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Results from the Norwegian Constraint-Induced Therapy Multisite Trial (NORCIMT)

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Norwegian University of Science and Technology

Doctoral thesis

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ISBN 978-82-326-3776-8 (printed ver.)
ISBN 978-82-326-3777-5 (electronic ver.)
ISSN 1503-8181

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Trondheim, March 2019

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Printed by NTNU Grafisk senter

Sammendrag på norsk

Armfunksjon tidlig etter hjerneslag

Resultater fra den Norske Constraint-Induced Therapy Multisenter Studien (NORCIMT)

Mange metaanalyser og nasjonale retningslinjer innen rehabilitering etter hjerneslag anbefaler intensiv og oppgaveorientert trening. Constraint-Induced Movement Therapy (CIMT) er én av treningsmetodene som har fokus på disse to elementene. Det finnes mange studier som har undersøkt CIMT i kronisk fase etter hjerneslag, men det er lite kunnskap om etterlevelse av en slik intensiv behandlingsprotokoll i tidlig fase. Det mangler også kunnskap om når det er best å starte opp CIMT. Dessuten er detaljert kunnskap om utvikling av grepstyrke begrenset.

Hovedmålsetning med denne avhandlingen var å bidra til økt kunnskap om 1.) etterlevelse av CIMT gjennomført i løpet av de første ukene etter hjerneslag, 2.) langtidseffekt av tidlig versus senere gjennomført CIMT, og 3.) hvordan forskjellige aspekter av grepstyrke utvikler seg i løpet av det første året etter hjerneslag. Datamaterialet fra deltakerne som ble inkludert i «Norwegian Constraint-Induced Therapy Multisite Trial» (NORCIMT) ble brukt i alle de tre artiklene i avhandlingen. Studien inkluderte 47 personer med mild til moderat hjerneslag.

I den første artikkelen ble etterlevelse av behandlingsprotokollen av NORCIMT undersøkt ved å analysere behandlingsskjemaene til de 24 deltagerne som fikk CIMT i tidlig fase (7-28 dager etter hjerneslaget). Resultatene viste generelt god etterlevelse av protokollen med tanke på tilstedeværelse i terapitimene, men deltakerne brukte mindre tid enn planlagt på trening av funksjonelle oppgaver. Kun en tredjedel av behandlingstiden ble brukt til ren motorisk aktivitet. Etterlevelsen av behandlingen var positivt assosiert med progresjon i behandlingen og negativt assosiert med alder.

I den andre artikkelen ble det gjennomført en studie hvor gruppen som fikk standardbehandling i tidlig fase fikk tilbud om CIMT 6 måneder senere. Dette for å sammenligne langtidseffekten av CIMT i tidlig fase med CIMT gjennomført i sen fase etter hjerneslaget. I løpet av 1-års oppfølging viste begge gruppene signifikant fremgang på alle utfallsvariabler. Gruppen som fikk tidlig CIMT viste imidlertid raskere gjenvinning av motorisk funksjon og finmotorikk, og var i mindre grad avhengig av hjelp etter intervensjonen. Etter 6 måneder hadde begge gruppene kun lett nedsatt funksjon og det var ingen forskjell mellom gruppene. Det var heller ingen forskjell mellom gruppene etter den sene intervensjonsperioden eller ved 1-års oppfølging.

I den tredje artikkelen ble utvikling av grepstyrke i det første året etter slaget undersøkt på en undergruppe av deltakerne i NORCIMT studien. I tillegg til økt trettbarhet, det vil si redusert evne til å opprettholde maksimal grepstyrke, viste detaljerte målinger at maksimal grepstyrke og evnen til å øke grepstyrke raskt var tydelig redusert i affisert hånd tidlig etter hjerneslag, sammenlignet med ikke-affisert hånd. Alle målinger viste markant forbedring i

løpet av 1-års oppfølging og nærmet seg verdiene på ikke-affisert side. Det var størst fremgang i løpet av de første 6 måneder.

Resultatene fra avhandlingen viser at deltakerne brukte mindre tid enn planlagt på trening av funksjonelle oppgaver. Tiden deltakerne var aktive var tydelig redusert, noe som indikerer behov for pauser mellom de intensive oppgavene. Videre var tidlig oppstart av CIMT like effektivt på lang sikt som senere oppstart. Både maksimal grepstyrke, evnen til å generere grepstyrke raskt og til å opprettholde maksimal styrke var tydelig redusert tidlig etter hjerneslaget.

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Finansieringskilder: NTNU, UiT, St Olavs Hospital

Ovennevnte avhandling er funnet verdig til å forsvares offentlig

for graden PhD i klinisk medisin.

Disputas finner sted i Auditoriet, MTA i Medisinsk Teknisk Forskningssenter

fredag 29. mars 2019, kl. 12.15

The hand is the cutting edge of the mind

Jacob Bronowski

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Summary

In stroke rehabilitation, intensive task-oriented training is recommended in many meta-analyses and guidelines, and Constraint-Induced Movement Therapy (CIMT) is one of the treatments that has intensity and task-oriented training as important components. However, there is a lack of knowledge about patients' adherence to the intensive treatment protocol and the efficacy of CIMT commenced in the first weeks after stroke. Furthermore, detailed knowledge about the longitudinal development of grip strength is scarce.

The main aim of this thesis was to increase knowledge about 1) the adherence to CIMT applied during the first weeks after stroke, 2) the long-term efficacy of early versus delayed CIMT intervention, and 3) how different aspects of grip strength evolve during the first year after stroke. Data from the participants included in the Norwegian Constraint-Induced Therapy Multisite Trial (NORCIMT), a single blinded randomized controlled trial, were used for all three papers included in this thesis. The study included 47 persons with mild to moderate stroke.

In paper 1, adherence to the treatment protocol of the NORCIMT study was assessed by analysing therapy schedules of the 24 participants who received CIMT early (7-28 days) after stroke. The results showed overall good adherence to the protocol regarding presence during treatment. However, they spent less time than intended in task training, and time spent in motor activity was only one-third of total treatment time. Adherence to the treatment was positively associated with treatment progression and negatively associated with age.

In paper 2, a cross-over design was used to compare the long-term efficacy of CIMT applied early after stroke with CIMT applied after 6 months. Both groups received standard rehabilitation otherwise. During the 1-year follow-up, both groups showed significant improvement in all outcome measures. However, the early intervention group showed faster recovery of motor function, dexterity and functional independence after the intervention. At 6 months, both groups showed only minor impairments, and no differences between the groups were found, either after the delayed group received CIMT or at 1-year follow-up.

In the third paper, the development of grip strength during the first year after stroke was assessed on a subsample of the NORCIMT study. In addition to increased fatigability, i.e. the

ability to sustain maximal strength, detailed measurements showed that maximum voluntary grip strength and the ability to generate force quickly were considerably reduced in the affected hand compared to the non-affected hand early after stroke. All measurements improved markedly during the 1-year follow-up and approached the non-affected side, with most progress during the first 6 months.

In conclusion, this thesis shows that the time spent in task practice and time exclusively spent in pure activity was markedly decreased when CIMT was applied during the first weeks after stroke, indicating substantial need for rest between the intensive tasks. Furthermore, commencing CIMT early was as effective as delayed intervention in the long term. Not only maximal grip strength was reduced early after stroke, but also the ability to generate grip force rapidly and to sustain maximal strength.

Acknowledgements

The work in this thesis has been carried out at the Department of Neuroscience at the Norwegian University of Science and Technology (NTNU) in collaboration with the Arctic University of Norway (UiT) and the Department of Physical Medicine and Rehabilitation at Trondheim University Hospital, all of them contributing to the funding of this work. The NORCIMT study, which this thesis is part of, was financed by the Northern Norway Regional Health Authority.

I would like to start by thanking the participants in the NORCIMT study – this thesis would not have been possible without their participation.

I especially want to express my gratitude to my main supervisor Torunn Askim for all her support during the work with the thesis. Her long experience and in-depth knowledge in the field of stroke research have been invaluable for me. Thank you, Torunn, for your systematic feedback and guidance through this work.

I would also like to thank my co-supervisors Audny Anke and Paul Jarl Mork. It was a pleasure working together with you, and I always received a quick response to the myriads of questions I had. Thank you, Audny, for many discussions and advices during the writing process and Paul Jarle for the support during the whole process of working with paper 3, no matter the time of the day.

Thanks to Gyrd Thrane, who has been co-author on all papers for the support during data acquisition, statistical advices, and feedback during the writing process. We spent countless hours discussing on e-mail, skype and on my visits in Tromsø. Thanks also to the co-authors in paper 1, Gunn Marte Karlsen, Anne Spendrup Erichsen and Ragna Gjone, for valuable comments.

I would also like to thank the colleagues at the Research Group of Geriatrics, Movement and Stroke (GeMS), especially my office-mates, for the many fruitful discussions and feedback; Bent Indredavik for his advice during the planning and designing of the NORCIMT study; all therapists involved in the NORCIMT trial; and Turid Follestad for statistical advice.

Thanks to my colleagues at Fys Med Lian for your flexibility and support when I was occupied with the study. Thanks to Anne Lise Brein, the head of the therapists at Fys Med Lian for

always having an open door, I always appreciated her “common sense” approach. Thanks to occupational therapist Eli Langørgen, both as a co-author and as a colleague over many years, for her enthusiasm in introducing and developing the treatment and broadening my view on therapy beyond the field of physiotherapy. Thanks also to May Elin Hulsund who continued the work of Eli and to Toril Skandsen and Tor Ivar Hansen for their advices.

Finally, I would like to thank my wife, Ingrid, for her patience and support during this long journey. Thank you for the many discussions we had, often while walking, and for your help during the writing process. Your questions and comments contributed to clarifying my own thoughts.

List of abbreviations

ADL	Activities of daily living
AVERT	A Very Early Rehabilitation Trial for stroke
CIMT	Constraint-Induced Movement Therapy
EXCITE	Extremity Constraint-Induced Therapy Evaluation trial
EXPLICIT	EXplaining PLastICITy after stroke trial
FMA	Fugl-Meyer Assessment
FMA-UE	Fugl-Meyer Assessment (Upper-extremity)
IADL	Instrumental activities of daily living
ICF	International Classification of Functioning, Disability and Handicap
NHPT	Nine Hole Peg Test
NIHSS	National Institutes of Health Stroke Scale
NORCIMT	Norwegian Constraint-Induced Therapy Multisite Trial
MAL	Motor Activity Log
mRS	Modified Rankin Scale
MVC	Maximum voluntary contraction
QOM	Quality of movement
RCT	Randomized controlled trial
RFD	Rate of force development
SIS	Stroke Impact Scale
SRRR	Stoke Recovery and Rehabilitation Roundtable
VECTORS	Very Early Constraint-Induced Movement during Stroke Rehabilitation Study
WHO	World Health Organisation
WMFT	Wolf Motor Function Test

List of papers

Stock, R., Thrane, G., Askim, T., Karlsen, G., Langørgen, E., Erichsen, A., Gjone, R., & Anke, A. (2015). Norwegian constraint-induced therapy multisite trial: Adherence to treatment protocol applied early after stroke. *Journal of Rehabilitation Medicine*, *47*(9), 816-823. doi:10.2340/16501977-2000

Stock, R., Thrane, G., Anke, A., Gjone, R., & Askim, T. (2018). Early versus late-applied constraint-induced movement therapy: A multisite, randomized controlled trial with a 12-month follow-up. *Physiotherapy Research International, 23*(1), e1689. doi:10.1002/pri.1689

Stock, R., Thrane, G., Askim, T., Anke, A., & Mork, P. J. Development of grip strength during the first year after stroke. *Journal of Rehabilitation Medicine* (submitted August 2018)

1 Introduction

Reduced motor control is commonly observed after stroke, and in particular the reduced ability to move the affected hand and arm can have severe consequences for coping with everyday life. During my clinical work as a physiotherapist I often meet patients in the first weeks and months after stroke and I am often asked how and how intensively they should train. However, patients' capacity seems to differ, and some of them express increased fatigability in their hand muscles. They often talk about their need for "charging their batteries" after having performed challenging activities. Furthermore, they struggle more with some type of grips than others. Some patients struggle to hold a firm grip over time and their goal is to carry a shopping bag in their affected hand without dropping it. Others complain about their reduced ability to adapt their grip rapidly, for example while squeezing objects or while holding a saw firmly when the saw meets resistance. All these activities are dependent on different aspects of strength in the hand and finger muscles.

This thesis intends to provide answers to patients' questions by addressing adherence and efficacy of intensive task-oriented training as well as various aspects of grip strength. The overall aim of this thesis is to contribute with new knowledge about how to optimize treatment of hand function after stroke.

2 Background

2.1 Stroke

According to the World Health Organization (WHO), stroke is defined as "rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 h or until death, with no apparent non-vascular cause" (WHO, 1988, p.108). Stroke is the second leading cause of death and the third most common cause of disability (Feigin, Norrving, & Mensah, 2017). Common symptoms after stroke are sudden, most often unilateral, paresis or reduced sensibility in the face, arm or leg; difficulties with walking, balance or coordination; problems with speaking or understanding speech; dizziness; severe headache or loss of consciousness (WHO, 2018).

Worldwide, the incidence of stroke is 17 million a year (Bejot, Daubail, & Giroud, 2016), with higher incidence rates in most Asian and African countries, 1.1 million in Europe (Bejot,

Bailly, Durier, & Giroud, 2016) and approximately 11 000 a year in Norway (Akerkar et al., 2018). During the last two decades, the age-standardized incidence decreased significantly in high-income countries, while it increased non-significantly in low and middle-income countries (Feigin et al., 2014). Even though stroke mortality rates decreased significantly worldwide from 1990 to 2010, the absolute numbers of strokes and the global burden of stroke increased during this period due to the growing size and aging of the population (Bejot, Daubail, et al., 2016; Feigin et al., 2014). The mean age for the stroke patients registered in the national stroke registry (n = 8650) in Norway is 77 years for women and 72 years for men. More men (mean 54%) than women (mean 46%) have a stroke, except for the age groups over 85 years (Fjærtoft et al., 2017).

2.2 The ICF classification framework

The International Classification of Functioning, Disability and Health (ICF) is the WHO's framework for health and disability (WHO, 2002). It is used both in clinical research and practice and provides a framework for this thesis. The ICF was historically a shift from emphasizing the disability of people to indicating their level of health (WHO, 2002). ICF categorizes disability into three levels (Figure 1): body functions and structure, activity and participation (WHO, 2002).

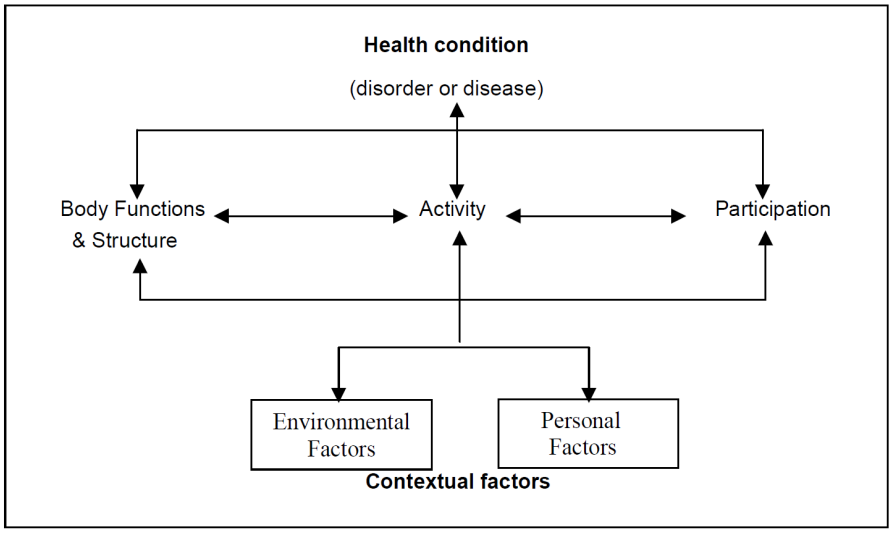


Figure 1. The International Classification of Functioning, Disability and Health (http://www.who.int/classifications/icf/icfbeginnersguide.pdf)

These three levels of the ICF interact with each other; they are based on the health condition and interact with contextual factors like environmental and personal factors (Levin, 2016; WHO, 2002). In the context of this thesis, examples of deficits in body functions and structures are loss of strength or lack of movement speed in the affected hand (Faria-Fortini, Michaelsen, Cassiano, & Teixeira-Salmela, 2011). Such impairments can lead to limitations in activities such as self-care and to restrictions in participation, for example related to work. Participation is a multidimensional concept and is defined as the individual's involvement in life situations (WHO, 2002).

The ICF can be used as a scientific framework in rehabilitation research to assess, plan and evaluate treatment (WHO, 2002). The ICF framework assesses functioning at the level of the whole human being in daily life (WHO, 2002). Independent of the reason of impairments, the ICF can be used as a tool to assess how a person functions in society (WHO, 2002). Many assessment tools used in rehabilitation research assess more than one level of the ICF and the levels may overlap, so that these assessments can also be regarded as a continuum between levels (Salter et al., 2005). Furthermore, the ICF differentiates between the concepts of capacity and performance (Cieza & Stucki, 2008). Capacity specifies the individual's ability to execute a task in a standardized environment, in contrast to performance, which describes what a person actually does in real-life situations (Cieza & Stucki, 2008). According to Faria-Fortini et al. (2011), every stroke trial should include outcome measures on the body function/structure, activity and participation level to provide a comprehensive understanding of the participants' health, functioning, disability and total situation.

2.3 Functional recovery after stroke

The ICF framework is often used to facilitate assessment and goal setting of the recovery process after stroke. The term "recovery" describes the extent to which body functions and structure as well as activities reach their pre-stroke state, and can be investigated by the change in an outcome that the patient achieves between time points (Bernhardt, Hayward, et al., 2017). Most of the functional recovery takes place in the first months after stroke, with little further improvement after 6 months post-stroke (Langhorne, Bernhardt, & Kwakkel, 2011). Several mechanisms have been identified which may be important for spontaneous recovery after stroke, such as neural plasticity, restitution of the non-infarcted

penumbral area, resolution of diaschisis and behavioural compensation (Kwakkel, Kollen, & Lindeman, 2004). The penumbral area is tissue around the infarction that is not irreversibly injured (Fisher, 2004); resolution of diaschisis means the reactivation of functionally suppressed areas distant from the primary injury (Feeney & Baron, 1986). Motor impairment occurs when the stroke affects the corticospinal system, i.e. the motor cortical areas and the corticospinal tract. The extent of this damage is predictive for both motor outcomes and how the patient will respond to treatment (Winstein et al., 2016).

A current problem in research on stroke rehabilitation and recovery is the lack of a standardized approach to measurement and a lack of clear definitions for the different stages after stroke (Bernhardt, Hayward, et al., 2017; Kwakkel et al., 2017). The terms acute, sub-acute and chronic are often used in research on motor recovery, with different and inadequate definitions. Therefore, a group of leading experts in the field of stroke research, the first Stroke Recovery and Rehabilitation Roundtable (SRRR), was established in 2017 to agree on new standards for research on recovery after stroke (Bernhardt, Hayward, et al., 2017; Kwakkel et al., 2017). SRRR developed a framework for the definition of the different phases after stroke based on research on recovery in both animal and humans (Bernhardt, Hayward, et al., 2017). They define the first day after stroke as the hyper-acute phase, while the acute phase last from day 1-7, followed by the early sub-acute phase lasting from 7 days to 3 months and the late sub-acute phase from 3-6 months. The time after 6 months post-stroke is defined as the chronic phase (Bernhardt, Hayward, et al., 2017). The acute and early sub-acute phase seem to be a critical time for neural plasticity, i.e. the capability of the brain to change the structure and function of neurons and neuronal networks (Buma, Kwakkel, & Ramsey, 2013; Li, 2017).

2.4 Motor control and motor learning after stroke

Motor control and motor learning theories provide a basis for treatments applied to facilitate motor recovery (Shumway-Cook & Woollacott, 2017). Because motor impairment after stroke often leads to less effective and less coordinated voluntary movements that affect activities of daily living (ADL), an important goal in stroke rehabilitation is to find motor relearning techniques that facilitate recovery of functional arm movements (Levin, 2016). The use of real objects during training seems to be important. It has been shown that movement kinematics are organized differently for real objects compared to artificial objects,

and the kinematics of reaching for a real object were more efficient than those of reaching for a stick (Trombly & Wu, 1999; Wu, Trombly, Lin, & Tickle-Degnen, 1998). In addition, task training in a natural context is important for motor learning and showed greater transfer to ADL activities (Winstein & Kay, 2015). Furthermore, problem-solving approaches are more effective for learning than repetition of previous solutions. Effective treatment must engage and empower the patient and at least three active components are important to translate evidence from brain science, cognitive and social science into effective therapeutic practice: it should be challenging; it should be progressive and optimally adapted; and it should promote intrinsic motivation and active participation from the participant (Winstein & Kay, 2015).

The field of motor learning has evolved from perspectives which were dominated by cognitive or information processing principles towards a blend of perspectives including neural science, social-cognitive-psychological science with increasing focus on motivational aspects and the needs of the patients (Winstein & Kay, 2015). This integration of knowledge leads to development of novel, evidence-based therapies, which aim to maximize motor recovery (Winstein & Kay, 2015).

Behavioural, emotional and cognitive processes are also important for recovery of motor function, and may explain why patients often do not fully use their affected upper limb in ADL (Banina, Mullick, McFadyen, & Levin, 2017; Levin, 2016). Even if patients have test scores indicating low impairment or activity limitation, they underutilize the arm when measured with accelerometers during ADL at home and use the non-affected arm up to three times more compared to the affected (Rand & Eng, 2015). Reduced use of the affected arm can be related to reduced arm and hand coordination, which made their interactions in a changing environment less effective and was associated with the patients' level of self-efficacy, i.e. the belief that they had the capability to achieve a goal while using the arm in ADL (Banina et al., 2017; Levin, 2016). Decreased confidence may influence task accomplishment, especially when patients have to solve problems in case of unexpected difficulties and may lead to performance below their capabilities, even in patients with good motor skills (Levin 2016). Low self-efficacy may also explain the discrepancy between upper limb activity capacity and performance, i.e. actual arm use in ADL, measured by accelerometry monitoring (Levin, 2016).

2.5 Active participation in rehabilitation

The importance of active participation as emphasized in motor learning theories is also visible in definitions of rehabilitation, for example in the definition of the Norwegian Directorate of Health (Helsedirektoratet, 2018). According to this definition, rehabilitation should be based on patients' circumstances of life and their goals. Goal-oriented collaboration between patients, relatives and health service providers is emphasized, and rehabilitation processes should be characterized by coordinated, coherent and evidence-based actions. Individual patients are at risk of sustaining limitations to their physical, psychological, cognitive or social functional ability. Thus, the aim of rehabilitation is to optimize patients' ability to cope and to function, to achieve maximal independence and participation in education and working life, as well as in social life and society (Helsedirektoratet, 2018).

The ICF, which also emphasizes participation, is commonly used as the underlying biopsychosocial model for rehabilitation to secure a holistic approach when clarifying the need for rehabilitation (Bernhardt, Hayward, et al., 2017; Helsedirektoratet, 2018). This requires the involvement of a multidisciplinary therapeutic team in order to take into account the whole person with the aim of improving the patient's functional independence and participation.

2.6 Effectiveness of post-stroke interventions for the upper limb

Many interventions used during post-stroke rehabilitation were developed with the intention to improve upper limb function after stroke. Common interventions for the upper limb are bilateral arm training, repetitive task training, motor imagery, mirror therapy, electrical stimulation, the Bobath approach, sensory interventions, robotics, strength training, virtual reality and Constraint-Induced Movement Therapy (CIMT) (Pollock et al., 2014). A recent meta-analysis of the effect of physical therapy after stroke included 467 randomized controlled trials (RCTs), 224 of them related to arm-hand activities (Veerbeek et al., 2014). The authors concluded that there is strong evidence for the effectiveness of high-intensity repetitive task-oriented training and that the effects are mostly restricted to the functions and activities specifically trained (Veerbeek et al., 2014). The findings suggest that intensity of training and more practice are beneficial, and that an additional therapy time of

17 hours over 10 weeks is needed to show significant positive effects on all three levels of the ICF (Veerbeek et al., 2014).

The Cochrane review from Pollock et al. (2014) assessed the effectiveness of rehabilitation treatments intended to improve upper limb function. The primary outcome measure was upper limb function, while secondary outcome measures were motor impairment and performance during ADL (Pollock et al., 2014). No high-quality evidence was found for any of the interventions currently used in rehabilitation of stroke patients, and the evidence is insufficient to compare the effectiveness of the interventions (Pollock et al., 2014). The results showed moderate-quality evidence for a positive effect of CIMT, mirror therapy, interventions for sensory impairment, mental practice, virtual reality, and a high dose of repetition during task practice, indicating that these interventions may effectively improve upper limb function (Pollock et al., 2014). Unilateral training for the upper limb seems to be more effective than bilateral training (Pollock et al., 2014).

However, there is a lack of knowledge about several aspects of interventions for the upper limb. No high-quality evidence related to the time when it is best to initiate treatment seems to be available (Bernhardt, Godecke, Johnson, & Langhorne, 2017; Coleman et al., 2017; Pollock et al., 2014). Animal research indicates that a therapeutic window of enhanced neuroplasticity exists early after stroke, i.e. that most recovery after stroke takes place during the first weeks after stroke and that it might be best to start treatment during the first days after stroke (Coleman et al., 2017). However, the large AVERT trial (A Very Early Rehabilitation Trial for stroke) showed that too intensive mobilization during the first 24 hours after stroke is harmful (Bernhardt et al., 2015). Furthermore, little is known about the long-term effect of early upper limb interventions after stroke (Pollock et al., 2014; Veerbeek et al., 2014), and adherence to the treatment is rarely reported in upper limb trials and often only as a secondary aim (Bonaiuti, Rebasti, & Sioli, 2007; Krekeler, Broadfoot, Johnson, Connor, & Rogus-Pulia, 2018).

2.7 Adherence to exercise interventions

In the field of general medicine and health, adherence can be defined "as the degree to which patient behaviours coincide with the recommendations of healthcare providers" (Vitolins, Rand, Rapp, Ribisl, & Sevick, 2000, p.188). The term compliance has often been used interchangeably with adherence. However, adherence has been increasingly used because it emphasizes the importance of the patients' perspective and active involvement in treatment, while compliance has more paternalistic connotations where a person acts in accordance with prescribed recommendations (Chakrabarti, 2014).

Increasing adherence to medical intervention has more impact on public health than improvements in medical treatments, and poor adherence to a treatment plan and clinical recommendations may lead to evidence-based treatments becoming less effective (Krekeler et al., 2018; Reach, 2016). Adherence to treatment will potentially influence the results of an intervention and should be quantified to assess the efficacy of a treatment (Krekeler et al., 2018). However, there is no gold standard for good or poor adherence which can be applied across different health behaviours (Van Dulmen et al., 2007; Vitolins et al., 2000). The best way of improving adherence will likely be dependent on individual factors and types of intervention (Krekeler et al., 2018; Vitolins et al., 2000).

Several barriers and facilitators associated with adherence to physical activity and exercise have been identified in healthy people, like age, gender, socioeconomic status, education, self-management skills, motivation and support (Herring, Sailors, & Bray, 2014). Factors that seem to facilitate adherence are social-cognitive variables such as self-efficacy, self-motivation, social support and striving to reach goals (Herring et al., 2014). A study with older community-dwelling adults showed that adherence to exercise was higher among participants who were female, were younger, had fewer cognitive deficits and were less dependent in instrumental activities of daily living (IADL) (Aartolahti, Tolppanen, Lonnroos, Hartikainen, & Hakkinen, 2015).

Some of the above-mentioned general barriers or facilitators may also apply to adherence to treatment after stroke, while others might not necessarily apply to stroke patients (Krekeler et al., 2018). Adherence to physical activities in stroke patients is influenced by factors such as lack of motivation, environmental factors, health concerns, stroke impairments, disempowerment, boredom, frustration and fatigue (Luker, Lynch, Bernhardsson, Bennett, &

Bernhardt, 2015; Nicholson et al., 2013). Facilitators for participation in physical activity are social support and the need to be able to perform ADL activities (Nicholson et al., 2013). Luker et al. (2015) suggest that rehabilitation could be improved by supporting patients' autonomy through patient-centred care as well as more effective information and communication. Reach (2016) stresses the importance of patient education to increase adherence and to change health behaviours. Patient education is a learning process that provides the patient with the necessary knowledge, skills, values and insights to change behaviour; it seeks to improve self-efficacy and can help to improve adherence to the intervention (Krekeler et al., 2018; Reach, 2016).

The intensity of exercise and perceived effort are negatively associated with adherence to exercise, and it may be especially challenging to adhere to interventions that are complex and time-consuming for patient and caregiver (Bourbeau & Bartlett, 2008; Herring et al., 2014). As intensity of the training is one of the key features in CIMT, both therapists and patients expressed concerns about the feasibility of the treatment and if patients would adhere to the treatment (Fleet et al., 2014; Page, Levine, Sisto, Bond, & Johnston, 2002; Pedlow, Lennon, & Wilson, 2014; Sterr, Szameitat, Shen, & Freivogel, 2006; Viana & Teasell, 2012). The results from the Extremity Constraint-Induced Therapy Evaluation (EXCITE) study indicate that the intensity of exercise is negatively associated with adherence, as the patients trained for only 4 hours of the intended 6 hours daily treatment time (Kaplon, Prettyman, Kushi, & Winstein, 2007). Since adherence seems to be diminished in the late sub-acute and chronic phase after stroke as in the EXCITE study, it is crucial to assess adherence to CIMT applied during the early sub-acute phase as in the Norwegian Constraint-Induced therapy Multisite Trial (NORCIMT) (Thrane et al., 2015). The capacity to adhere to intensive treatment is probably even more reduced early after stroke. Reporting the actual content and adherence to CIMT might provide useful information about how to adapt and develop this very intensive treatment.

2.8 Constraint-Induced Movement Therapy (CIMT)

The intensive nature of CIMT is only one but an important feature of the treatment. Even though CIMT has been used for nearly two decades, the underlying mechanisms for CIMT are poorly understood, according to Kwakkel, Veerbeek, van Wegen, and Wolf (2015).

CIMT was developed by the behavioural psychologist Edward Taub to increase the use of the more-impaired arm in stroke patients (Morris, Taub, & Mark, 2006). CIMT is based on the "learned non-use theory": Many persons cannot use their affected arm effectively after a stroke – their movements become clumsy and ineffective and use of the arm leads to failure, which in turn results in less use of the arm (Taub et al., 1994; Taub, Uswatte, Mark, & Morris, 2006). They manage reasonably well when using mainly the non-affected hand instead of the affected, i.e. they do not use the arm as much as they might be able to do, and this "learned non-use" becomes an established pattern over time (Taub et al., 2006).

The content of CIMT is defined differently in different CIMT studies (Kwakkel et al., 2015). The treatment protocol from Morris et al. (2006) gives the most comprehensive description of CIMT and is regarded as the original CIMT protocol (Kwakkel et al., 2015). It is also used in the so far largest RCT, the EXCITE study. According to Morris et al. (2006), CIMT consists of three main elements: 1) intensive repetitive task-oriented training, 2) adherence-enhancing behavioural strategies, also called transfer package and 3) constraining the use of the affected arm. Originally, CIMT was applied for 6 hours per day during a 2-week period. Task-oriented training was provided by shaping and task practice. During shaping, tasks of short duration were trained repetitively, and task difficulty was progressively adjusted in accordance with the participant's ability (Morris et al., 2006). Task practice is less structured, compared to shaping, and functional activities are performed continuously. Adherence-enhancing behavioural strategies, the so-called transfer package, have the purpose of transferring the gains made in therapy into the home environment of the participant. In addition, a mitt which restricts the movements of the fingers in the non-affected arm, but still allows use of the arm to prevent falls, is often used to constrain the non-affected arm (Morris et al., 2006).

The original protocol of 6 hours' daily treatment has been modified in several CIMT studies. The daily duration of the treatment sessions varied from 30 min to 6 hours a week, the frequency ranged from 2-7 sessions a week and the overall duration from 2-12 weeks (Kwakkel et al., 2015). Several studies concentrated mainly on the use of the constraint, without additional specific treatment of the affected arm, also called "Forced-use therapy" (Hammer & Lindmark, 2009; Kim et al., 2008; Ploughman & Corbett, 2004). Some studies

applied CIMT at home, without direct involvement of a therapist (Azab et al., 2009; Barzel et al., 2015; Tariah, Almalty, Sbeih, & Al-Oraibi, 2010).

According to a meta-analysis from Etoom et al. (2016), most of the included CIMT studies enrolled patients with no cognitive impairment and no or limited pain or spasticity, who were able to extend the wrist at least for 20 degrees and the fingers for at least 10 degrees. The latter was chosen because active repetition of the task is impossible without being able to extend the wrist and the fingers (Etoom et al., 2016). The inclusion criteria of CIMT in the different trials indicate that CIMT seems to be mainly restricted to participants with mild to moderate stroke (Etoom et al., 2016).

Several meta-analyses confirm the short-term effectiveness of CIMT in the chronic phase after stroke, while there is conflicting evidence about the long-term effect of CIMT (Corbetta, Sirtori, Castellini, Moja, & Gatti, 2015; Etoom et al., 2016; Kwakkel et al., 2015; Thrane, Friborg, Anke, & Indredavik, 2014). Only a few CIMT studies followed the participants beyond 6 months (Brogardh, Flansbjer, & Lexell, 2009; Brogardh & Lexell, 2010; Taub et al., 2013; Wolf et al., 2006). The EXCITE trial investigated the effect of the original CIMT protocol in 222 patients in the late sub-acute and chronic phase (3-9 months) after stroke (Wolf et al., 2006). The RCT showed significant improvement in arm motor function, self-reported arm use and quality of arm use after the treatment compared to a standard rehabilitation group. The results remained significant different between the groups both at 12-months and 24-months follow-up.

The meta-analyses from Thrane et al. (2014) and Kwakkel et al. (2015) also reported long-term effects of CIMT, while Etoom et al. (2016) and Corbetta et al. (2015) could not find evidence supporting the long-term effect of CIMT. An explanation for the diverging conclusions could be that Etoom et al. (2016) and Corbetta et al. (2015) included home-based CIMT interventions and “Forced-use” interventions without differentiating between the interventions. Kwakkel et al. (2015) found no evidence for the efficacy of forced-use therapy. The recent large RCT from Barzel et al. (2015) indicates that the same applies to home-based CIMT.

In contrast to CIMT applied in the chronic phase, fewer studies are available that assess CIMT in the early sub-acute phase after stroke (Liu, Huai, Gao, Zhang, & Yue, 2017). One of

these studies, the Very Early Constraint-Induced Movement during Stroke Rehabilitation Study (VECTORS), reported that 3 hours with CIMT was less beneficial compared to low-intensity (2 hours) CIMT or control treatment if CIMT is applied very early, i.e. mean 9.7 days after stroke (Dromerick et al., 2009). However, most other studies in the early sub-acute phase did not commence treatment as early. The evidence for the short-term efficacy during the early sub-acute phase is conflicting, and the data about the long-term effect of CIMT are limited (Etoom et al., 2016; Liu et al., 2017; Thrane et al., 2014).

The primary results from the NORCIMT study showed a short-term effect of CIMT in the early sub-acute phase, but no long-term effect (Thrane et al., 2015). The main aim of the NORCIMT trial, which this thesis is part of, was to assess whether CIMT treatment is effective and suitable during early rehabilitation after stroke and to compare the effectiveness of CIMT applied early with a later CIMT intervention. The recent EXplaining PLastICITy after stroke (EXPLICIT) trial confirms the short-term effectiveness of CIMT in the early sub-acute phase, but the differences between the groups were no longer significant after 6 months (Kwakkel et al., 2016). Wolf et al. (2010) compared CIMT applied early (3-9 months post-stroke) to delayed (15-21 months post-stroke) and found that the early group showed greater functional improvement than the delayed group from pre-treatment to 12 months. However, no differences were found between the groups at 24-month follow-up.

2.9 Grip strength after stroke

A common impairment in the upper limb after stroke is muscle weakness, which also leads to decreased grip strength. Reduced muscle strength contributes to reduced ability to use the arm and the hand during ADL (Ekstrand, Lexell, & Brogardh, 2016a). Muscle weakness after stroke is due to primary weakness resulting from reduced signal transmission along descending neural pathways, which causes loss in voluntary activation of the muscles, as well as secondary weakness caused by reduced physical activity and immobility (Aaron, Hunnicutt, Embry, Bowden, & Gregory, 2017). Loss of muscle strength seems to contribute more to reduced motor function than loss of dexterity early after stroke, at least for elbow muscles (Canning, Ada, Adams, & O'Dwyer, 2004). Harris and Eng (2007) showed that upper limb strength, grip strength and muscle tone were the impairments most strongly related to ADL in a group of community-dwelling persons with chronic stroke. Handgrip strength is correlated with upper limb function; it is associated with performance in bimanual activities

after stroke and independence in ADL, while the associations between grip strength and participation measures seem weak (Bae et al., 2015; Basilio et al., 2016; Faria-Fortini et al., 2011; Mercier & Bourbonnais, 2004). Ada, Canning, and Low (2003) assessed the effect of muscle length on strength in the elbow muscles after stroke. They found that the patients were relatively weaker in a shortened testing position. There are no studies available that have evaluated if selective weakness also applies to the hand muscles.

Recovery of grip strength in acute stroke patients is one of the most sensitive assessments of initial recovery of the upper extremity and a good prognostic factor for later recovery (Heller et al., 1987; Sunderland, Tinson, Bradley, & Hewer, 1989). Grip strength measurements are easy to perform, they are less time-consuming than measurements of arm muscle strength and can be a representative measure of muscle weakness of the entire arm in persons in the chronic phase after stroke (Ekstrand et al., 2016a). In addition, grip strength seems to be an overall indication of the integrity of the central nervous system, and reduction in grip strength also reflects changes in processes related to aging, such as frailty in elderly people as well as cognitive function, and has predictive potential regarding morbidity and mortality (Fritz, McCarthy, & Adamo, 2017; Norman, Stobaus, Gonzalez, Schulzke, & Pirlich, 2011).

With the development of electromechanical dynamometers, it has become possible to measure not only maximal voluntary grip strength, but also how grip strength changes over time. The recording of a strength-time curve made it possible to assess the rate of force development (RFD) and a person's ability to sustain maximum grip strength. RFD is a measure of explosive strength and depends on how rapidly contractile elements in the muscle can produce force (Aagaard, Simonsen, Andersen, Magnusson, & Dyhre-Poulsen, 2002). High RFD seems to be associated with better performance of functional daily tasks (Maffiuletti et al., 2016).

RFD seems to be impaired after stroke in both the upper and lower limb (Canning, Ada, & O'Dwyer, 1999; Fimland et al., 2011; McCrea, Eng, & Hodgson, 2003). In the study by Canning et al. (1999), the subjects were half as strong as healthy controls 6 weeks after stroke. It took 2-3 times longer for the stroke patients to produce torque in elbow flexors and extensor muscles; however, their values were within normal limits at 25 weeks after stroke. Canning et al. (1999) conclude that reduced RFD (torque development) may have significant implications for situations in which the muscles are very weak or where force has

to be generated rapidly. The reduced ability to generate force is an important obstacle to recovery after stroke and related to decreased upper limb function (McCrea et al., 2003). DeJong, Schaefer, and Lang (2012) demonstrated that people with hemiparesis were able to move faster if they were asked to do so during "reach-grasp-lift" movements. Both reach and grasp phase duration decreased, and the reach phase durations approached the preferred speed of healthy controls (DeJong et al., 2012). During the fast condition, not only did the movements became faster, but movement quality improved as well: reach trajectories were straighter and peak hand apertures were greater in the fast condition. DeJong et al. (2012) conclude that the instruction to move faster could be used to effectively increase training intensity in stroke rehabilitation. There are currently no studies about RFD in hand and finger muscles, and the development of RFD during the first year after stroke.

Fatigue and fatigability are two different concepts: fatigue refers to subjective sensation, fatigability to objective changes in performance (Kluger, Krupp, & Enoka, 2013). While fatigue after neurological impairment can be defined as a subjective lack of physical and mental energy interfering with daily activities, fatigability is an objective decline in muscle strength over time (Dobkin, 2008). Fatigability is either measured dynamically by repetitive movements or statically as sustained force measurements (Dobkin, 2008). Kamimura and Ikuta (2002) assessed the decline of maximal sustained grip force in stroke patients as the percentage of maximum voluntary contraction (MVC) force and found that the affected hand reached values below 80% faster than the non-affected hand. In addition, they assessed whether sustained grip strength is associated with activity limitation in participants with mild stroke. They reported that there was a positive relationship between task difficulty and the participants' ability to sustain grip strength (Kamimura & Ikuta, 2002). The ability to sustain grip strength may have consequences for many ADLs which demand prolonged activation of the finger and hand muscles, such as carrying a shopping bag.

3 Rationale for the thesis and knowledge gaps

Adherence to treatment is important for the efficacy of interventions, and reduced adherence can potentially influence efficacy of a treatment. This applies especially to complex and time-consuming interventions. CIMT is one of the treatments applied after stroke that is complex and time-consuming for both participants and therapists. However, adherence to CIMT protocols is rarely reported, and it is therefore of great interest to increase knowledge about adherence to CIMT, especially when it is applied during the first weeks after stroke. Without knowing what the participants have actually done during an intervention, it is difficult to compare interventions. Paper 1 addresses the adherence to the treatment protocol applied in the early intervention group in the NORCIMT study.

There is evidence about the effectiveness of CIMT in the chronic phase after stroke; however, the evidence about the effectiveness of CIMT applied in the early sub-acute phase after stroke is sparse and conflicting. Furthermore, there are few studies with a long-term follow-up beyond 6 months. In order to gain more knowledge about the efficacy of CIMT, a direct comparison between CIMT applied during the first weeks after stroke and in the chronic phase is needed. Paper 2 in this thesis addresses the long-term comparison between early and delayed application of CIMT.

Many people experience reduced grip strength in their hand and fingers after stroke, which affects coping with daily life activities. Various aspects of grip strength influence the functional use of the paretic hand during ADL: reduced maximum strength, the reduced ability to generate grip strength rapidly and fatigability during prolonged griping. These aspects of grip strength have never been studied comprehensively, and no information about the long-term development of these aspects is known. To investigate the different aspects of grip strength would not only add understanding about how grip strength develops during the first year after stroke but may also have implications for how task-oriented training could be adapted to increase adherence and possibly also efficacy of the treatment. Paper 3 addresses the long-term development of grip strength during the first year after stroke and will help to increase insight into how various aspects of grip strength might influence patients' performance. This knowledge can possibly contribute to adapting the treatment to the individual patient's needs.

3.1 Aims and research questions

The overall aim of this thesis was to increase knowledge about processes important for intensive rehabilitation of motor function in the upper limb during the first year after stroke by addressing adherence and efficacy of CIMT as well as the development of grip strength.

3.2 Paper 1

The main aim was to investigate the adherence to the treatment protocol in the patients included in the early intervention group of the NORCIMT study. Secondary aims were to assess the associations between treatment time variables and perceived exertion after the task practice sessions, quality of movement (QOM) and treatment progression, and whether the baseline characteristics age, sex, time since stroke or motor function influenced adherence to the components of the protocol.

3.3 Paper 2

The main aim was to compare the long-term effects of CIMT applied in the early phase after stroke, i.e. within 28 days post-stroke, with CIMT applied in the chronic phase, i.e. 6 months after stroke. Secondary aims were to assess the immediate effect of CIMT applied in the chronic phase and to compare the time course of CIMT applied early versus later.

3.4 Paper 3

The aims were to assess multiple aspects of grip strength: the long-term development of grip strength in both the affected and the non-affected hand in five different gripping positions from narrow to wide grip as well as grip strength in three different finger grip positions, if patients were relatively weaker in a narrow compared to a wide grip position, the ability to generate grip force quickly, and fatigability during sustained gripping.

4 Materials and methods

4.1 Study design and setting

The present thesis reports results from the NORCIMT study, a single-blinded multicentre randomized controlled trial, recruiting participants from five hospitals in Norway. A crossover design was applied, where the early intervention group received treatment 1-2 days after inclusion, while the people randomized into the delayed intervention group received treatment 6 months later. Both groups received 2 weeks with 3 hours of CIMT daily.

4.1.1 Participants

The participants were recruited from five Norwegian hospitals: The University Hospital of North Norway; St. Olavs Hospital (Trondheim University Hospital); Oslo University Hospital; Vestfold Hospital and Telemark Hospital. Participants were recruited from October 2008 until June 2012 and the actual study completion date, i.e. the date when the last participant was examined, was June 2013. The original estimated enrolment was 120 participants. As the study was halted in June 2012, 47 subjects have been included. The characteristics of the participants included in the papers is shown in Table 1.

The inclusion criteria were: more than 5 days and less than 26 days after stroke, either first stroke or second stroke (without detectable weakness after the first stroke), modified Rankin Scale (mRS) before admission 0-2 (no symptoms – slight disability), persistent hemiparesis in hand or arm (Scandinavian Stroke Scale items: hand motor function 2-4 or arm motor function 2-5), ability to extend the wrist at least 10 degrees from full flexion or to extend two fingers with the forearm placed in pronated position on the table, ability to follow a two-step command and a Mini Mental State examination score of > 20 (or >16 if the patient had expressive aphasia).

Exclusion criteria were: mRS > 4 (moderately severe disability) after the stroke, not able to give informed consent, hemispatial neglect (more than 2 cm on the Line Bisection Test), life expectancy < 1 year due to other illness, injury or condition in the affected arm that limited use prior to the stroke and other neurological conditions affecting motor function.

Table 1. Baseline characteristics of participants in the three papers included in this thesis

	Paper 1	Paper 2	Paper 3
Age, years, mean (SD)	65.3 (8.0)	63.2 (11.9)	59.1 (10.5)
Females, n (%)	5 (21)	11 (23)	3 (27)
Days post-stroke, mean (SD)	16.6 (7.2)	17.3 (6.9)	16.4 (7.1)
NIHSS (0-42), mean (SD)	1.7 (1.9)	1.7 (1.8)	3 (1.9)
FMA-UE (0-66), median (IQR)	53.5 (43–59)	51 (46-57)	48 (47-52)
mRS (0-6), mean (SD)	2.5 (0.7)	2.6 (0.8)	2.6 (0.8)
Affected side, right, n (%)	10 (42)	22 (47)	6 (55)
Dominant side affected, n (%)	16 (67)	26 (57)	7 (64)
Ischemic stroke, n (%)	23 (96)	43 (96)	11 (100)

FMA-UE: Fugl-Meyer Assessment of the upper extremity; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; SD: Standard deviation

A computer-based block randomization scheme was used to randomize the patients to either the early or the delayed CIMT group (Thrane et al., 2015). The clinical research centre at the University Hospital of North Norway was responsible for the randomization. All three papers are based on the participants of the NORCIMT study. Figure 2 shows the flow of the patients in the three papers. Paper 1 assessed the adherence of the participants randomized to the early intervention group, paper 2 was a long-term follow-up of the efficacy of CIMT comparing early versus delayed applied CIMT, paper 3 assessed various aspects of hand and finger grip strength in a subgroup of patients included in one of the centres (Trondheim University Hospital).

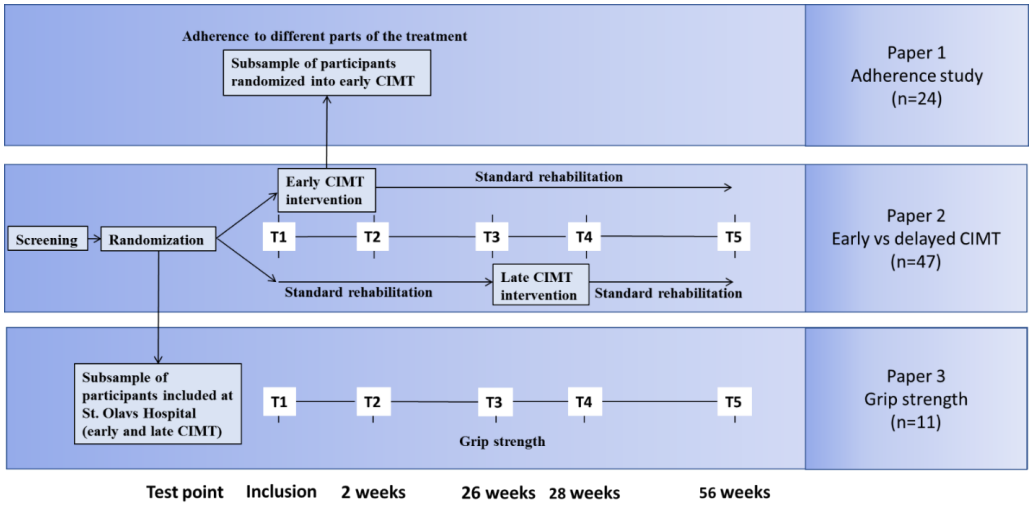


Figure 2. Study design and how the 3 papers included in this thesis are related

4.2 Intervention

The early CIMT group started CIMT treatment between 7 and 28 days after stroke, whereas the delayed CIMT group commenced CIMT 6 months after inclusion (Figure 2). It was intended that the patients should train for 3 hours daily, 150 min with intensive task-specific training and 30 min with adherence-enhancing behavioural methods, the so-called transfer package. The intensive task-specific training consisted of two different parts: 120 min with shaping tasks and 30 min with standard task practice exercises. Shaping exercises included highly structured tasks of short duration, whereas standard task practice consisted of continuously performed tasks. Appendix A shows the therapy schedules for the first two treatment days.

On the first treatment day, the participants received detailed information about the treatment, including task practice, the transfer package and the use of a mitt. They were encouraged to wear a restraining mitt on the less affected hand during 90% of waking hours. The participants received a booklet where they recorded when and how often they took off the mitt. The mitt needed to be removed when the participant was handling hot objects or in contact with water, and during walking if the participants had reduced balance. The mitt included a solid plastic sheet on the volar side, allowing the participant to use the arm as support during standing and preventing them from grasping objects with the mitt. A mesh fabric on the dorsal side of the mitt ensured good circulation.

4.2.1 Shaping

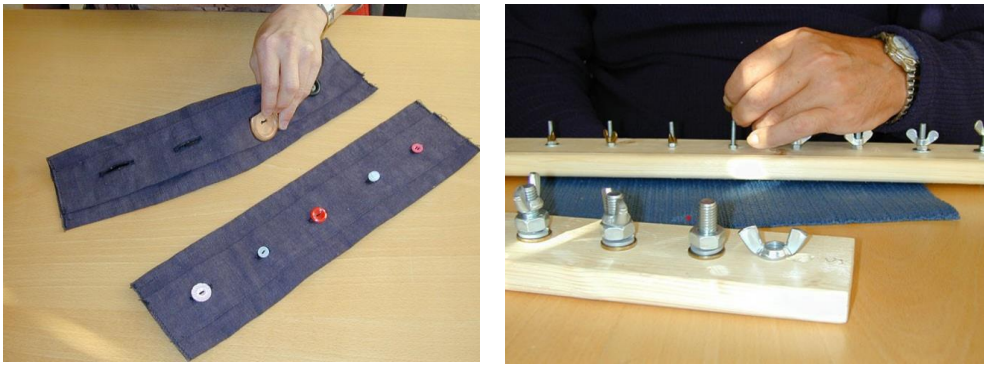
Shaping exercises consisted of 6-7 tasks which were repeated 10 times. The tasks were intended to last at least 30-60 sec, and not more than 120 sec. The tasks were selected by considering the motor capacity of the participant, the greatest expected potential for improvement and the participant's preference among tasks. The shaping quality of movement scale was used to grade the performance of a task and the selected tasks were to be between 2-4 on this scale depending on the participant's motor capacity (Appendix B). The selected task was intended to be challenging, but feasible. Ideally, the difficulty of the tasks should be slightly greater than what patients were able to perform without difficulty. The set-up for the shaping tasks was described in detail in the bank of tasks. If meaningful, new tasks could be added. Task difficulty could be adjusted individually to the patients' motor abilities and demands. During shaping tasks, the exact set-up of the task was recorded by the therapist on a shaping registration form (Appendix C). As shaping tasks were chosen from the collection of tasks, the starting position, set-up and other task conditions were suggested and could be adapted depending on the needs of the participant.

During shaping tasks, the patients were seated in front of a table with the midline of the body oriented towards the midline of a template fixed to the table. The template on the table made it possible to locate the exact placement of objects on the table, as well as the final position when objects had to be moved between two target positions. After each task, the patient received feedback on performance (e.g. feedback on time to perform a task or number of repetitions during a specified time interval) as well as feedback on quality of movement. In addition, the therapist gave encouraging feedback during the performance if appropriate. The results from each shaping task were recorded on a shaping schedule (Appendix D). The shaping tasks selected during the first day were repeated every second day and a new set of exercises was selected at day two. The tasks were repeated reciprocally. As the shaping tasks were intended to be challenging, short rest breaks between the 10 repetitions of one task were included to give the patient the possibility to recover, to reposition equipment if necessary and to document task performance.

4.2.1.1 Progression parameters

Progression parameters were used to assess and adapt task difficulty during shaping. As a patient made progress, and a task was no longer perceived as difficult, one element of task

performance could be adjusted after discussion between participant and therapist. Possible progression parameters were: distance or height (e.g. increasing distance to target of the movement, for example placing a bottle further away from the participant), number of repetitions (e.g. four buttons instead of three), weight, diameter or form of an object (e.g. medium-sized buttons instead of large).



A) B)

Figure 3. Examples of possible progression parameters applied during shaping exercises. Task difficulty is increased by adjusting A) the size of the manipulated object, in this case smaller buttons which are more difficult to manipulate are used instead of the larger buttons; B) the size or form of the nut (wing nut or screw nut)

4.2.2 Standard task practice

The aim of standard task practice was to encourage the use of the most affected arm during functional activities. The selection of tasks was based on the patient's goals and interests. Examples of tasks were: ironing clothes, preparing coffee, emptying the dishwasher or playing an instrument. Like the shaping tasks, the tasks in standard task practice were intended to be challenging, but feasible for the patient. Each task was to be trained for 10-30 minutes. Feedback on results was given at the end of the task, and feedback on performance was given during the tasks, but not as systematically and often as during shaping tasks. Feedback was intended to be encouraging, including suggestions on how to improve performance. Time spent on each standard task practice task and feedback given was recorded.

Before treatment start, the patients were asked about how they performed activities of daily living, which activities were challenging, as well as which activities, hobbies and interests

were important for them. Goal Attainment Scaling (Kiresuk & Sherman, 1968) was used to formulate three goals related to ADL, hobbies or participation in social activities. The goals were formulated at the end of the first treatment day. They needed to be related to upper limb function and it should be expected that it is possible to achieve the goal during 2 weeks with intensive training. The participant rated how important the goal was and how difficult it would be to achieve the goal. Information from goal setting and the transfer package, which will be described in the next paragraph, was used to select tasks for both shaping and standard task training. The tasks were chosen in cooperation between therapist and participant. The goals formulated by the participant were to be trained daily, not only as part of organized treatment, but also outside the therapy setting during home exercises.

4.2.3 Transfer package

The aim of the transfer package was to encourage the participant to use the affected arm as much as possible during the intervention period. It consisted of a treatment contract, Motor Activity Log (MAL), home diary and home exercises (Morris et al., 2006).

4.2.3.1 Treatment contract

The purpose of the treatment contract was to increase participation in the treatment protocol outside the treatment setting. The aim was that the participants should use the most affected arm as much as possible during waking hours, and they were encouraged to explore how to use the affected arm at home. The treatment contract was discussed with the participant at the end of the first treatment day and was repeated and modified at least once during the treatment period. Before the treatment contract was discussed with the participant, the usual daily activities performed during weekdays and weekend were registered to get an overview of the person's habits, interests and hobbies. These activities were the basis for the treatment contract. Additionally, the therapist and the participant discussed the activities during which the participant should use the affected arm only, both arms or the non-affected arm. The affected arm was not to be used during activities where the use of the affected arm could be potentially dangerous.

4.2.3.2 Home diary

The home diary was used to register the activities the participant performed outside the therapy setting. The participant was also encouraged to write down how the activities were performed, when the non-affected arm was used or if they needed assistance during activities. The intention of the home diary was to increase the participants' awareness of using the affected arm most effectively outside the treatment setting and to increase their responsibility for training at home. In addition, the home diary gave both patient and therapist the possibility to discuss new solutions for how the arm could be used more effectively outside the treatment hours.

4.2.3.3 Home exercise

The aim of home exercise was that the patient took responsibility for task-specific training outside the therapy setting and to increase the use of the arm. Ten activities were chosen every day, ideally five fairly demanding activities and five less difficult ones. The participants were encouraged to spend approximately 30 min per day on home exercises. Home exercises were introduced on the second treatment day, and the therapist discussed and adjusted the home exercises in cooperation with the participant every morning. Home exercises could be related to daily activities like personal hygiene, preparing and eating meals, housekeeping, shopping, office work, gardening, outdoor activities and hobbies.

4.2.3.4 Motor Activity Log (MAL)

The MAL is a structured interview used to assess how well (Quality of Movement) and how often (Amount of Use) the affected arm is used outside the laboratory, in this case outside the treatment session (Morris et al., 2006; Taub et al., 1993). Only the "how well" part of the MAL was used as part of the transfer package, which consisted of 30 questions related to daily life activities such as opening a drawer, using a mobile phone, opening the fridge, using a remote control, picking up a glass, or buttoning a shirt. The patient was asked to answer the first 15 questions of the "how well" part of the MAL on the first treatment day and the remaining 15 questions on day 2. From day 3, alternating 15 questions were asked every day with the intention to increase the participant's awareness of how to use the affected arm more effectively during daily living.

4.3 Control group treatment (standard rehabilitation)

All participants initially took part in the multidisciplinary treatment approaches in their respective stroke units. Later, both the early and the delayed intervention group received physical and occupational therapy which was individually adjusted to the needs of the participants, either in an inpatient rehabilitation service or in community-based rehabilitation. Standard rehabilitation was based on the Norwegian guidelines for stroke (Indredavik, Salvesen, Ness, & Thorsvik, 2010). These guidelines recommend the use of task-oriented training; however, they do not specify the recommended intensity of treatment after stroke. In community-based rehabilitation it is common practice that stroke patients receive 1-3 times 45-60 min physiotherapy per week and probably slightly less occupational therapy during the first 6 months and sometimes even longer. In inpatient rehabilitation services, the participants received the same amount of daily therapy 5 times a week for 1-3 months.

4.4 Data collection

The data collection in the NORCIMT study was performed by examiners who had completed a 4-day training programme on the data collecting and testing procedures. Data about earlier stroke, type of stroke, localization of stroke, where acute treatment took place, and demographic background such as age, gender were collected. Additional information on data collection is described in section 4.5.

4.4.1 Outcome measures after ICF

Figure 4 provides an overview over the outcome measures used in the three papers of this thesis, structured by the conceptual framework of the ICF (see details about the outcome measures in section 4.5). The outcome measures are displayed on a continuum, rather than categorizing them in only one of the three main categories for the ICF.

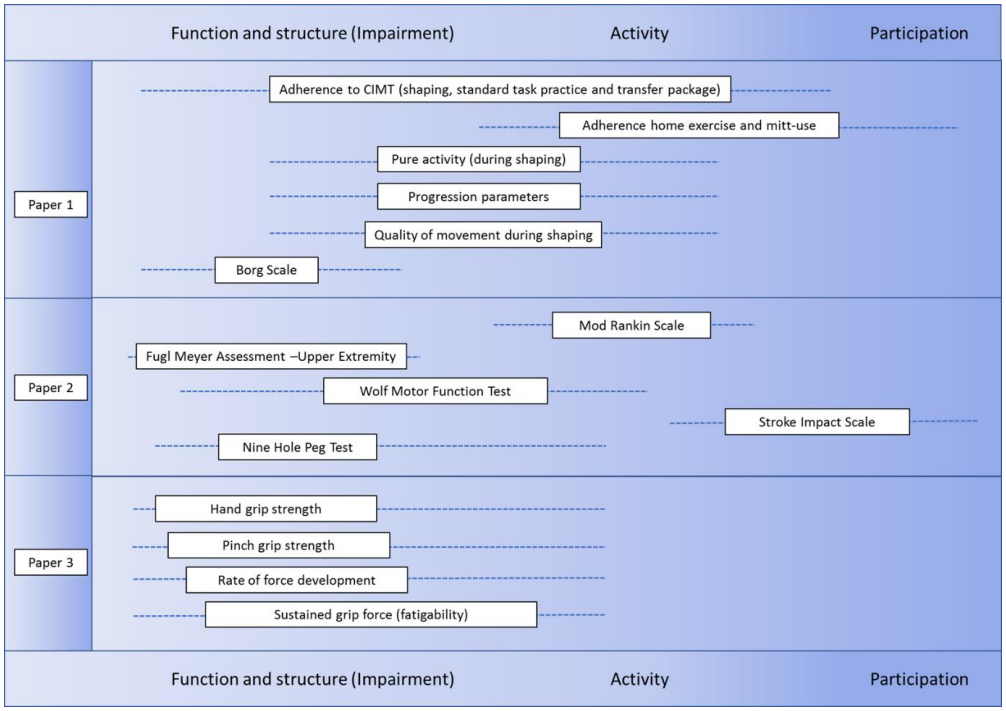


Figure 4. Localization of the outcome measures used in paper 1-3 on the continuum of the three levels of the ICF classification (body function/structure, activity and participation)

4.4.2 Reliability and validity

Reliability is defined as the degree to which an outcome measure is free from measurement error, in the case of test-retest reliability if the score for participants who have not changed are the same over time during repeated measurements (Mokkink et al., 2010). Inter-rater reliability describes the agreement of different assessors on the same occasion, i.e. the consistency between different raters. Intra-rater reliability assesses the consistency of the same rater. A further aspect of reliability is internal consistency, i.e. the consistency of a measure across items (Mokkink et al., 2010; Vitolins et al., 2000). Test-retest and inter-rater reliability of the outcome measures used in this thesis will be reported in Table 2-4, if available.

Validity refers to the degree to which an instrument measures the constructs it intends to measure and can be subdivided into face, content, construct and criterion validity (Mokkink et al., 2010). Face validity assesses the degree to which an outcome measure appears to measure what it intends to measure, i.e. the acceptability of the measure to the participants

(Mokkink et al., 2010; Vitolins et al., 2000). Content validity is about the comprehensiveness of the measurement tool, if it represents all essential elements of an outcome measure. For example, an assessment of adherence to an exercise program that only measures how many times a participant participates during a week has poor content validity because it does not consider other aspects of exercise like intensity and duration (Vitolins et al., 2000). Construct validity assesses the degree to which a measurement tool measures the construct it was designed to measure (De Vet, Terwee, Mokkink, & Knol, 2011; