIA	10 U	10 U	2 x 40 U	40 U	50 U	60 U		73,3	3.4 U

included flexor carpi radialis (30U-2x 30U), biceps brachialis (2x 20U – 2x 50U), brachioradialis (40-2x 40U) and flexor pollicis brevis (5 U). The number of units per total body weight varied from 2.9 – 5.8 U (table 1).[24]

OUTCOME MEASURES

Clinical

Clinical outcome measures were active (AROM) and passive range of motion (PROM) of wrist and elbow extension (measured with a Mie goniometer)[26]. stretch resisted angle (SRA)[27] and Ashworth score (AS)[28].The Melbourne assessment of unilateral upper limb function (MA) reliably measures upper limb function in children with spasticity in the studied age group.[29] The MA was scored from video recordings. These were coded and scored by trained movement scientists who were blinded to the treatment arm of the study.

Experimental

Five different levels of constant generated force (GF) were measured at 12, 24, 36, 48 and 60% of the maximum force using the set-up and procedure of Smits-Engelsman et al.[21]

Procedure

All participants were tested individually in the rehabilitation centre. The clinical tests were administered on the same day as the experimental data was obtained. To perform the isometric force tasks, the subjects were seated on an adjustable chair, forearms resting on the table in front of a PC monitor on which visual feedback was given. The subjects had to apply force, with their index and middle finger positioned onto the end of a high quality strain lever (Sokki Kenkyujo; type CLS-20KA). The forearm and hand had to stay on the table in order to control

wrist position. The forces were transmitted onto a force transducer (Burster; type 9154), creating a direct rise of the cursor on the monitor. An amplifier (Burster; type 9154) delivered its output to a 12-bit AD-converter (DAS800). Sampling rate was 1000 Hz.
Maximum force was measured three times and the means were used. In the experiment five different levels of constant force of 10 seconds duration per level, were recorded, ranging from 12 to 60% of the maximum force. A random design was used. An auditory start and stop signal was used. Each force level was measured 5 times for 10 seconds. The GF and Error were computed for each force level.

STATISTICS

Clinical outcome measures

For clinical data, non-parametric statistics included the Wilcoxon signed rank test to assess changes over time between baseline and 2 weeks (short term), baseline and 6 months (long term); 6 and 9 months follow up. The Mann-Whitney U was used to test for differences between sessions for the combined groups and between sessions and the 2 groups at baseline, 2 weeks, and 6 and 9 months. Alpha was set at 0.05. Power for primary clinical outcome measures of ROM was 0.6 (matched pairs).

Isometric task outcome measures

The differences between the GF and the required force were calculated and used as the measure of error (Error) and categorized as over- and undershoots. [30,31] The dependent variables GF and Error were evaluated by means of the General Linear Model (Polynomial), repeated measures design, with group (2) as between, and occasion (5), force level (5) and blocks of trials (5) as repeated measures variables.
For significant GLM intervention outcomes post hoc analyses were used to further analyze:

1. Baseline versus 2 weeks period (short term effect);
2. Baseline and 6 months related (long term effect) and;
3. 6 months versus 9 months (follow up).

Spearman rank correlation was used to examine if isometric task outcome measures (GF and Error) at baseline correlated with the outcome of the MA, and if changes in GF and Error would correlate with changes in the MA. For post hoc analysis and correlations, alpha was corrected (Bonferroni) for multiple testing and set at 0.02. For the PT/OT group, the first two measurements can be considered as an indicator of the stability for all measures used, since the therapy program only started 2 weeks after the BTX injections for all participants.

RESULTS

Clinical outcome

AROM, PROM, SRA and AS

Main effects of intervention

No children were lost in follow up (figure 1). During the therapy period an increase of 26.4° (25.6) was found in the AROM of the wrist ($p<0.001$) and this gain remained during follow up at 20.2° (28.5). For the SRA of the wrist, long-term improvement of 12.1° (15.6) ($p=0.03$) was found, and again this effect was not lost in the 3 months without therapy and remained at 13° (15.5). SRA of the elbow improved 22° (39.6) ($p=0.02$) at 6 mo and this improvement lasted throughout the follow up. The AROM of the elbow increased by 7° (13.8) ($p=0.03$) at 6 mo and after the follow up period it reached 9.5° (12.8) (table 2). The AS improved at the wrist and elbow at 6 mo ($p=0.02$ and $p=0.005$, respectively) and continued at 9 mo. (figure 2). No significant improvement on the percentile scores of the MA was found on any test occasion.

Differential effect of intervention between the two groups

No significant differences between the BTX+ group and PT/OT group were found on any of the clinical outcome measures over 9 mo (table 3). An increase in AROM of the wrist showed a trend ($p=0.09$) to increase within the first 2 weeks, which indicates a possible effect of BTX since PT/OT had not yet begun. Although no significant difference on Ashworth scale was found between the groups (figure 2), the BTX+ group showed only zero scores for wrist extension directly after BTX, indicating the expected early effect of BTX on muscle tone.

Experimental outcome measures

Contrary to the clinical measures, significant differences were found between the BTX and PT/OT group on the experimental force task. An overall mean increase of the GF was found during the therapy period, as shown with the grey dotted line in figure 4. This was confirmed by a main effect for intervention [$F(4,72)=8.33$, $p<0.001$]. However, a significant interaction effect was found for group, force level and intervention [$F(16,288)=2.07$, $p=0.009$]. As seen in figure 3 the participants could generate less force after BTX.

Post hoc analysis of the short-term effect revealed that the BTX+ group showed a significant immediate decrease in mean force from 2.89N (0.19) to 2.14N (0.12) (averaged over all force levels) and the non-treated PT/OT group maintained equal values from 3.05N (0.2) to 3.06N (0.2) (grey dotted line in figure 4). These results were confirmed by a significant interaction of group-by-intervention [$F(1,18)=4.35$, $p=0.005$]. Changes induced by BTX in GF after 2 weeks were most clearly present at higher force levels (48% and 60%) but less for the lower levels (figure 3). This was confirmed by an interaction effect of group and force level [$F(4,72)=25.70$, $p<0.001$].

Table 2. Changes in SRA, AROM, PROM of wrist and elbow, and MA scores over both groups during period of therapy and follow up.

Clinical data: Mean and standard deviation in degrees (°), Newton (N) or percentages (%)	**Intervention (n=20)**		
	Baseline	**Long term**	**Follow up**
Stretch Restricted Angle wrist (°)	57.7 (21.1)	69.9 * (17.5)	70.7 (15.6)
Stretch Restricted Angle elbow (°)	136.7 (36)	158.7 * (29.8)	167.5 (21.7)
Active dorsal flexion wrist (°)	-3.7 (37)	22.7 * (31)	16.5 (34.1)
Active extension elbow (°)	165.5 (15.5)	172.5 * (13.1)	175 (8.5)
Passive dorsal flexion wrist (°)	72.5 (12.4)	74.7 (12.9)	74.5 (14)
Passive extension elbow (°)	176.2 (13.1)	177.7 (7.8)	178.7 (5.8)
Melbourne assessment (%)	64 (10)	67 (9.9)	66.6 (11.9)

* significant change

Table 3. Differences in changes in SRA, AROM, PROM of wrist and elbow, MGF and Melbourne assessment scores of BTX+ group and PT/OT group during period of therapy and follow up. (no significant changes)

Mean data, standard deviation	**BTX+ group (n=10)**					**PT/OT group (n=10)**				
m=months Dif=difference	Baseline	6 m	Dif Baseline –6 m	9 m	Dif 6 m–9 m	Baseline	6 m	Dif Baseline –6 m	9 m	Dif 6 m–9 m
Stretch Restricted Angle wrist (°)	62 (18.1)	72.8 (12.2)	10.8 (14)	73 (12)	0.2 (1.9)	53.5 (23.9)	67 (21.8)	13.5 (17.8)	68.5 (19)	1.5 (5.7)
Stretch Restricted Angle elbow (°)	148 (31.9)	156 (33.3)	8 (43)	161.5 (27.6)	5.5 (15)	125.5 (37.9)	161.5 (27.3)	36 (31)	173.5 (12.5)	12 (23.5)
Active dorsal flexion wrist (°)	-2.7 (37.7)	31.5 (29)	34.2 (31)	28.3 (29.1)	-3.2 (12)	-4.7 (38.5)	13.9 (31.9)	18.6 (18)	4.8 (36.2)	-9.1 (22.3)
Active extension elbow (°)	165.5 (15.2)	169.5 (16.9)	4 (11)	173 (10.8)	3.5 (6.5)	165.5 (16.7)	175.5 (7.7)	10 (16)	177 (5.4)	1.5 (3.3)
Passive dorsal flexion wrist (°)	75.5 (10.4)	76.5 (12.5)	1 (7)	78 (11.8)	1.5 (2.4)	69.5 (14)	73.5 (13.7)	4 (7.8)	71 (15.7)	-2.5 (5.3)
Passive extension elbow (°)	174 (10.7)	175.5 (10.1)	1.5 (4.7)	177 (7.1)	1.5 (7.4)	178.5 (7.4)	180 (4)	2.5 (3.3)	180.5 (3.7)	0.5 (1.6)
MGF flexors wrist/fingers (N)	11.2 (6.0)	14.0 (4.5)	2.8 (4.3)	14.5 (7.0)	0.5 (1.2)	9.7 (6.7)	15.6 (9.7)	5.9 (5.6)	14.3 (8.8)	-1.3 (1.1)
Melbourne assessment percentile score (%)	65.8 (8.7)	68.4 (9.2)	2.6	68.7 (10.2)	0.3	62.3 (11.3)	65.6 (10.8)	3.3	64.4 (13.6)	-1.2

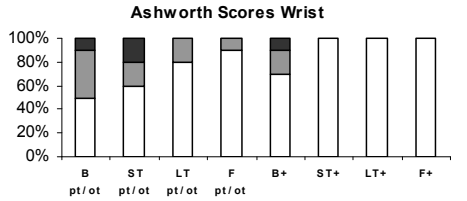
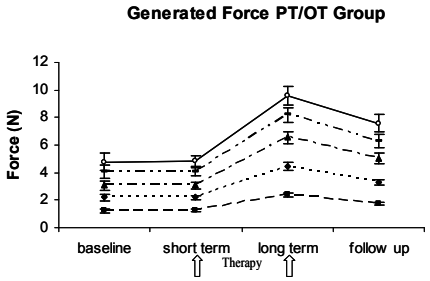


Figure 2. Ashworth score of wrist and elbow extension (in percentage per measurement setting) for both groups: at baseline, short term, long term and follow up period. +=BTX group, PT/OT=physical and occupational therapy group. B=baseline, ST=short term, LT=long term and F=follow up. Ashworth score 0=no increase in tone; score 1=slight increase in tone giving a catch when the limb is moved in flexion or extension; score 2=more marked increase in tone but the limb easily flexed.



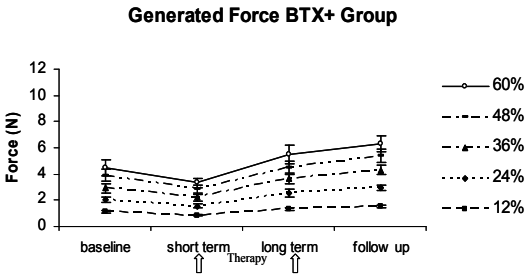


Figure 3. Changes in Amplitude of Generated Force during and after therapy in both groups. Error bars are +/- 1 S.E.M

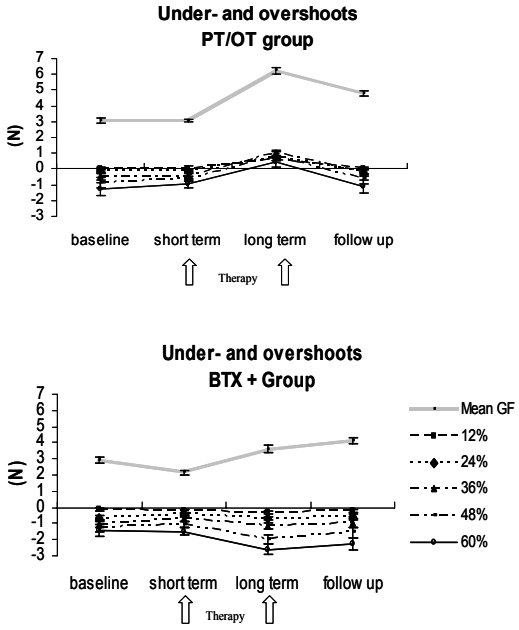


Figure 4. Under- and overshoot errors during period of therapy. Mean generated force (GF) was plotted into the figure to see the relation between the mean GF and the under- and overshoots. After 6 months (long term) significant differences were revealed in occurrence of under and overshoots between BTX+ group and PT/OT group. Error bars are +/- 1 S.E.M

The post hoc analysis of the long term period showed a similar pattern (interaction of group-by-intervention and force level [F(4,72)=4.04, *p*=0.005]). Although force production improved in both groups, the PT/OT group showed a better capability to produce mean force at 6 months to 6.24N (0.37) compared to 3.48N (0.19) for the BTX+ group.

Post hoc analysis during follow up revealed that the group-by-force level by intervention interaction remained significant [F(4,72)=3.807, *p*=0.007]. The BTX+ group continued to show a slight increase in force at all levels, which was most profound at highest force levels, while the PT/OT group displayed a slight decrease at all levels after the program had stopped (figure 3). However, the PT/OT group remained above baseline and above the BTX+ group. Overall the BTX+ group improved from 2.89N (3.0) to 4.1N (3.8), while the PT/OT group improved from 3.05N (2.8) to 4.8N (4.0) (grey dotted line in figure 4).

Over- and undershoots (Errors)

As expected more errors were made with increased force level. This was illustrated by a significant main effect of force level [F(4,72)=18.48, p<0.0001]. A significant interaction effect of group by intervention and force level was found [F(4,72)=1.39, *p*=0.02]. As depicted in figure 4, the participants of the BTX+ group did not reach the required force levels during the total therapy period. Remarkably, their mistakes increased when they regained force. Interestingly in the PT/OT group the size of the errors did not change but the sign did. The latter group changed from small undershoots to small overshoots at the end of the therapy period. Con-

trary to the BTX+ group the PT/OT group was able to generate force accurately despite their increase in generated force.
In a short-term post hoc analysis (see figure 4), we found the level of force the children had to produce was comparable in percentage to their GF, but not in absolute values. In the period from baseline to 2 weeks after BTX, when a significant decrease of GF the BXT+ group occurred, a decrease in the absolute undershoots was also seen from -1.13N (0.1) to -0.78N (0.07) (averaged over all force levels). The PT/OT group showed no change in errors over this period.
The long-term post hoc analysis showed a significant interaction effect of group-by-intervention, force level and blocks [$F(16,288)=1.80$, $p=0.003$]. The disadvantage in errors for the BTX group remained and was even clearer when force levels were higher (figure 4). A remarkable finding was that the BTX+ group never reached the required force over the therapy period. Over the total therapy period they became 14.9% less accurate. Even after regaining most of their force, the BTX+ group did not seem to benefit with respect to error

control from the increase of strength. Contrary, the PT/OT group showed a slight improvement in accuracy (decrease in undershoots), which switched to a comparable overshoot at 6 mo. This indicated that the therapy group was very able to reach the required force level with their increasing muscle force with only small errors. Three months after termination of therapy, the gain in accuracy (smaller errors) of the PT/OT therapy group diminished and returned to the same mean error as at baseline.

Correlation between clinical and experimental outcome variables
The GF of the isometric task correlated significantly (0.53 p=0.016) with the functional tasks of the Melbourne Assessment at baseline. Because the MA scores did not change during intervention, there was no point in correlating changes in the percentile scores of the MA to the changes in the GF and Error.

DISCUSSION

In this clinical trial, children with spastic hemiplegia were randomized to receive a standardized physical and occupational therapy protocol either with or without BTX. An overall increase in performance on the clinical outcome variables was found from baseline to 3 mo after termination of the rehabilitation therapy. Moreover, the clinical outcome measures showed convincing evidence that standardized functional task training can increase the strength of the isometric wrist flexors, improve range of motion and decrease spasticity. This force increase was larger than one would expect on the basis of development (see Smits Engelsman, 2004)[10] and can therefore most likely be attributed to the intervention. Although not specifically investigated it is not likely that spasticity, AROM and PROM would change purely based on development without intervention.

In light of this result, an important question relates to the additive effect of BTX. Muscle tone, measured with Ashworth and SRA scores, showed no significant difference between both groups over time. Only an immediate trend to improvement of the active wrist extension was found 2 weeks after BTX. One reason could be the fact that both groups received the same kind of intensive therapy and splinting, showing a decreasing effect on SRA scores and Ashworth score, especially in the PT/OT group. However both groups showed a lasting improvement of AROM of the wrist and SRA of the wrist and elbow. The expectation was that the effects of tone reduction and greater AROM after BTX would create a window of opportunity for the therapy and new possibilities to learn and improve manual skills.[32,33] However, this was not confirmed by our data, since none of the clinical outcome measures showed a significant difference between groups during the total follow-up period. BTX, however, led to a drop in muscle force, which may have led to less ability to benefit from force training and skill learning. The decrease in generated force, especially at higher force levels, and the decreased accuracy support this contention. One reason for the reduced strength is the 3 mo long or more peripheral paralyzing effect of BTX caused by chemodenervation. [17,34,35] Furthermore, BTX reduces the number of muscle fibres per injected muscle that can be activated and induces collateral sprouting so that less accurate muscle fibre recruitment is possible, leading to greater force fluctuations.[36,18] These factors could be an explanation for the increase in error found in the therapy and follow up period. Moreover, if muscle force has to be generated with fewer muscle fibers this may lead to smaller training effects.

From the perspective of motor learning, BTX creates a new but unstable neuromuscular situation. Firstly, reduced muscle tone leads to a small increase in active range of motion. This is the intended effect of the BTX treatment. On the other hand, the children lose force and the capability to accurately tune submaximal force directly after BTX. The expectation is that they will adapt to these immediate changes and gain better functional skills after training, because of the opportunity to learn these skills within a period of diminished influence of the spastic antagonist. However, after 6 mo, no advantage was found for the BTX+ group compared with the PT/OT group, indicating that within this intervention period, children were not able to benefit from the BTX induced changes. Moreover, the effects of BTX are expected to diminish approximately 3 months after the injection. This was not confirmed by our data because spasticity did not return. In contrast, the PT/OT group stayed in a stable neuromuscular situation during the 6-month intervention period and could benefit from the specific skill training.

With respect to GF (generated force) both groups showed an improvement. Regarding the differences of changes in mean GF in both groups, we express the changes in the mean GF in percentages change related to baseline. This will visualize the increase or decrease of the mean GF during the treatment period, more explicitly. Motadi et al 1990, considered an increase of 15% in strength as clinically relevant.[37] This increase was obtained for the BTX+ group after 3 mo (19 %). However the PT/OT group had reached this level 1 mo after start of the therapy. At 6 mo (long-term) the clinical improvement for BTX+ group was 23 % and 104% for the PT/OT group. After 9 months a clinically relevant increase was maintained (56% for the BTX+ group and 81% for the PT/OT group; figure 5).

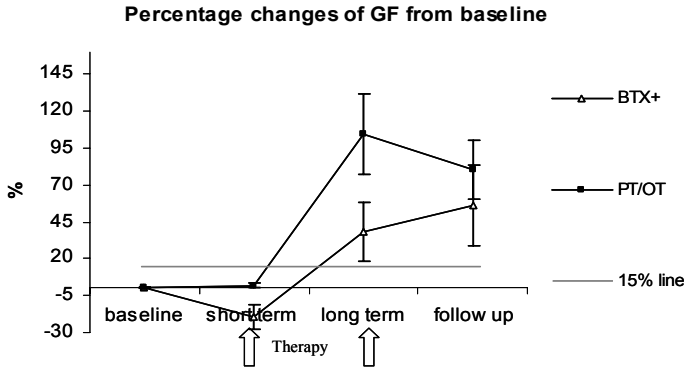


Figure 5. Percentages of changes of the mean GF from baseline. Grey line represents 15% improvement from baseline. Improvement above this line has been considered clinical relevant.37 Error bars are +/- 1 S.E.M

The significant correlation between strength and the percentile scores of MA at baseline corresponds with findings in the literature.[18] Contrary to the expectation based on this correlation however, the gain in strength and accuracy was not translated into more dexterity as measured by the MA. One major finding of the present study was the lack of effect of any of the therapies on MA. It is possible that the MA is not sensitive enough to measure changes.[29] The numbers of subjects in this study was modest, so the power may not have been adequate to see differences.. However the effects of PT/OT and BTX+ group for clinical measures were all in a positive direction, indicating the clear effect of the intense and prolonged course of rehabilitation therapy. As can be seen in table 3 the differences between the two groups are small. Adding more subjects may lead to statistically significant differences but it also has a disadvantage because it emphasizes small effects which may not be clinically important. Moreover, on all but one of the clinical measures (the reported trend on AROM wrist) the PT/OT group showed larger clinical improvements than the BTX+group. Therefore it is not to be expected that an increase of the number of participants would change the results of the study in favour of the BXT+ group. Finally, because we measured muscle strength in an isometric task; one has to be cautious when generalizing our conclusions to daily activities and more dynamic manual tasks.

CONCLUSIONS

Children with spastic hemiplegia improved during 6 months of PT/OT training both on active range of motion and tone of wrist and elbow muscles. No evidence was found for an added benefit of BTX on function and strength.

Acknowledgements
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7

Effect of standardised therapy on dynamic manual skills measured with kinematic aiming tasks in children with spastic hemiplegia: What does Botulinum toxin-A add?

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Submitted

ABSTRACT

Background: Standardised task oriented manual rehabilitation in children with hemiplegic cerebral palsy has not been compared to the same intensity of therapy combined with injected botulinum toxin.

Objective: To measure the effect of intensive therapy and the lasting effect of a standardized functional training program with versus without the addition of chemodernervation of forearm and hand muscles.

Methods: Twenty children with spastic hemiplegia, aged 4-16 years, were matched for baseline characteristics and then randomized to standardized task oriented physical and occupational therapy for 6 mo (PT/OT group) or to the same therapy plus multi-muscle BTX (BTX+ group). Dynamic kinematic outcome measures as speed (expressed in movement time (MT)), accuracy (expressed in Percentage successful movements (PSM)) and endpoint spread (END) and performance (expressed in Index of performance effective (IP-E)) were used. Furthermore active and passive range of motion by goniometry (ROM), stretch restricted angle (SRA) of joints, Ashworth scores at the elbow and wrist, and the Melbourne assessment of unilateral upper limb function were administered. All measures were performed at baseline, 2 weeks after BTX and 6 months (end of therapy), then 3 months after termination of the therapy.

Results: Clinical measures (muscle tone, active ROM of wrist and elbow) showed improvement in both groups. However no significant differences emerged between groups on functional measures. Directly after the BTX injection all kinematic outcome measures showed a decrease but baseline values were re-established during the therapy period. The BTX+group showed temporarily a significantly higher increase in speed and IP-E. However accuracy decreased slightly but not significantly.

Conclusions: Intensive functional therapy with and without BTX decreased spasticity and increases AROM of the wrist for both groups. The BTX+ group showed a larger significant benefit for speed and performance in an alternating task. These results illustrate the need to find appropriate quantitative tests to reveal effects of BTX.

INTRODUCTION

Children with spastic hemiplegia (CSH) encounter many problems performing manual tasks, like manipulating cutlery, dressing and undressing, grasping, lifting and carrying objects.[1,2] The problems in these tasks are most pronounced when the assistance of the affected hand is essential. Research in the last decade has lead to a better picture of the movement characteristics of the affected upper limb. [2-12] So far it has been reported that compared to typically developing children, children with CSH show slower upper limb movements, and demonstrate an increased number of sub movements combined with excessive trunk movements.[2-12].

