Chapter 6

Characterizing the intervention protocol for early modified Constraint Induced Movement Therapy in the EXPLICIT-stroke trial

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ABSTRACT

Constraint-induced movement therapy (CIMT) is a commonly used rehabilitation intervention to improve upper limb recovery after stroke. CIMT was originally developed for patients with a chronic upper limb paresis. Although there are indications that exercise interventions should start as early as possible after stroke, only a few randomized controlled trials have been published on either CIMT or modified forms of CIMT (mCIMT) during the acute phase after stroke. The implementation of (m)CIMT in published studies is very heterogeneous in terms of content, timing, and intensity of therapy. Moreover, mCIMT studies often fail to provide a detailed description of the protocol applied. The purpose of the present article is therefore to describe the essential elements of the mCIMT protocol as developed for the EXplaining PLastICITy after stroke (EXPLICIT-stroke) study. The EXPLICIT-stroke mCIMT protocol emphasizes restoring body functions, whilst preventing the development of compensatory movement strategies. More specifically, the intervention aims to improve active wrist and finger extension, which are assumed to be key factors for upper limb recovery. The intervention starts within 2 weeks after stroke onset. The protocol retains 2 of the 3 key elements of the original CIMT protocol, i.e. repetitive training and the constraining element. Repetitive task training is applied for 1 hour per working day, and the patients wear a mitt for at least 3 hours per day for 3 consecutive weeks.

INTRODUCTION

Stroke is one of the main health problems in the Western world.[1] Since about 80% of the survivors have an upper limb paresis immediately after stroke onset,[2] a wide range of interventions have been developed to improve upper limb function.[3] Systematic literature research shows that the most evidence-based intervention for upper limb function is constraint-induced movement therapy (CIMT).[3, 4] CIMT is a neurorehabilitation approach developed by behavioural neuroscientist Dr. Edward Taub and colleagues.

The original CIMT treatment protocol is clearly described and includes 3 main elements:[5] (I) repetitive, task-oriented training of the more impaired upper limb for 6 hours a day, on 10 consecutive weekdays; (II) a transfer package of adherence-enhancing behavioral methods designed to transfer the gains made in the clinical setting to the patient's real world environment and; (III) constraining the less impaired upper limb to promote the use of the more impaired upper limb during 90% of the waking hours.[5] To date, several modified forms of CIMT (mCIMT) have been developed, resulting in heterogeneity with respect to the application of (m)CIMT in terms of content, timing and intensity of therapy. In addition, mCIMT studies often fail to provide a detailed description of the protocol they applied.

CIMT was originally developed for patients with a chronic upper limb paresis[6] and most of the research so far has therefore focused on the chronic phase after stroke.[7, 8] There are indications, however, that exercise interventions should start as early as possible after stroke,[9] and a number of recent (animal) studies have suggested the presence of a critical time window of heightened, reactive neuroplasticity during the first 3 to 4 weeks after stroke.[9, 10] Neuroplasticity may be augmented by rehabilitative therapy and may lead to enhanced recovery.[11] Therefore, these first 3 to 4 weeks of heightened neuroplasticity may offer a therapeutic window for evidence-based therapies such as (m)CIMT in acute stroke survivors. In 2000, Dromerick and colleagues[12] published the first randomized clinical trial of mCIMT during acute stroke rehabilitation. The results of this trial suggest that mCIMT during acute rehabilitation is feasible and reduces arm impairments at the end of the treatment. However, since then, only 5 randomized controlled trials have been published on either CIMT or mCIMT during the acute phase after stroke. A recent meta-analysis of these studies revealed a trend toward positive effects of (m)CIMT in the first weeks, but also suggested that modified forms of CIMT, with lower treatment doses (less than 3 hours) of repetitive training may be more beneficial during this period than a more intensive 3-hour dose of CIMT or more per day.[13] Heterogeneity of included studies was a major concern in this meta-analysis, for instance due to the variation in inclusion criteria regarding initial upper limb function. Furthermore, there were obvious differences in the therapy dosage. And although most included studies fail to provide a detailed description of the intervention protocol they had applied, the content of the therapy is likely to have varied as well. Researchers should be aware that transparency regarding the treatment protocol applied is essential to allow clinicians to implement the protocol in practice and to allow other researchers to replicate the claimed findings of published clinical trials. This element is considered an important but neglected cornerstone in evidence-based medicine.[14, 15]

The purpose of the present paper is therefore to present and explicate the essential elements of the mCIMT protocol developed for the EXplaining PLastICITy after stroke (EXPLICIT-stroke) program and to argue the choices that were made in establishing the protocol (www.explicit-stroke.nl). EXPLICIT-stroke is a single-blinded, randomized multicenter trial that is being conducted in The Netherlands, focusing on upper limb rehabilitation in the acute phase after stroke.[16] The EXPLICIT-stroke program is still ongoing, and the first results of the trial are expected in spring 2013. One of the main aims of this trial is to determine the effectiveness of applying mCIMT in the first weeks after stroke onset in patients with a favorable prognosis for upper limb recovery.[17] The mCIMT intervention starts within 2 weeks after stroke onset. The mCIMT protocol developed for the EXPLICIT-stroke trial is aimed at neurological repair by applying an impairment- focused intervention emphasizing the improvement of wrist and finger extension as key factors for regaining dexterity. At the same time, the protocol aims to prevent early development of compensatory movement strategies in the aforementioned critical time window, during which heightened neuroplasticity is believed to exist. Furthermore, the protocol retains 2 of the 3 main elements of the original CIMT protocol, i.e. the repetitive training and the constraining element. Repetitive task training is applied for 1 hour per working day and the patients wear a mitt for at least 3 hours per day for 3 consecutive weeks.

PROTOCOL DESCRIPTION

The therapy described in the protocol is aimed at recovery of upper limb function during the first weeks after stroke onset. The early start of mCIMT is mainly based on the suggestion of a limited time window of heightened homeostatic plasticity during the first 3 to 4 weeks post stroke.[10] Neuroplasticity may be augmented by exercise therapy and may lead to enhanced recovery.[11] Recovery is a complex process that probably occurs through a combination of spontaneous and learning-dependent processes, including restitution, substitution and compensation[4, 18, 19] (Figure 1.2). The therapy as described in the protocol is aimed at recovery in terms of neurological repair, by applying an impairment-focused intervention, whilst preventing the development of compensatory movement strategies. This approach is specified as the *bottom-up* approach in the EXPLICIT-stroke mCIMT protocol, referring to the hierarchical levels of the ICF. The decision to focus on restoring impairments during the first weeks after stroke in order to regain activities is in line with the review by Langhorne and colleagues,[4] which discussed the pattern of recovery after stroke, combined with the timing of intervention strategies.

The bottom-up approach

Improving active voluntary extension of the fingers plays a dominant role within the bottom-up approach, knowing that finger extension is a key factor for regaining dexterity.[17, 20-22] Fritz and colleagues showed that finger extension is a predictor for outcomes in a CIMT study.[20] In 55 stroke patients who were subjected to CIMT, early return of finger extension according to the FM hand score was the only significant predictor of a favorable outcome of upper limb function.[20] In addition, Kwakkel and Kollen found on the basis of longitudinal regression analysis of change scores that functional improvement of the upper paretic limb is mainly driven by improvement of the paretic hand, explaining about 60% of the variance of outcome, followed by synergistic independent movement of the paretic arm.[21]

To structure the therapy according to the bottom-up approach, a treatment matrix was developed, to provide a step-by-step strategy (Figure 6.1).

Domains		
Level 1 → Gross arm movements	Level 2 → Grasps / grips	Level 3a In-hand manipulation
Aims	Aims	Aims
1: Activating wrist and finger extension through proximal control of the shoulder girdle.	1: Improving the cylinder grip with the focus on extension of wrist and fingers.	1: Improving the in-hand manipulation of objects and fine motor control of the hand.
2: Motor control of the arm, emphasizing protraction of the shoulder and extension of the elbow.	2: Improving the five finger grasp, by motor control of the intrinsic muscles and extension and flexion of the fingers	2: Improving selective movements of the fingers and the thumb.
3: Motor control of the proximal arm, emphasizing wrist and finger extension.	3: Improving the pinch grip, with the focus on the extension of the fingers and wrist.	3: Improving motor control of the intrinsic muscles of the fingers and the hand.
4: Motor control of the distal arm in different directions, emphasizing wrist and finger extension.		Level 3b ADL related tasks Aim
5: Motor control of the arm, emphasizing isometric, eccentric and concentric extension of the elbow.		Improving dexterity
6: Motor control of the arm in different directions, emphasizing extension of the elbow in combination with a grip.		

Figure 6.1 The Matrix.

Level 1 and 2 of this matrix are hierarchically organized, going both from left to right and from top to bottom. The different levels are based on the domains of the Action Research Arm Test (ARAT),[23] starting with gross movements, whilst activating wrist and finger extensors and subsequently working towards the ability to grasp, still with the focus on finger extension. Due to individual differences not all patients will easily fit into this hierarchy, so therapists need to evaluate each patient continually and adapt the exercises accordingly.

Level 3a involves in-hand manipulation exercises, essential for regaining dexterity and bridging the gap between level 2 and level 3b, the latter involving activities of daily living.

Repetitive training, contsraining and the Transfer Package

The mCIMT protocol applied in the EXPLICIT-stroke trial, retains 2 of the 3 main elements of the original form of CIMT, i.e. repetitive training and the constraining element and is applied for 15 consecutive weekdays. The bottom-up approach determines how the repetitive training and the constraining element of CIMT are implemented, so the application differs from the original form of CIMT, as described and explained below:

Repetitive training

Patients receive 1 hour of individual training on each working day during a 3-week period, starting within the first or second week after stroke. Depending on the patient's ability to sustain training, the hour can be divided into two 30-minute or four 15-minute sessions per working day. A dose of 1 hour was chosen since care must be taken not to overload patients in the acute phase after stroke. A recent meta-analysis also suggested that CIMT with treatment doses of less than 3 hours of repetitive training per day may be more beneficial during this period than a more intensive dose of CIMT.[13] In line with the original CIMT protocol repetitive training consists of 'Shaping' and 'Task Practice'.

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Shaping: During each session, shaping principles play a dominant role. Shaping is defined as a training method in which a motor objective is approached in small steps by successive approximations.[5] For instance, the task difficulty can be incrementally increased in accordance with a patients' capabilities or the requirements for speed performance can be progressively augmented.[5] The main objective is to encourage the patient to use the more affected upper limb repeatedly to overcome (or prevent) learned non-use and to induce activity dependent cortical reorganization.[5] Also, feedback provided during shaping should be immediate and specific and emphasize only positive aspects of the patients' performance to motivate the patient to apply continued and maximal effort. Shaping is mainly applied at levels 1 and 2 of the treatment matrix.

Task practice: Task practice is a less structured way of training than shaping. Task practice is defined as a training method in which functional tasks are practiced. It is implemented mainly at level 3 of the matrix, when a patient has successfully completed levels 1 and 2 and is able to integrate the improved control of the extensors in functional unilateral tasks (i.e. eating, cutting bread, cleaning a table, ironing or writing). However, therapists still need to focus on finger extension and prevent compensatory movements. Therapists should discuss personal goals with each patient and structure the treatment sessions based on these goals, which means that the therapy is individualized.

Constraining

In the EXPLICIT-stroke program, patients wear a padded safety mitt on the less affected hand during each training session and for at least 3 hours per day to force them to use the more affected limb only. The mitt restricts the ability to use the less affected hand during most tasks, whilst still allowing protective extension in the elbow in case of imbalance. Patients receive homework at the end of each training session, according to the treatment aims, to encourage them to exercise the more affected limb during the 3 hours when the mitt is worn outside therapy sessions. The homework is discussed and evaluated at the beginning of the next therapy session.

Transfer Package

The Transfer Package is, besides repetitive training and constraining another main element of CIMT in its original form. However, the Transfer Package is not fully included in the EXPLICIT mCIMT protocol for medical-ethical and practical reasons. An important element of the Transfer Package is the behavioural contract. Patients in the acute phase are usually emotionally not yet capable to make such a strong commitment. In addition, from a practical point of view, some elements of the transfer package are not applicable in the acute phase, since patients are often still staying in a clinical setting during the first weeks after stroke. However, although some components of the Transfer Package are not applicable in the acute phase, some of its subcomponents are included. For instance, patients are given homework, and patients also have to keep a diary, to encourage them to take the mitt practice seriously. The patient diary is filled in daily and checked by the therapist. The time dedicated to shaping and task practice during the training session as well as the level and aim that the patient is working on, are documented by patient and therapist. In addition the times when the mitt is put on and taken off have to be specified in the diary. The information recorded in the patient diary is useful as motivational feedback to the patient by demonstrating improvements in level and aim over time.

Patient selection

In order to increase the efficiency of stroke care, only patients expected to benefit most from a particular therapy should be selected. Appropriate patient selection early post stroke also reduces unrealistic patient expectations. Hence, it is paramount for clinicians to be aware of prognostic determinants that predict upper limb outcome after stroke. The improvement of finger extension is not only a key factor in regaining dexterity, but the presence of some finger extension within the first week post stroke seems to be the most important prognostic determinant of the outcome of upper limb function as well.[17] It probably reflects the (partial) intactness of fibers of the corticospinal tract system in the affected hemisphere after stroke.[24, 25] Therefore, the ability to exert some voluntary motor control of finger extensors at this early stage may be required for a positive effect of (m)CIMT.

Based on this knowledge, the most important criteria for enrolment in the EXPLICIT-stroke mCIMT trial are the presence of (I) at least some voluntary extension of the fingers of the affected hand and (II) proximal voluntary activity as indicated by a score of 1 or 2 on item 5 (arm motor) of the National Institutes of Health Stroke Scale (NIHSS). Other criteria for participation are (III) first-ever ischemic stroke within 14 days; (IV) no upper extremity orthopedic limitation that would affect the treatment and results; (V) no severe deficits in communication, memory or understanding (MMSE >22).

Implementation of the protocol in clinical practice

The feasibility of applying mCIMT during inpatient rehabilitation depends on several aspects: for instance, a successful application requires well-trained therapists and a well-organized multidisciplinary rehabilitation team. Using a multidisciplinary approach, which promotes collaboration and communication between physical and occupational therapists, can reduce the time investment by each profession. It is also important that the patients' family and the nursing staff are well informed and able to support the patient when necessary during the 3 hours of wearing the mitt and while doing the homework in the absence of the therapist.[26]

Evaluation

Since the mCIMT protocol typically requires intensive unilateral practice with the most impaired upper limb only, the EXPLICIT stroke program uses assessment tools that quantify upper limb performance during unilateral motor tasks are used, specifically the Action Research Arm Test (ARAT)[23] and the Wolf Motor Function Test (WMFT).[27] In addition, since the therapy focuses on the immediate treatment of impairments, the Fugl-Meyer motor assessment for the arm (FM-arm)[28] is used as well. Assessments should be conducted at least before and after the intervention period. Reassessments should be done after, for instance, 3 and 6 months, to assess long-term effects of the therapy.

DISCUSSION

The aim of mCIMT in the EXPLICIT-stroke trial is to improve upper limb function during the first 5 weeks after stroke onset. The early start of mCIMT is mainly based on the suggestion of a limited time window of heightened homeostatic plasticity during the first 3 to 4 weeks post stroke.[10] The EXPLICIT-stroke mCIMT protocol uses a bottom-up approach which emphasized the restoration of body functions, whilst preventing the development of compensatory movement strategies. More specifically, improving active voluntary extension of the fingers plays a dominant role in the protocol, knowing that finger extension is a key factor for upper limb recovery.[17, 20, 22, 29] The protocol retains 2 of the 3 main elements of the original CIMT protocol, i.e. repetitive training and the constraining element.

The EXPLICIT-stroke mCIMT protocol was developed for the acute phase after stroke, whereas the original CIMT protocol was developed for patients with a chronic upper limb paresis. Original CIMT is aimed at (I) inducing activity-dependent cortical reorganization[30] and (II) overcoming learned non-use.[31] The rationale behind our early use of CIMT is slightly different. With respect to the first aim, activity-dependent neuroplasticity is also expected to occur in the early phase after stroke. As mentioned above, a number of recent studies even suggest that there may be a critical time window of heightened reactive neuroplasticity induced by a reactive upregulation of growth promoting factors such as GAP 43 and MARCK during the first 3 to 4 weeks after stroke, followed by an upregulation of growth-inhibiting factors such as NOGO.[4, 10, 32] In line with this increased homeostatic neuroplasticity, there are accompanying mechanisms such as salvation of penumbral tissue by reperfusion as a result of increased angiogenesis and changing hemodynamics, as well as resolution of suppressed areas that are anatomically related to the infarcted area (i.e., elevation of diaschisis).[18, 33] These different processes are likely to contribute to the process of spontaneous neurological recovery early after stroke. Rehabilitation is believed to modulate this non-linear pattern of recovery, probably by interacting with these underlying processes.[18] Therefore, the limited time window in which these mechanisms operate may offer an opportunity for therapists to successfully apply evidence based-therapies such as (m)CIMT for acute stroke survivors. This suggestion is supported by an animal study by Biernaskie and colleagues,[11] which showed a marked improvement in a forelimb reaching task when training was started at 5 days post stroke. In contrast, less improvement was found when the training started at 14 days post stroke, whereas recovery was diminished when the training started at 30 days post stroke such that motor function did not differ from the animals in the control group.

The second aim of CIMT for patients with a chronic upper limb paresis is to overcome learned non-use. The general principle of the learned non-use concept is that a certain proportion of the motor deficit, associated with the damage to the nervous system is not necessarily a direct result of the damage. Instead, it could result from a learning phenomenon stemming from the damage, whose core is the learned suppression of movement.[31] While the occurrence of learned non-use may be negligible in the early stages after stroke, early application of (m)CIMT might minimize or even prevent the phenomenon in the long run.[34] Preventing learned non-use might in fact be easier and more feasible than attempting to extinguish it once it is established.

The purpose of the current paper was to describe the application of mCIMT within the EXPLICIT-stroke trial in much more detail than is normally allowed in studies published in peer reviewed journals. With the presentation of this intervention protocol, supported with evidence derived from well conducted (pre-) clinical studies, we like to implement this evidence into the real world of therapists. In our opinion, this black box is seen as an important road block in the translation from evidence based knowledge to the implementation of this evidence in the real world.[35, 36] Transparency about protocols applied will benefit both researchers and clinicians. Since such transparency is essential for the implementation of scientific results in clinical practice, we hope that more journals will follow the example of Physiotherapy Research International in publishing treatment protocols in the future.

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