As expected, children with spastic hemiplegia also have decreased scores in manual performance tests, such as the Jebsen Taylor test,[13] Melbourne assessment of unilateral upper limb (MA)[14] and Quality of Upper Extremity Skills Test (QUEST),[15] compared to the typically developing children.[16] Altogether, the results on performance tests and kinematic recordings confirm the long-established clinical finding that the children with spastic hemiplegia have difficulties to perform manual tasks. A very important question arises, namely which underlying causes can be pointed out for this deficit?

The primary motor cortex is crucially involved in movement execution of the fingers and often damaged in hemiparesis.[17-18] This results most often in spasticity and pareses.[19-21] Spasticity has been mentioned most frequently as one of the primary elements causing a decrease in dexterity, range of motion, and muscle force Moreover, disordered co-ordination, increased co-activation and stereotyped movement synergies have been reported.[21-24]

If spasticity is the major factor to elicit such impairments then two questions are very important, namely whether spasticity can be decreased by intervention and if so, whether this will lead to positive changes in hand function. The third (more clinical) question is what instruments and tests could be used to measure these changes.

One intervention frequently used to treat spasticity is injections with Botulinum Toxin-A (BTX).[25-26] BTX has a paralyzing effect on the injected muscles and blocks the release of acetylcholine in synapses of the motor units the coordination of the muscles. BTX decreases spasticity and muscle strength in the injected muscles and increases active range of motion of its antagonists.[26-28] However, both increase and decrease on the functional outcomes like the MA, Jebsen test and QUEST have been described.[28-29] Furthermore a temporary decrease in grip strength has been described as a result of BTX.[26-27] Based on the available evidence no conclusive positive or negative effect of BTX on manual function can be postulated until now.[30-32]

This lack of consistency illustrates the need for more rigorous quantitative tasks. Some groups have used grip force and found a temporary decrease in grip strength.[30-32] In our own work the focus was on isometric wrist flexor force tasks (subjects had to apply force, with their index and middle finger positioned onto the end of a strain lever). It was seen that the wrist flexor force immediately decreased after BTX and showed a small increase at the end of the therapy period, whereas a very large increase was found for the stand alone treatment group (without BTX). (Rameckers 2008).[33]

It may be argued that some of these quantitative tests do not sufficiently represent daily life activities. Therefore, in parallel we used a kinematic aiming task (KAT) as a quantitative and reliable way to assess changes in arm movements after BTX injections in children with spastic hemiplegia.[27] It was found that directly after BTX the accuracy and speed of movements were diminished in such aiming tasks.[27]

A first rationale for the current study was to expand these tasks so as to mimic even more the activities normally performed by these children. Three different kinematic aiming tasks with a light digital pen (10 gram) were developed, namely, a discrete lift task, a discrete shift task and an alternating shift task. All 3 tasks represent different aspects of movements occurring in activities of daily life, such as writing, lifting a small object and placing an object.

In the discrete lift and shift tasks the movements have to be made with start and stop signals for each movement. These tasks are chosen to test the ability to accelerate and slow down the object guided by visual information, which is essential to do these tasks accurately.[34-36]Compared to the shift tasks, the load on muscle strength in proximal arm muscles in the lift task is higher, because the whole arm has to be lifted from the surface. In the alternating task fast movements had to be made between two targets. Controlled activation and release of agonist and antagonist muscles are required to perform this task well.[8,10,35,36]

Kinematic recordings of these simple goal directed movements could have the required level of details and reliability.[27] For evaluating purposes it is obligatory that the data have small measurement error in order to be able to detect change over time. Such objective and clinical essential data are provided by parameters such as accuracy and movement speed. Both are important elements determining the performance in a goal directed task. It could be an advantage to move faster in a goal directed movement but not if one is not landing on target. This speed accuracy trade off is expressed in a mathematical relationship in Fitts' law.[37] Importantly, Fitts' Law can be used to equate the performance of the motor system by combining the speed and accuracy in one outcome measure, namely in the Index of Performance Effective (IP-E).[5]

In the present study we were interested in the effect of standardised therapy (PT/OT) and BTX on the changes in accuracy and movement speed.

In our previous KAT study we found that BTX had an inverse effect in the precision task when accuracy is important, and it had a positive effect when speed prevails.[27] From this background several predictions can be made for the current series of tasks. After BTX, it is assumed that muscle tone and co-contraction is decreased.[25] If so, this may allow to move faster towards an object. This effect is predicted to be most outspoken in the alternating aiming tasks, because such tasks have a robust advantage in speed accuracy trade-off over discrete tasks.[5] Smits Engelsman et al., 2006 found that movement speed was higher in cyclical alternating movements. This was based on incorporated stretch-shortening cycles. The muscles can generate more force after stretch and benefit from the energy stored in the elastic tissue, which is released during muscle shortening. This will enable to move with more speed.[5] In contrast, discrete aiming task may have an advantage with respect to accuracy because all attention can be given to the homing-in phase, when the target is nearly reached. Hence, accuracy will

be most important in the discrete aiming tasks and these are therefore likely to be performed at lower speed.
A second rationale for the present study was that there is a need to evaluate the long-term effects of BTX. In an earlier study, it was shown that, directly after BTX the accuracy and speed of movements were diminished in KAT tasks[27] but it is not known what the long-term effects are on this type of tests. In the present study we are interested in the effect on speed and accuracy after a long period of PT/OT with or without additional BTX. The present study took place over a period of 6 months therapy and 3 months after the therapy period. In addition to the outcome measures of the KAT tasks, changes in range of motion of the wrist and elbow, the spasticity and the scores in Melbourne Unilateral Upper Limb Assessment (MA) were also assessed. A randomized design was used with 2 groups. One group received intensive physical and occupational therapy with additive BTX (BTX+ group). The other group received intensive therapy as stand alone treatment (PT/OT group).

Our aims were:
- To evaluate if spasticity and range of motion correlates with movement time and accuracy at baseline.
- To evaluate the main effect of intensive therapy on movement time and accuracy in aiming tasks.
- To evaluate the additive effect of BTX on movement time and accuracy in aiming tasks.

METHODS

Participants
Twenty children with CP participated in this study, aged 4-16 years (mean 9.5), They were diagnosed spastic hemiplegia according to Hagberg classification[38] and were classified based on the severity of the hand function using the Zancolli classification (pattern of hand function impairment, pattern I, IIa, IIb).[39] Exclusion criteria were: children with a cognitive level below 3 years, with Zancolli III and movement limitation of wrist or elbow extension of more than 30 degrees. An overview of the baseline and follow up characteristics of the participants is given in table 1. A specific PT/OT program adapted to each Zancolli level was developed. The current data were collected in conjunction with the study of Speth et al 2005.[28] The parents gave informed consent and the Medical Ethics Committee of the Rehabilitation Foundation Limburg approved the study.

Design
Ten pairs of children were formed after matching according to age and Zancolli level (I and II). A BTX+ group and PT/OT group were formed after random allocation within each pair. Only one pair was formed with different Zancolli levels (I II). No significantly differences at baseline were found for both groups.

Table 1. Changes in SRA, AROM, PROM of wrist and elbow, and MA scores over both groups during period of therapy and follow up.

Clinical data: Mean and standard deviation in degrees (°), Newton (N) or percentages (%)	Both groups (n=20)		
	Baseline	Therapy period	Follow up
Stretch Restricted Angle wrist (°)	57.7 (21.1)	69.9* (17.5)	70.7 (15.6)
Stretch Restricted Angle elbow (°)	136.7 (36)	158.7* (29.8)	167.5 (21.7)
Active dorsal flexion wrist (°)	-3.7 (37)	22.7* (31)	16.5 (34.1)
Active extension elbow (°)	165.5 (15.5)	172.5* (13.1)	175 (8.5)
Passive dorsal flexion wrist (°)	72.5 (12.4)	74.7 (12.9)	74.5 (14)
Passive extension elbow (°)	176.2 (13.1)	177.7 (7.8)	178.7 (5.8)
Melbourne assessment (%)	64 (10)	67 (9.9)	66.6 (11.9)

*significant change at 0.05

Outcome measures were collected at baseline (2 weeks before BTX), 2 weeks after BTX and at 3, 6 and 9 months after start of the therapy. PT/OT group was tested in the same weeks as the BTX+ group. No children were lost in follow up.

Therapy Program and Splinting

The specific therapy program was standardised and task oriented. Training of skills[40] and strength[41] was performed within task specific activities, based on the individual demands and specific goals of each child. A thermoplastic night splint was used to improve PROM - the elbow extended, a neutral forearm, 20 degree extension of the wrist and thumb in abduction. For the participants graded Zancolli IIB a cock up splint (wrist in 20 degree extension) was made and they wore the splint during the day. Duration of the therapy was 30 minutes of physical and occupational therapy each, during 6 months, three times a week, supervised by experienced therapists.

Injection technique and dosage

Botox® from Allergan was used (dilution 5 U/0.1 ml). Dosage was 2-3 U/kg bodyweight in the upper arm, 1-2 U/kg bodyweight in the fore arm, with a maximum of 50 units at any one site, with an overall maximum dose of 400 U/Kg total bodyweight.[25] Predominantly the m. adductor pollicis (10 U), the m. flexor carpi ulnaris (2 x 20U -2x 40U) and the m. pronator teres (30-50U) were injected and less frequent injections were given in the m. flexor carpi radialis (30U-2x 30U), m biceps brachialis (2x 20U – 2x 50U), m. brachioradialis (40-2x 40U) and m. flexor pollicis brevis (5 U). Number of units per total bodyweight varied from 2.9 – 5.8 U.[28]

Outcome measures

Experimental outcome measures

In the 3 KAT tasks, the children held a digital pen embedded in a custom made puppet (length 7 cm, diameter 2.5 cm) in their affected hand and they could directly see their movements.

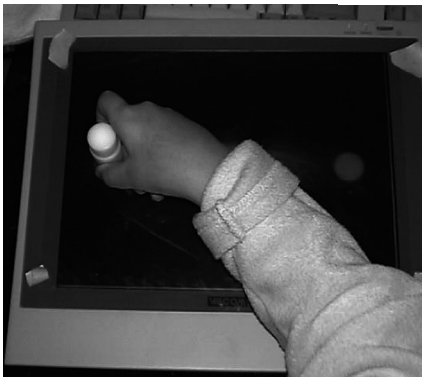


Figure 1. The experimental set up with a digitizer as color LCD monitor. The tablet is placed directly in front of the participant. The digital pen is embedded in a "puppet" of 2.5 cm by 7 cm.

Movements were made on a digitizer (Wacom, type Cintiq 18sx, sample rate 206 Hz). This digitizer was also a SXGA full 24-bit color LCD monitor and was placed directly in front of the participant (see figure 1). The glass surface of the monitor made the shifting movement very easy.

Three tasks were performed, a discrete visually-guided tapping task (lift task), a discrete visually-guided shift task (shift task) and a alternating visually guided shift task (alternating task). Oasis software was used to program the three tasks.[42] Movements were made over 20 cm distance and to a target with the same diameter as the puppet (2.5 cm).

The goal for the children in these aiming tasks was to get the puppet in the target circle (2.5 cm diameter) while performing a substantial arm movement (20 cm). After putting the puppet on the digitiser in the starting circle at the left side the investigator pressed the start button. After a random period (between 0.5 -1.5 s) a tone sounded and the other target appeared on the right side of the digitiser, 20 cm from the left target. This was the 'go' signal for the child who was then required to move as fast and as accurately as possible to the target.

In the lift task the puppet had to be lifted and had to land on the target that had appeared. In the shift task the puppet had to be shifted. If the puppet landed in the target and was kept stationary (if speed was below 0.2 cm/s) a new starting sound was given and the puppet had to be moved to the other side. Total number of movements was restricted to 10 per trial.

In the alternating task a start signal was given and during 20 seconds the puppet had to be shifted between both targets as often as possible with the highest accuracy. After 20 seconds a stop signal was given.

The tasks were presented in the same order to all the children namely lift, shift, and alternating task. This was done because random order led to too many mistakes in performance. After a practice session for all tasks the experiment began.

Signal analysis

Spatial accuracy was calculated in two ways: first using the dichotomy between the correct and incorrect responses (Proportion Successful Movements) (PSM), second, as the distance of the centre of the puppet to the centre of the target (Endpoint Spread) (END, mm). Movement Time (MT, s) per segment was calculated as temporal variable. The MT started when a puppet was lifted/ shifted and ended when speed of the puppet in the target dropped below 0.2 cm/s in the target. The Index of Performance Effective (IP-E, bits/s) was calculated, expressing the relation between movement speed and accuracy in goal directed movements.[37] In formula format the definition is:

$$IP\text{-}E=a+b*Log_2 (2A/ ETW) /MT$$

(a and b are empirical constants, A=distance between targets, ETW=effective target width, MT=movement time). The ETW is calculated as the distance between the centre of the target and the centre of the puppet

Outcome measures for spasticity and mobility

Spasticity was measured with the Ashworth scale (AS) and the stretch restricted Angle (SRA) for the extension of the wrist and elbow.[43,44] Spasticity was measured in supine position. The SRA was assessed by moving wrist and elbow as fast as possible (within one second) through the whole range of motion.[44]

Mobility was registered by measuring the Active and Passive Range of Motion (AROM and PROM) of wrist and elbow extension. Sitting position of the participant was used to measure AROM, PROM of wrist and elbow. Standardised goniometry (Mie, medical research Ltd clinical goniometry) was used to measure SRA, AROM and PROM.[45]

Manual ability of the affected hand was measured with the Melbourne Unilateral Upper Limb Assessment, because of the reliability and validity for unilateral upper limb function in children with spasticity in the studied age group.[14] MA was scored from video recordings, after encoding and randomisation (children and occasions of measurements). Trained movement scientists (double blinded) scored the videos.

The clinical outcome measures have been reported earlier.(Rameckers, 2008)[33] and will the used in the study to evaluate if spasticity, range of motion showed a correlation with movement time and accuracy at baseline and after the end of the therapy.

Statistics

KAT task outcome measures

The dependent variables PSM, END, MT, and IP-E were evaluated by means of the General Linear Model (Polynomial), Repeated Measures design, with group (2) as between, session (5)

and task (3) as within subject variables. Post hoc analyses were used if appropriate to further analyze:

1. Baseline and 6 months (to measure the effect of therapy)
2. Baseline and 9 months (to measure the long term effect) and
3. 6 months versus 9 months (to measure the lasting effect after ending the therapy)

Alpha level was set at 0.05. For post hoc analysis, alpha was corrected (Bonferroni) for multiple testing (3) and set at 0.02.

Spearman rank correlation was calculated to examine if the outcome measures -AROM, PROM, SRA and AS correlated with MT, END, and IP-E at baseline and at the end of the therapy period. Alpha level was set at 0.05.

RESULTS

All participants completed the therapy and the measurement programme. There was no loss to follow up. There were no statistical differences between the groups at baseline.

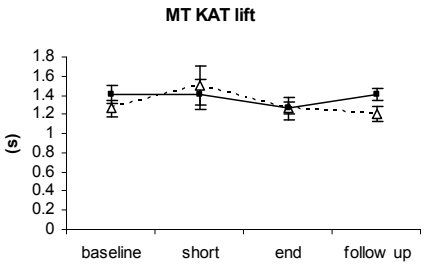
Outcome measures for spasticity, mobility and manual ability

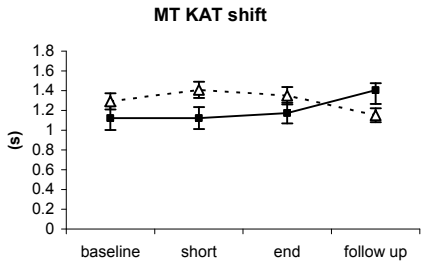
The results on the clinical tests after the intervention have been described in a previous publication on the same group (Rameckers 2008).[33] Since these findings are essential to compare with the present experimental data the results are briefly summarized in table 1, showing the significant changes. In summary, calculated over all children, AROM and SRA of the wrist increased and Ashworth scores decreased. For both groups combined a significant increase for AROM and SRA of the wrist was found at the end of the therapy period. Furthermore, a significant decrease of Ashworth scores of the wrist and elbow were found at the end of the therapy period. The percentile scores of the MA did not show any significant improvement at any of the test occasions. Importantly, no significant differences were found between the groups.

Experimental outcome measures

Overall

A significant main effect of task was found for all the outcome measures [MT $F(2,36)=8.07$, $p=0.001$; PSM $F(2,36)=2.6$, $p=0.008$; IP-E $F(2,36)=8.55$, $p=0.001$], indicating that the three tasks tested different elements of an aiming task. No main effect was found for intervention. However, a significant interaction effect of task and intervention was shown for each outcome measure [MT $F(8,144)=14.47$, $p<0.001$; PSM $F(8,144)=23.28$, $p<0.001$; END $F(8,144)=6.25$, $p<0.001$; IP-E $F(8,144)=18.65$, $p<0.001$], indicating that intervention resulted in different effects on the underlying mechanisms measured with the tasks. Only significant interactions of task, intervention and group were found for MT [$F(8,144)=4.21$, $p=0.04$] and for IP-E [$F(4,188)=5.34$, $p=0.03$], indicating that the groups performed differently over time on the tasks related to MT and IP-E. (see also figures 2,3,4,5)





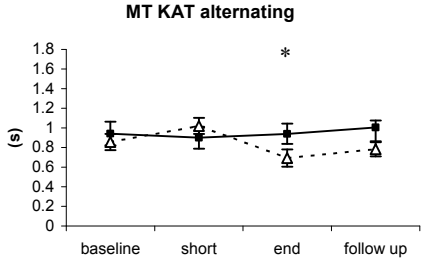
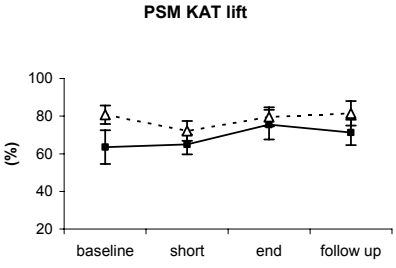
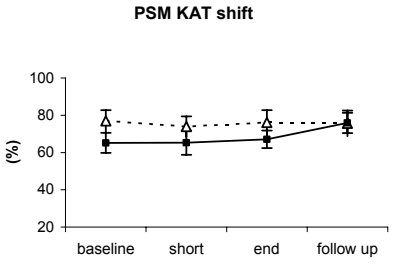


Figure 2. MT in all three KAT tasks. Measurement at baseline, after 2 weeks (short), at the end of the therapy period (end) and 3 months after the end of therapy (follow up). Error bars are +/- 1 S.E.M. *=significant at post hoc testing.





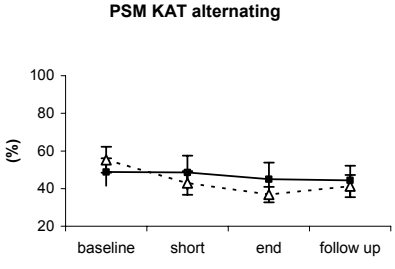
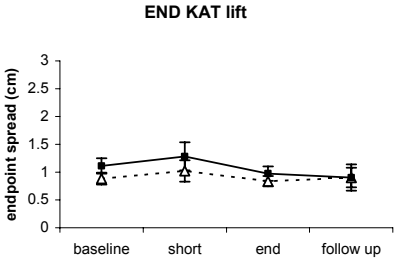
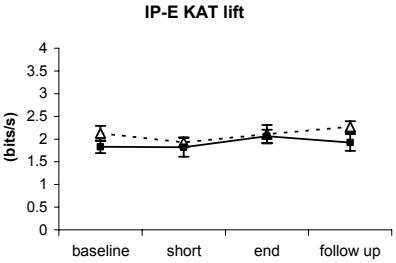


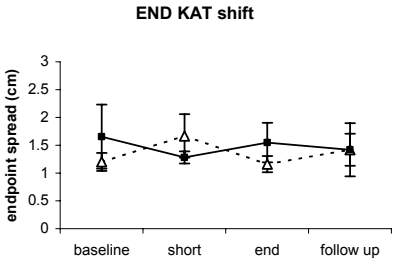
Figure 3. PSM in all three KAT tasks. Measurement at baseline, after 2 weeks (short), at the end of the therapy period (end) and 3 months after the end of therapy (follow up). Error bars are +/- 1 S.E.M

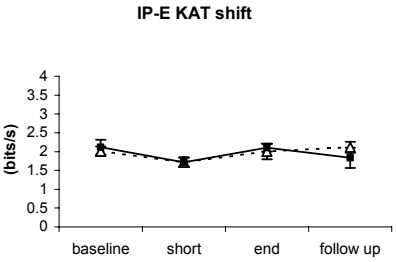
Movement Time

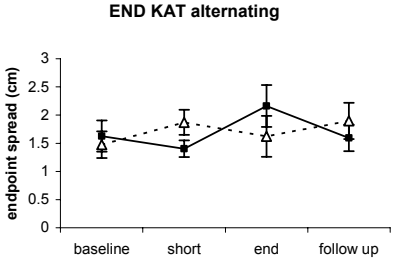
As seen in figure 2 the PT/OT group showed very similar performance at the end of the therapy in the shift task (from 1.1s (0.07) to 1.2s (0.09)), and in the alternating task (from 0.9s (0.12) to 0.95s (0.1)). On the other hand, a minor decrease of MT was found in the lift task from 1.4s (0.09) to 1.2 s (0.06), meaning that they moved slightly faster. The BTX+ group showed a small decrease both in the lift task (from 1.4s (0.09) to 1.2 s (0.07)), and in the shift task (from 1.4s (0.1) to 1.3s (0.1)), whereas a clear decrease of MT was found in the alternating task (from 1s (0.08) to 0.7s (0.07)), indicating a positive influence of the added BTX in fast alternating movement tasks. Post hoc analysis of the period baseline and the end of the therapy showed a











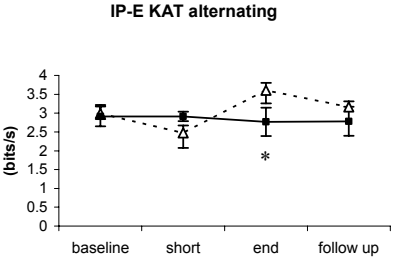


Figure 4. END in all three KAT tasks. Measurement at baseline, after 2 weeks (short), at the end of the therapy period (end) and 3 months after the end of therapy (follow up). Error bars are +/- 1 S.E.M

Figure 5. Index of performance Effective (IP-E) in all three KAT tasks. Measurement at baseline, after 2 weeks (short), at the end of the therapy period (end) and 3 months after the end of therapy (follow up). Error bars are +/- 1 S.E.M. *=significant at post hoc testing

significant interaction of tasks by intervention by groups [F (2,36)=3.76, p=0.03]. This is mainly caused by the larger difference in MT between both groups in the alternating task at the end of therapy, this effect was diminished 3 months after the ending of the therapy.

Accuracy (percentage successful movements and endpoint spread)

Both PSM as END did not show effects of group, and there were no interactions with task or intervention. In figure 3 it is shown that at the end of the therapy in the lift task both groups improved their PSM. In contrast, in the shift task they did not improve. In the alternating task both groups showed a decrease of PSM, indicating that in these fast movements the accuracy was not improved in either group.

END

As illustrated in figure 4 the spread of endpoints showed a non significant small decrease in the lift task and in the shift task for both groups at the end of the therapy period. In the alternating task both groups showed a non significant small increase in END, indicating that both groups could not improve their accuracy if speed is involved, despite of intensive intervention.

Index of performance effective

Both MT and END are essential elements of the performance in the aiming tasks, and influence each other negatively. Therefore we used the IP-E as a measure capturing the two elements and correcting for the speeds accuracy trade off.[37] The analysis of the period baseline and the end of the therapy showed a significant interaction of tasks by intervention by groups [$F(2,36)=2.85$, $p=0.01$]. This is mainly caused by the difference in performance in the alternating task. As illustrated in figure 5 for the alternating task a clear increase was found for IP-E for the BTX+ group from 2.9 bits/s (0.2) to 3.6 bits/s (0.4) and a small increase was found for the PT/OT group at the end of the therapy from 2.9 bits/s (0.2) to 3.1 bits/s (0.3). In the lift task just a slight improvement of IP-E was seen for the PT/OT group at the end of the therapy from 1.8 bits/s (0.1) to 2.1 bits/s (0.1), whereas the BTX+ group showed no differences (from 2.1 bits/s (0.1) to 2.1 bits/s (0.1). In the shift task the PT/OT group and the BTX+ group performed comparably and showed equal scores at baseline and at the end of the therapy.

Hence the only gain was seen in the alternating task and this gain was more beneficial for the BTX+ group. IP-E decreased after the end of the therapy in the alternating task in both groups (to 3.1 bits/s (0.2) in the BTX+ group and to 2.8 bits/s (0.2) in the PT/OT group), indicating that three months after the ending of the therapy the gain of the therapy was diminished.

Correlation between clinical and experimental outcome variables

As seen in table 2 a significant correlation at baseline was present for AROM of the wrist with IP-E in the lift task (rho 0.67) ($p=0.001$). In all tasks AROM of the wrist had a significant negative correlation with the accuracy parameter END, most probably indicating that active wrist mobility is important for accurate task performance. At baseline there was a significant positive correlation of Ashworth score of the wrist with MT in the lift task (rho 0.49) ($p=0.02$) and a negative correlation of Ashworth score with IP-E (rho -0.52) ($p=0.02$) in the alternating task, indicating that if high flexor tone of the wrist is present, movements are slow and IP-E will be low in an accuracy task if either speed or lifting an object is important.

A significant negative correlation was found for MA with END in the shift task (rho -0.63) ($p<0.01$) and with END in the alternating task (rho -.65) ($p<0.001$) and a significant positive correlation with IP-E in the lift task (rho 0.53) ($p=0.01$), indicating that if the ability to perform movements accurately is high, MA scores will be high as well.

Table 2. Correlation of MT, PSM. END and IP-E with the clinical measures (SRA, AROM, PROM, AS and MA) at baseline. Only significant correlations are presented. (alpha was set at 0.05)

Lift task	**Baseline**			
Both groups (n=20)	**MT**	**PSM**	**END**	**IP-E**
Active dorsal flexion wrist (°)	-0.46 (0.02)		-0.89 (0.000)	0.67 (0.001)
Ashworth Score wrist	0.49 (0.02)			-0.52 (0.02)
Melbourne assessment (%)				0.53 (0.01)
Shift task				
Both groups (n=20)	**MT**	**PSM**	**END**	**IP-E**
Active dorsal flexion wrist (°)			-0.68 (0.00)	
Ashworth score elbow		0.51 (0.01)		
Melbourne assessment (%)			-0.63 (0.00)	
Alternating task				
Both groups (n=20)	**MT**	**PSM**	**END**	**IP-E**
Active dorsal flexion wrist (°)			-0.81 (0.000)	
Ashworth Score wrist	0.58 (0.007)			-0.58 (0.006)
Melbourne assessment (%)			-0.65 (0.00)	

DISCUSSION

Standardised therapy was performed in this RCT during a 6 month period. The standardised therapy was based on task-oriented training, strength training and the use of splints. Half of the group received additional BTX. For both the PT/OT and BTX+ group this resulted into a clinically relevant increase of AROM of the wrist and elbow. In addition the scores on Ashworth scale decreased. The decrease of spasticity and increase of AROM are mentioned in most of the studies in the period of 3 weeks after BTX, indicating a tone reducing effect of BTX.[28-33]

The crucial question is how these changes affect functional manual ability and whether it is possible to identify tasks in which such ability is improved. The present study shows that even when global assessments of manual ability fail to show improvement one can quantify improvement in very specific subtasks.

For the global assessment the MA test was used. Both groups showed a small non significant increase on MA scores of 3 percentiles which is less than the smallest detectable difference (8.9 percentile for the Melbourne Assessment).[46] This is in coherence with all review studies on BTX and treatment of the upper limb, also showing no clear improvement on functional clinical measures .[30-32] Furthermore in a prospective longitudinal study of 2 years, Satila et al., 2006 concluded that the reduction in muscle tone after BTXA treatment did not translate into better gripping or quality of fine motor functions (Melbourne Assessment) of the affected hand.[47]

The MA assesses many aspects of motor control however and it is possible that more detailed analysis is needed to reveal functionally important changes in manual ability. To identify such

subtle changes a battery of 3 simple tests was used and performance was evaluated in terms of parameters of speed (MT), accuracy (PSM and END) and their combination (IP-E). In the alternating task the IP-E of the PT/OT group showed a small increase at the end of the therapy period and the BTX+ group improved significantly more. This increase was related to a significant decrease in MT while accuracy measures were unchanged (or even showed a non-significant decrease). Hence the PT/OT moved slower and somewhat more accurately. This resulted into the benefit of the BTX+ group regarding IP-E. In the alternating task a fast alternating contraction and release of forearm muscles (wrist and elbow) is needed to perform this task adequately.[48] The children have to master the degrees of freedom of the musculoskeletal system to control these fast alternating goal-directed movements.[49-51] The tone reducing effect of BTX indeed seems to facilitate the programming and execution of these movements with higher speed, resulting in better IP-E for the BTX+ group.

CONCLUSION

We can conclude that intensive functional therapy with and without BTX decreased spasticity and increased AROM of the wrist for both groups, with a slight non-significant benefit for the BTX+ group. Kinematic outcome measures show a larger and significant benefit for the BTX+ group for speed and performance in the alternating tasks. This increase is based on the gain in movement speed but relative loss of accuracy. In contrast performance in the alternating task for the PT/OT group did not show this benefit. More generally it can be concluded that adequate AROM of the wrist is required to successfully perform discrete movement tasks while a decrease of spasticity is needed to perform fast alternating tasks.

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8

General discussion and conclusion

The aim of this thesis was to examine manual force control in children with spastic hemiplegia. Firstly, a comparison of the affected with the unaffected hand and the preferred and non-preferred hand of controls was made, both for the isometric force regulation and for the dynamic force control in aiming tasks. Secondly, the influence of visual feedback on manual isometric force regulation was examined. Finally, the effect of therapeutic intervention with and without BTX on isometric force regulation and dynamic force control, both at the onset and at the end of the therapy was studied. The results may be helpful to determine potential benefit of these interventions in the future.

Causes of the impairments in muscle function in manual force control in children with CP.
It is often argued that both spasticity and the existence of co-activation / active resistance of the spastic muscles can result in lower levels of net force.[1-3]However the lack of correlation between spasticity (Ashworth scores) and generated force, and variability of force contradicts this theory. Likewise in the legs the theory of active resistance leading to decreased muscle force of the antagonistic muscle has been rejected in a study of Damiano et al 2000.[4] No relation was found between co-contraction ratios to normalized strength of the knee flexor or extensors. Others have shown that there is no correlation between spasticity of the antagonist and strength of the agonist in the leg.[5] In our data the only significant correlation was found between Ashworth score of the elbow flexors and steadiness of isometric force control at higher force level (36% or more).
If spasticity is not the cause of muscle weakness what are the alternative possibilities? A reduced output from the brain and damage to the pyramidal tract may lead to disuse, which then can lead to secondary loss of central output capabilities.[6-8] Furthermore, it has been shown that distal muscles are more affected in CP[3,5,9,10] and that direct cortical innervation is more pronounced to wrist and finger muscles motor units.[7-8]
Dietz et al.,1991 presented a third possibility for the reduced force production, namely that the muscles involved are structurally different. Muscles in children with cerebral palsy undergo substantial remodeling.[7] In spastic muscles the cross-sectional area was found to be less than one third of normal, while spastic fibres showed decreased sacromere length at rest, selective atrophy of type 2b muscle fibres and relative increased type 1 muscle fibres and increased elastic modulus of muscle fibres (stiffness) in subjects with chronic spasticity.[2,11-17] At higher levels of isometric force children with CP have to use these atrophied type 2b muscle fibers. Disuse could be the main cause of this atrophy.[18]
In this thesis (Chapter 2 and 5) we found fewer problems in generating accurate force at low than at high percentage level of MVC. This is in accordance with the concept of more tonic force production accounted for by the type-1 fibres. At higher levels (needing type-2 fibre activation) children with CP had problems to continue generating high power and decreased their level of force during task performance.

Development of force control and variability in children with spastic hemiplegia

Isometric force regulation

In typical development both an increase of force production was found and a decrease of variability of force using the preferred hand.[19,20] In our study we found that children with spastic hemiplegia are very well able to scale the size of contraction, although with a higher variability around the correctly chosen force level, compared to controls. The performance of the NAH was comparable to the hands of the control children (Chapter 2). For the AH a normal increase of variability was seen with higher force levels although the increase of the variability was larger compared to controls. One important factor could be that motor unit reorganization after early brain damage contributes to enhanced force fluctuations in muscle force. There can be a changed or lacking influence from the upper motor cortex in the early stages of development. This can alter the fibre type distribution (Ito et al. 1996), which diminished fine motor control in the children with congenital hemiplegia.[11]

Another possible explanation for increased variability is that feedback loops are abnormal in CP. Several results suggest that the impaired force control in the involved hand is not purely a sensory feedback or motor problem, but instead is due to an inability to appropriately integrate sensory information with subsequent motor output of the same hand.[21-23] In our studies (Chapter 2 and 3) children with spastic hemiplegia above 10 years continue to use the visual feedback loops, instead of increased use op kinesthetic feedback.[24] However omitting the use of visual feedback (Chapter 3) had little effect and showed that children with spastic hemiplegia are very well capable to produce stable force under these circumstances. They keep the capacity within their range of force generation with and without visual feedback to control their force.

A next possible explanation for increased variability is based on the idea that the deficit is primary caused by the inability of the agonist muscle to generate sufficient force.[25] Results from grip tasks show that children with hemiplegia have problems with the adaptation of the lift force to the weight of the object (grip-lift force synergy) compared to control children.[26,27] Similarly, the ability to maintain force in a pinch task clearly was affected[28] and the grip-release force synergy was impaired.[29] In these studies, grip lift and release force are measured, in which combined wrist and finger flexor and wrist extensor muscle force is necessary to lift or release an object.[28,29]

Our experiments focus on the impairments of the force control in isometric wrist and finger flexor tasks. Muscle force regulation was impaired both in MVC as well as in generated force. Increased reaction time and increased variability (co-efficient of variation) were found in selective isometric force tasks at maximal and sub maximal force level in the spastic wrist and finger flexor muscles both affected and unaffected hand . In particular, the fact that we selectively tested the spastic flexor muscles with low complexity of a task indicates that abnormal production of force in spastic muscle groups is a possible primary source for motor performance deficits in CP (Chapter 2). These results are in line with studies of Valvano and Newell, Gordon and Duff Forsberg et al.,[27,28,30]

We found that children with spastic hemiplegia generated only one third of the isometric wrist and finger flexor muscle force with the affected hand, compared to the unaffected hand. This is important because it means that most daily activities (lifting a cup of tea, glass of water) will demand a very high proportion of the maximum grip force. As a result more muscle groups have to be used and the muscle tone has to increase in the spastic muscle, affecting the force control in a negative way again.[7] Impaired recruitment of type II motor units in the agonist muscles and the inability to selectively activate the agonist muscle contribute to the deficit in motor performance in spastic paresis.[31]
An important conclusion of this study is that the long lasting assumption that spastic muscles are strong can be rejected for the wrist and finger flexors.
Alarming is the indication of deficiency in isometric force control in the unaffected hand in children with spastic hemiplegia after the age of 10 years. They could not generate the same force as the younger group of CP children tested before 10 years of age. Both force control at sub maximal level and maximal force showed a decrement in the older group indicating the central effect on the force regulation. Regression of force has not been described at this young age and needs more research, for example in a longitudinal design.[20]

Control of dynamic movements

In the clinical field, various dynamic performance tests – the Jebsen Taylor test, the Melbourne Unilateral Upper Limb test, and the Quality of Upper Extremity test - are used to measure manual ability of the child with spastic hemiplegia. During a follow up period of 13 years Eliasson et al 2006 found that children with spastic hemiplegia showed a decrease of test time (45%) in the Jebsen Taylor test, a decrease of grip-lift task time of 25% and a decrease of grip force/load ratio from 1.7 to 1.35. However, in intervention studies with Botulinum toxin, it seems to be very difficult to measure the subtle differences with these tests during the intervention period.[32,33] Furthermore these tests do not measure the underlying mechanisms constraining the manual ability. To examine the underlying mechanisms, simple dynamic movement tasks with low cognitive load and low complexity (Fitts' tasks) were developed (Chapter 4, 5 and 7).
Furthermore, it is well established that children with hemiplegia have difficulties to make fast manual movements and to perform very fine manipulative tasks. However, quantitative data were lacking. The strict relationship between movement speed and accuracy of goal directed movements (speed accuracy trade off) is expressed in Fitts' law (Fitts 1954).[34] In chapter 3, using a Fitts' tapping task, it is tested if children with spastic hemiplegia obey Fitts' law. Compared to typical developing children decreased Index of performance, a longer reaction time and movement time were expected, and this increase would be enlarged if the task difficulty was higher (as measured by the index of difficulty). Indeed the index of difficulty was found to be a good predictor of movement time. This is in line with the results in the studies of Rao et al 2000, Gump et al 2002.[35,36] Prolonged reaction time and movement time were found in all indices of difficulty, confirming the expected poorer performance in children with central brain damage.

Finally, most impressive was the finding that movement time in the children with cerebral palsy is similarly related to index of difficulty as in typical developing children. Based on these results, it could be concluded for the first time that children with spastic hemiplegia obey Fitts' law despite very obvious limitations in fine motor control.

Treatment and its effect on isometric muscle force regulation and dynamic force control. Possibilities and constraints

This thesis has implications for the clinic as well. Clinicians have long argued against strength training in children with CP since it was thought to exacerbate spasticity and the spastic muscles were estimated to be strong.[37-39] If any strength training was given at all, this was always to the muscles opposing (or antagonist to) those that were spastic. In this study we wanted to measure the capacity of one group of spastic muscles (the wrist and finger flexors) to exert force and to grade force.

Because low correlations were reported between clinical spasticity scales, EMG activity[40] and functional measures,[4,41] we also looked into the possible relationship between clinical measures and experimental force variables.

In our study (Chapter 5, 6 and 7) a significant correlation was found between active range of motion of the wrist and co-efficient of variation in the isometric force task. Furthermore, a significant correlation was found of Ashworth scores of elbow with co-efficient of variation in the isometric force task. Wrist and finger flexor spasticity and active range of motion of the wrist on the other hand showed significant correlation with movement time and index of performance in the lift and the fast alternating shift task (at baseline and at the end of an intervention). Most importantly, a decrease of spasticity (measured with Ashworth Scale and Stretch Restricted Angle) was found due to intensive therapy with strength training element, with and without BTX, confirming that intensive training does not increase spasticity but can even reduce it. This low degree of correlation between spasticity and our outcome measures is in line with Damiano et all 2000, Gordon et al 1999, indicating that spasticity is not the primary indicator for poor motor performance.[27,42]

One very fundamental question that we tried to answer is whether it is possible to change the isometric or dynamic force regulation by training.

In chapter 5 reliability and sensitivity of the isometric force regulation tasks and the dynamic tasks have been shown to be very high, indicating that these isometric and dynamic tasks can be used for the evaluation of intervention studies to measure changes in force control in children with spastic hemiplegia.

A next important question is if the children with spastic hemiplegia are capable to perform better on manual tests after intensive therapy. In perspective of the frequency of studies reporting effects of physical or occupational therapy it can be concluded that intensive therapy in a functional context can result in higher scores on functional tests such as Pediatric Evaluation of pediatric Inventory (PEDI), however not on the Gross Motor Function Measure (GMFM).[43,44] Furthermore, higher score on the GMFM were reported after task oriented strength training compared to usual care.[45,46] Grip lift force and release improved after a short term exercise of

isometric grip tasks – 2-3 weeks - .[28,47] In some studies manual task oriented training and intensive therapy resulted in increased use of the affected hand in activities of daily live and games up to 25%.[48,49] In our study (Chapter 6) we found that wrist and finger flexor force increased after functional standardized strength training with and without BTX. However, this did not result in a significant increase of scores on the Melbourne Test.
A next question is if additive BTX increases the effect of intensive task oriented therapy.
In chapter 6 and 7 a RCT is described in which a standardized intensive task oriented program has been given to 2 groups of children with spastic hemiplegia.
One group received physical and occupational therapy 3 times a week, with upper limb splints during the night. Duration of the therapy was 6 months. The second group had injections of BTX in the upper limb and followed afterwards the same intensive therapy program as the first group. Both pediatric physical and occupational therapists performed the therapy. This therapy was based on the individual demands of the child/parents.
The most important elements of this task oriented therapy were based on motor learning principles.[50] In this approach muscle strength training and use of splints was embedded. To describe the effects of the intervention measures on different levels of the ICF is used.[51]

Melbourne Unilateral Upper Limb Assessment (level of activity)
As stated in the Cochrane review of Wasiak et al 2004, and two reviews of Park et al 2007 and the AACPDM no indication can be given that the use BTX is of additional value in treatment of manual performance in children with spastic hemiplegia.[32,33,52] In our RCT the same conclusion can be made related to the results on the Melbourne unlilateral upper limb assessment. Both groups improved equally on this measure.

Muscle tone (level of function)
The muscle tone, measured with the Ashworth scale did not show a significant difference between the groups; in fact a similar decrease was found the non BTX group compared to the BTX group. After BTX the wrist and finger flexor tone was immediately reduced to zero. However, for combined groups in this RCT a significant reduction of muscle wrist and finger flexor tone was found at the end of the therapy. Furthermore muscle tone was measured using the stretch restricted angle of the wrist and elbow. Again both groups improved similarly by the end of the therapy.
One explanation, due to the intensive training, is an increase of muscle force. This increase can decease the muscle tone and lengthen the muscle fibres.[41,42,45]
An alternative explanation, besides the intensive training, for these tone reduction findings could be that both groups received night splints. This is in coherence with findings of the effect of splints in the studies of Kinghorn et al.,1996, Carmick et al.,1997, Wilton et al., 2003 and Burtner et al., 2008.[53-56]

Passive and active range of motion (level of function)

Both groups improved only slightly their passive range of motion in elbow and wrist. This is an indication that neither the night splint, nor the BTX or the task oriented training were effective in increasing the length of the muscle in passive motion.

However, for both groups active range of motion of the wrist extension did improve by the end of the therapy. This increase of active wrist extension after BTX already showed a trend ($p=0.09$) to improvement within the first 2 weeks, which indicates an effect of BTX.

Furthermore, active range of motion of the wrist showed a positive significant correlation with the Melbourne Assessment at baseline and after 6 months of therapy. Additionally a significant positive correlation of active range of motion of the wrist was found with index of performance effective in the Aiming Tasks, indicating that active movement of the wrist goes with better performances on manual dynamic tasks.

Isometric force regulation (underlying mechanism)

Vaz et al., 2006 compared the isometric strength of wrist and finger flexors and extensors between children with cerebral palsy (CP) and typically developing (TD) children.[57] It was concluded that strength of flexors and extensors was reduced in children with CP. This confirms our results reported in chapter 2. Due to the BTX we expected a further decrease of the isometric wrist and finger flexor strength, because of the paralyzing effect of BTX. This decrease was indeed found in our study. Full recovery of muscle strength was expected, because this is mentioned in earlier studies.[32] However, in most studies grip strength was used. We focussed on isometric wrist and finger flexor strength and found quite different results (Chapter 6). There was an increase in strength but less than in the therapy group without BTX. The BTX group showed a 19% increase of wrist and finger flexor strength after 3 months of therapy, increasing to 23% gain after 3 months after the end of the therapy. Hence, one can say that the paralyzing effect of BTX is temporary and the muscle strength can improve again by training. In comparison, the group without BTX reached the level of 19% gain already one month after start of the therapy. Furthermore, at the end of the therapy the clinical improvement for the training group without BTX was 104%.This advantage for training group without BTX remained even 3 months after the end of the therapy.

Based on these results it can be stated that the paralyzing effect of BTX is temporary but that BTX hampers the strength development of the spastic wrist and finger flexor muscles in training. Considering the already decreased capacity of strength production in the spastic muscles one should question the use of BTX under these circumstances.

One important clinical implication is that the muscle strength has to be taken into account when considering BTX. This is confirmed in the review of Park et al 2006.[57] An implication could be to give strength training of the spastic muscles before the use of BTX. If the spastic muscles are stronger, the effect of BTX will be less disastrous for the wrist and finger flexors. It should be tested if the remaining strength in that case is higher after BTX.

Another advantage of the strength training of the spastic muscle is that with a higher capacity of force generation the fine tuning of the force will be easier in activities of daily life. Activities

will be performed at lower levels of MVC, which by definition leads to less variability in the movements.

Dynamic force control

In our study we tested the performance of the affected hand in Kinematic Aiming Tasks (KAT). In these tasks without high complexity and with low cognitive load we measured movement time, spatial precision (proportion good hits and the endpoint spread) in a discrete lift and shift task and in a continuous shift task. Using these parameters the Index of performance effective (IP-E) can be calculated. In the RCT it was expected that IP-E would decrease directly after BTX, because of the paralyzing effect on the forearm flexor muscles. Indeed this was partly confirmed in our study (Chapter 6). The effect of BTX was only measurable in the continuous or alternating shift task, when speed was an important feature of the task. Decrease of muscle tone can facilitate speed and counter movements, if grip strength is sufficient. In particular, after BTX movement speed and not accuracy increased (Chapter 7).

Moving at high speeds depends on the possibility to alternately activate and release the forearm muscles. Movement speed has been improved if task oriented training was combined with BTX.

Importance of the results for manual activities of daily life

Most manual activities are composed of discrete movements. Examples are manipulating cutlery, dressing and undressing, grasping, and lifting carrying objects.

More continuous movements are seen in controlling a cycle steering wheel, writing and painting. In contrast, clinical tests such as the Melbourne assessment, Jebsen test , Assisting Hand Assessment and Quest use specifically discrete movement tasks.

Almost no differences were found in these tests when additional BTX has been used in intensive therapy.[32,33,52] This is a clear indication that these may be the wrong tests to measure the effects related to BTX and secondly that BTX does not have an additional effect in discrete tasks in activities of daily life. Standardised task oriented intensive therapy without BTX should be the primary method of choice to increase performance on manual abilities. The results of other intensive treatments as (modified) constraint induced therapy (CIMT), in which the un-affected arm is prohibited to participate, validate this proposition.[58-60]

Evaluating the effects of intensive exercise treatment in comparison to studies using BTX, the question arises if and when BTX should be used for the upper limb.

Limitations of the thesis

The small group size in this study can be a point of criticism. However, when examining the means of outcome variables in the tasks presented in this thesis, it can be seen that an increase of the number of subjects would probably not have changed the outcome. Furthermore, it is very difficult to include equally matched (level of impairment, side of the lesion) pairs of subjects, that are willing to be including if the treatment given not known because it is randomized. Importantly, the use of our very sensitive and reliable instruments with many

repetitions of each measurement in a high frequency is a great advantage to get reliable results even when smaller groups are used.
One more point of discussion is the fact that the children were only clinically examined for other limitations and objective sensibility measures are lacking.

Suggestions for future research
A very important goal for future research is to investigate the effects of strength training of the affected upper limb on muscle strength and on manual performance. Manual performance has to be measured with both standardized activities as used in the Melbourne assessment and QUEST, and with very simple motor tasks using quantitative registration methods. This will shed new light on the relation between muscle strength and manual performance in children with spastic hemiplegia, which may lead to fine tuning of the intensive task-orientated training used in this study.
Research is needed to develop criteria for muscle force needed to perform specific tasks. In addition, evaluating the effect of BTX on strength and manual performance after strength training of the upper limb muscles is an important goal for future. The question, whether BTX has a similar effect as shown in this thesis on strong spastic muscles is very important.

Overall conclusions
The use of very reliable and sensitive instrumented measures has given us new insights in the underlying force control mechanisms of the spastic hand.

- Spastic flexor wrist and finger flexor muscles are overall weak compared to the un-affected hand and controls.
- The wrist and finger flexors of the unaffected hand seem to be weakened in the children above the year of 10.
- Children with spastic hemiplegia show decreased generated force and increase variability in isometric tasks. However, if normalized for their maximal force children with spastic hemiplegia perform comparable to typically developing children.
- Active range of motion of the wrist seems to be one of the most important factors for manual accuracy.
- Standardized intensive task-oriented manual program increases muscle strength and decreases muscle tone.
- BTX combined with intensive task-oriented standardized PT/OT decreases spasticity. Stand alone PT/OT shows comparable effect after 3 months of therapy.
- BTX hampers the strength training of the wrist and finger flexors, compared to intensive therapy without BTX.
- BTX increases the movement speed and not accuracy in fast ongoing alternating tasks. This improvement is not shown in discrete tasks.

These new insights are only gained by using very precise and objective data. In the clinical field these kinds of instruments are more and more needed to make clinical decisions for treatment.

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Summary

More than half of the children undergoing treatment in Dutch pediatric rehabilitation centers have been diagnosed with Cerebral Palsy (CP). CP is characterized by a persistent movement or posture deficit that results from a non-progressive disorder in the developing fetal or infant brain. CP is the most common motor disability in childhood, with an incidence of 1-2 per 1000 in western countries, according to the Surveillance of Cerebral Palsy in Europe, according the SCPE. CP is a condition with many clinical manifestations. Spastic hemiplegia refers to one sided body involvement with a relative sparing of the contra lateral body side.

In children with constraints in manual performance, loss of strength can be a primary issue. Strength related to reach and grip tasks has been investigated in the past years, especially in children with CP. To measure the effect of upper limb training on muscle strength and manual performance, quantitative tests are needed related to strength and force regulation in specific manual tasks. Therefore, the research on manual strength capacity in both isometric and dynamics tasks in the affected hands in children with spastic hemiplegia is the main focus of this manuscript. The general objective of this thesis was to study how quantitative tests can contribute to the assessment of fine motor control in CP. For this purpose several methods were used, including the testing of isometric and dynamic manual force regulation and the testing of aiming movements.

In chapter 2 the first method mentioned (manual isometric force generation) was used to test both children with spastic hemiplegia and controls. Both maximum force and generated force at 5 sub maximal force levels and the co-efficient of variation of force were discussed in this chapter. The expected outcome was that the effectiveness of force production would be decreased and relative force variability would be enhanced in the affected hand. An isometric force production task at five different levels of their maximum voluntary contraction was performed. Results showed that maximum voluntary contraction generated with the affected hand was only one third of the non affected hand, time to peak was almost two-fold at the highest force level and the coefficient of variation was twice as high. The non affected hand did not differ from the control children. Correlations between clinical and experimental variables were significant for the relation between the Ashworth score for the elbow flexors, maximum voluntary contraction and variability at the highest force level. It was concluded that the finding of reduced maximum voluntary contraction in the affected hand suggests that strength training should be considered for agonist spastic muscles.

In Chapter 3 we used the same method as in chapter 2 to explore the importance of visual feedback on manual isometric force generation in children with spastic hemiplegia compared with controls. In this chapter the hypothesis is tested if children with spastic hemiplegia rely more on externally guided visual feedback when trying to keep isometric force constant with their affected hand as compared to their non-affected hand and as compared to controls. Absolute error, normalised force and power spectra analysis are used to test this hypothesis. An isometric force task was used, in which a cursor had to be moved to a visually specified target that disappeared half way the task. It was found that the deterioration of performance after withdrawal of target visualization did differ between affected hand and non-affected hand and controls. However if normalized for their force level, the normalized force error and

co-efficient of variation showed a similar increase between groups. Furthermore, power spectrum density analysis of the force signal showed that both hands in both groups had a similar loss in the energy in the 2-3 Hz range when target visualization was removed. These results suggest that CP children are equally able to produce stable force without visually monitoring their performance than children without CP, provided they are allowed to operate within their own force range.

In chapter 4 the second method (aiming movements) was introduced. Manual dynamic force regulation of children with spastic hemiplegia was compared with controls. Primary question in this chapter is whether children with spastic hemiplegia obey Fitts' law, despite their motor difficulties. In a simple tapping task reaction time, movement time and accuracy were measured to compare the performance of children with spastic hemiplegia with theirs controls. Fitts' law is commonly found to apply to motor tasks involving precise aiming movements. Children with cerebral palsy have severe difficulties in such tasks. If Fitts' law still does apply to these children, this would indicate that it is extremely robust and that even performance of children with damaged central nervous systems can adhere to it. Using this Fitts' aiming task, prolonged reaction and movement time were found in the affected hand in children with spastic hemiplegia as compared to controls. Like in the control group, movement time in children with spastic hemiplegia was related to Index of Difficulty. In conclusion, children with spastic hemiplegia obey Fitts' law despite very obvious limitations in fine motor control.

Both the kinematic aiming tasks and the isometric maximum force task provided reliable data and showed a high Intra Class Correlation movement time, spread of endpoints, index of performance and maximum voluntary contraction. Having established that the two types of tests can be used to test children with CP the question arose whether these same tests could be used to evaluate the effectiveness of interventions. For this purpose an intervention was evaluated consisting of an intensive task oriented therapy with and without additive Botulinum Toxin-A. The oriented therapy was based both on motor learning of skills tailored to the demands of the child and on functional strength training within task specific activities and skills. Based on individual goal setting, weights or body weight were used which were adapted to the force and performance level of the child. All children wore a thermoplastic night splint. A specific wrist splint was worn during the day by the children graded Zancolli IIB.

The therapy was performed 3 times a week during 6 months. For the evaluation of these interventions a distinction was made between short term (2 weeks after Botulinum toxin-A) and long term effects (6 and 9 months after botulinum Toxin-A). The additional effect of Botulinum toxin-A on intensive task oriented manual training was studied in a randomised clinical trial (RCT).

We explored the potential of isometric force testing to evaluate the functional outcome after BTX, either in the short run (chapter 5 and 6) or in the long run (chapter 6 and 7) and in parallel we used several aiming tests.

In Chapter 5 the direct (short-term) effect of BTX on manual dynamic force regulation in a RCT is reported. For the aiming tasks the same methods were used as described in chapter 3,

except that 2 new variations of the aiming tasks were used, namely a shift version of discrete movement task and a continuous or alternating kinematic aiming task.
After BTX a significant increase of spread of endpoints and decrease of index of performance effective was shown if precision demand in the tasks was high, while the inverse occurred when speed was more important. These functional changes coincided with a significant decrease of the maximum voluntary contraction of the flexor muscles of the forearm, showing the direct effect of BTX. The Kinematic aiming tasks are an adequate and reproducible way to quantify functional changes after BTX in the upper limb. BTX has an inverse effect in the precision task when accuracy is important but a positive effect when speed prevails.
In chapter 6 the long-term effects were examined with the isometric force regulation test, as applied during the therapy period and follow up. The same method was used as described in chapters 2 and 3 to quantify the changes in isometric force (with over- and under-shoot as force production error), active and passive range of motion, stretch restricted angle of joints, Ashworth scores at the elbow and wrist, and the Melbourne assessment of unilateral upper limb function. Clinical measures (muscle tone, active range of motion of the wrist and the elbow) showed improvement in both groups. However no significant differences emerged between groups on functional measures. Generated force decreased directly after the BTX injection, but increased during the therapy period. The group without BTX, however, showed a significantly higher increase in force and accuracy with therapy compared to the group with additional BTX. Functional rehabilitation therapies for the upper extremity increased manual isometric flexor force at the wrist and range of motion, but BTX injections caused weakness and did not lead to better outcomes than therapy alone.
In chapter 7 the three aiming tasks (lift, shift and alternating aiming measuring dynamic force regulation) were used to investigate the short-and long term effects of BTX based on the same RCT as mentioned above. Outcome measures were movement time, endpoint spread, percentage successful movements and performance in both lift and shift tasks. Directly after the BTX injections all kinematic outcome measures showed a decrease but baseline values were re-established during the therapy period. The group with additional BTX showed temporarily a significantly higher increase in speed and performance. However accuracy decreased slightly but not significantly. The group with additive BTX showed a larger significant benefit for speed and performance in an alternating task. These results illustrate the need to find appropriate quantitative tests to reveal effects of BTX.
In summary, this thesis has shown that the use of very reliable and sensitive instrumented measures has given us new insights in the underlying motor control mechanisms of the spastic hand. One can describe the insights in 8 fundamental points

1. Spastic flexor wrist and finger flexor muscles are overall weak compared to the un-affected hand and controls.
2. The wrist and finger flexors of the unaffected hand seem to be weakened in the children above the year of 10.

3. Children with spastic hemiplegia show decreased generated force and increase variability in isometric tasks. However, if normalized for their maximal force children with spastic hemiplegia perform comparable to typically developing children.
4. Active range of motion of the wrist seems to be one of the most important factors for manual accuracy.
5. Standardized intensive task-oriented manual program increases muscle strength and decreases muscle tone
6. BTX combined with intensive task-oriented standardized therapy decreases spasticity. Stand alone therapy shows comparable effect after 3 months of therapy.
7. BTX hampers the strength training of the wrist and finger flexors, compared to intensive therapy without BTX.
8. BTX increases the movement speed and not accuracy in fast ongoing alternating tasks. This improvement is not shown in discrete tasks.

These new insights are only gained by using very precise and objective data. In the clinical field these kinds of instruments are more and more needed to make effective clinical decisions for treatment.

Samenvatting
(Dutch Summary)

In de Kinderrevalidatie in Nederland bestaat de helft van de behandelingen uit de behandeling van kinderen met een cerebrale parese (CP). CP is gedefinieerd als een klinisch syndroom gekenmerkt door een persisterende houding- of bewegingstoornis ten gevolge van een niet-progressief pathologisch proces dat de hersenen tijdens hun ontwikkeling heeft beschadigd. De prevalentie voor de Europese populatie is rond de 2 per 1000 levend geboren kinderen. CP kent veel klinische manifestaties, zoals spastische hemiplegie of unilaterale CP. Deze wordt gekenmerkt door een halfzijdige bewegingsstoornis. Bij kinderen met een unilaterale CP worden vaak beperkingen geconstateerd in de aangedane arm en hand. Verhoogde tonus en verlies van kracht zijn hierbij primaire factoren. Kracht gerelateerd aan reiken en grijptaken is in het laatste decennium veelvuldig onderzocht, speciaal bij kinderen met een unilaterale CP.
Om het effect van training van de arm/hand te meten op gebied van vaardigheid en kracht(regulatie) zijn kwantitatieve specifieke manuele testen nodig. Dit is de primaire focus van het manuscript. De isometrische en dynamische manuele krachtregulatie van de aangedane hand van kinderen met een unilaterale CP staan centraal in dit proefschrift. Het algemene doel van dit proefschrift was het bestuderen hoe kwantitatieve testen bij kunnen dragen aan het assessment van de fijn motorische manuele controle in CP. Voor dit doel zijn verschillende methoden gebruikt, waaronder het testen van isometrische krachtsregulatie en dynamische krachtsregulatie gericht op doelgerichte bewegingen.

In hoofdstuk 2 wordt de eerste methode (gericht op isometrische krachtsgeneratie) gebruikt om kinderen met een unilaterale CP te vergelijken met controle kinderen. Zowel maximale kracht als gegenereerde submaximale kracht op 5 krachtsniveau's (van 12-60% van de maximale kracht) als ook de co-efficient of variation zijn bediscussieerd in dit hoofdstuk. De verwachte uitkomst was dat de effectiviteit van de gegenereerde kracht in de aangedane hand bij kinderen met een unilaterale CP verminderd zou zijn en de variabiliteit van de geleverde kracht vergroot zou zijn. De resultaten laten zien dat de maximale kracht ongeveer een derde was van de niet aangedane hand. De time to peak was ongeveer verdubbeld op het hoogste krachtsniveau en de co-efficient of variation was 2 keer zo hoog. De niet-aangedane hand verschilde niet veel van de controle groep onder de leeftijdsgroep van 10 jaar. Echter boven de 10 jaar waren zowel de maximale kracht verminderd, de time to peak en de variabiliteit toegenomen in beide armen en handen van de kinderen met een unilaterale CP. De correlaties tussen de klinische en de experimentele variabelen waren significant voor de relatie van de Ashworth scores voor de flexoren van de elleboog, de maximale kracht van de polsflexoren en de variabiliteit op de hoogste krachtsniveau's. De conclusie was dat het resultaat van de afgenomen maximale kracht in de aangedane hand krachttraining legitimeerde voor de spastische polsflexoren.
In hoofdstuk 3 werd dezelfde methode gebruikt als in hoofdstuk 2 om het belang van visuele feedback voor isometrische krachtsregulatie bij kinderen met een unilaterale CP aan te tonen, in vergelijking met controle kinderen. De hypothese werd getest of de kinderen met een unilaterale CP meer gebruik maken van externe visuele feedback mechanismen als zij de isometrische kracht stabiel moeten houden met de aangedane hand ten opzichte van de niet aangedane hand en de controle kinderen. Absolute error, genormaliseerde kracht en power

spectrum analyse werden gebruikt om deze hypothese te testen. Een isometrische taak werd gebruikt, waarbij de cursor naar een zichtbaar doel werd bewogen dat halverwege de tijd van het beeldscherm verdween. De cursor moest dan op de denkbeeldige positie gehouden worden. De resultaten gaven aan dat de verslechtering van de uitvoering nadat het doel uit het zicht verdween verschilde tussen de aangedane en niet aangedane hand en de handen van de controle kinderen. Echter na normalisatie van de krachtwaarden lieten de genormaliseerde kracht error en variabiliteit een vergelijkbare toename zien in alle groepen. Bovendien toonde de spectraalanalyse dat beide handen in beide groepen een vergelijkbaar verlies in de 2-3 HZ band hadden als het doel verdween. Deze resultaten tonen aan dat vergeleken met controle kinderen, de kinderen met een unilaterale CP op gelijkwaardige manier de kracht kunnen reguleren als zij geen visuele feedback krijgen. De voorwaarde is dat zij binnen hun eigen mogelijkheden van de krachtsgeneratie kunnen werken.
In hoofdstuk 4 werd de tweede methode geïntroduceerd. De manuele dynamische krachtsregulatie bij kinderen met een unilaterale CP werd vergeleken met die van controle kinderen. De primaire vraag in dit hoofdstuk was of Fitts' law ook opgaat bij de kinderen met een unilaterale CP, ondanks hun motorische beperkingen. In een eenvoudige tap taak werd de reactietijd, snelheid en precisie gemeten om het vaardigheidsniveau te bepalen. Fitts' law gaat meestal op bij motorische precisie taken gericht op een doel. Deze taken zijn zeer moeilijk uitvoerbaar bij kinderen met een unilaterale CP. Als Fitts' law opgaat bij deze doelgroep kinderen, dan houdt dit in dat Fitts' law een krachtige wetmatigheid inhoudt die opgaat bij kinderen met een beschadigd centraal neurologisch systeem. De resultaten gaven een verlengde reactietijd en verminderde snelheid aan bij kinderen met een unilaterale CP ten opzichte van de controle groep. Echter voor beide groepen gold dat als de taak moeilijker (index of difficulty groter) werd, de snelheid afnam. Concluderend kan gesteld worden dat Fitts' law ook opgaat voor kinderen met een unilaterale CP, ondanks grote beperkingen in de fijn motorische controle.
Zowel de dynamische krachtsregulatie als de isometrische krachtsregulatie taak toonden zeer betrouwbare data en hadden een hoge intraclass correlatie met snelheid, spreiding van de eindpunten, index of performance (vaardigheidsniveau) en maximale kracht. (hoofdstuk 5). Nu gebleken was dat deze twee soorten testen gebruikt kunnen worden bij kinderen met een CP wilden we de volgende vraag beantwoorden. Namelijk of de gehanteerde instrumenten geschikt zijn om de effectiviteit van interventies te kunnen evalueren. Hiervoor werd een intensieve taak georiënteerde therapie toegepast met en zonder additief Botuline Toxine-A (BTX) in de arm spieren. Hierbij is een onderscheid gemaakt tussen korte termijn effect (2 weken na de BTX) en de lange termijn effecten (na 6 maanden therapie en 9 maanden na de BTX of start van de therapie). De intensieve taak georiënteerde therapie bestond uit het motorisch aanleren van vaardigheden, afgestemd op de individuele hulpvraag van ieder kind. Verder functionele krachttraining gericht op de individuele hulpvragen en aangepast aan het optimale gewicht dat een kind kon hanteren in de functionele taken. Een nachtspalk werd gedragen. Overdag werd door de kinderen met Zancolli IIB een specifieke pols spalk gedra-

gen. De therapie duurde 6 maanden met een frequentie van 3x per week fysiotherapie en ergotherapie. Het design was een randomised clinical trial.
De isometrische uitkomstmaten in de interventie zijn beschreven in hoofdstuk 5 (korte termijn) en hoofdstuk 6 (lange termijn). De dynamische uitkomstmaten in de interventie zijn beschreven in hoofdstuk 5 (korte termijn) en hoofdstuk 7 (lange termijn).
In hoofdstuk 5 is het korte termijn effect van BTX beschreven op de manuele dynamische krachtregulatie. Dezelfde methode werd gehanteerd zoals beschreven in hoofdstuk 3. Echter nu werden 2 nieuwe taken uitgevoerd. De discrete shift taak en de continue of alternerende shift taak (beschreven in hoofdstuk 5 en 7). Na BTX verslechterden alle variabelen van de dynamische discrete taken een significante toename van de variabiliteit rondom de doelen en een significante afname van de index of performance was te zien als grote precisie gevraagd werd in de taak. Een toename van de index of performance was te zien in de continue taak, waarbij de snelheid het belangrijkste was. Deze veranderingen liepen parallel met een significante afname van de maximale kracht in de polsflexoren. De conclusie kan getrokken worden dat BTX een negatief effect heeft op precisie en een positief effect op snelheid in een taak.
In hoofdstuk 6 is het effect van de interventie op de isometrische uitkomstmaten beschreven. Hierin is dezelfde methode gebruikt, die in hoofdstuk 2 en 3 beschreven is. Nu werden de veranderingen in de isometrische kracht (gegenereerde kracht, foutmarge en de over en onder "shoots") beschreven als ook de veranderingen in de klinische maten
(actieve en passieve mobiliteit, de "catch" en de Ashworthschaal bij pols en elleboog en de Melbourne assessment of unilateral upper limb function). De klinische maten lieten allen positieve vooruitgang zien bij beide groepen. Echter er ontstond geen significante verschil tussen beide groepen. De gegenereerde kracht direct na de BTX daalde significant en steeg tot boven het uitgangsniveau na de therapie. Echter de groep zonder BTX toonde een significante hogere verbetering na de therapie ten opzichte van de groep met BTX.
Taak georiënteerde therapie voor de bovenste extremiteit laat een toename zien van de isometrische polsflexie kracht en de range of motion. De BTX injecties veroorzaakten krachtverlies en hebben niet geleid tot betere toename dan de therapie zonder BTX.
In hoofdstuk 7 werd in dezelfde RCT het additionele lange termijn effect van BTX en intensieve therapie vergeleken met de identieke therapie zonder BTX. Zowel snelheid, precisie en vaardigheidsniveau in de tapping, shift en continue taak werden vastgelegd gedurende de interventie. De achteruitgang van de variabelen direct na de BTX werd na de therapieperiode weer hersteld. De groep met BTX liet een tijdelijke significant hogere snelheid en index of performance zien in de continue taak ten opzichte van de groep zonder BTX. De precisie werd iets minder maar niet significant verschillend tussen de groepen. In de tapping en de shift taak waren er geen significante verschillen tussen de beide groepen.
Deze resultaten tonen aan dat de juiste kwantitatieve testen nodig zijn om de veranderingen na de BTX en therapie aan te geven. In alle hoofdstukken die er beschreven zijn, was het primaire doel gelegen op manuele krachtsregulatie.

Deze thesis laat ons zien dat het gebruik van betrouwbare en sensitieve instrumenten met grote precisie nieuwe inzichten hebben gegeven in de onderliggende motorische controle mechanismen van de spastische hand bij kinderen met een unilaterale CP.
Samengevat kan dit weergegeven worden in 8 punten:

1. De spastische pols en vinger flexoren zijn veel zwakker dan die van de niet aangedane hand en de handen van controle kinderen.
2. De pols en vinger flexoren van de niet aangedane hand worden zwakker bij de kinderen boven de 10 jaar.
3. De kinderen met een unilaterale CP laten een achteruitgang zien in de krachtsgeneratie en de variabiliteit in een isometrische taak. Als men de waarden normaliseert ten opzichte van de eigen maximale kracht dan presteren ze gelijkwaardig ten opzichte van controle kinderen indien de visuele feedback wegvalt.
4. Actieve mobiliteit van de pols lijkt een van de belangrijkste factoren te zijn om met precisie te kunnen werken.
5. Gestandaardiseerde taak georiënteerde therapie gericht op manuele vaardigheden vergroot de spierkracht van de polsflexoren en verlaagt de spiertonus.
6. BTX gecombineerd met intensieve taak georiënteerde therapie verlaagt blijvend de spiertonus tot 3 maanden na de therapie. De therapie zonder BTX laat vergelijkbaar resultaat zien na 3 maanden therapie.
7. BTX beperkt de mogelijkheden tot krachtstoename in de pols en vingerflexoren ten opzichte van therapie zonder BTX.
8. BTX verhoogt de bewegingssnelheid en niet de precisie in snelle heen en weer gaande continue bewegingen. Dit effect is in de discrete taken afwezig.

Deze nieuwe inzichten zijn alleen verkregen door met grote precisie kwantitatieve objectieve data te verzamelen. In de kliniek zullen deze instrumenten nodig zijn om effectieve klinische beslissingen voor behandeling te onderbouwen.

About the author

Eugène Rameckers was born on the 22th of August 1958 in Bergen op Zoom in the Netherlands. After high school at the Gymnasium Rolduc in Kerkrade (Limburg), he studied education in sports in Tilburg (graduated 1980) and Physical Therapy in Heerlen (graduated 1985). In 1988 he graduated in Maastricht at the First Degree Teachers Academy and in 2001 he finished his Master of Research in Neuromotor Science in Nijmegen. From 1985 until now he worked as pediatric physical therapist in the Rehabilitation Centre SRL, in Franciscusoord (Valkenburg-Houthem). In 1986 he started as a teacher in physical therapy in Heerlen until 1990 and prolonged his teaching profession in the First Degree Teachers Academy in Maastricht until 1995. From 1996 until now he started as a teacher in Breda at the Master Programs Pediatric Physical Therapy Avans+ University for Professionals.
In 2001 he combined his work in the SRL with a job as physical therapist in the gait laboratory in Academic Hospital Maastricht. In 2005 till 2007 he participated in the Dutch guideline for treatment for children with spastic cerebral palsy. In 1999 until now he combined his work as physical therapist with a job as chief editor for the Dutch Journal for Pediatric Physical Therapy. His participation in a randomised clinical trial in the additive effect of Botulinum Toxin-A on intensive manual task oriented therapy in children with spastic hemiplegia (Lucianne Speth et al 2005), combined with the Master study in Nijmegen was the start of this PhD project. Eugène will continu his work as pediatric physical therapist and researcher in the field of rehabilitation.

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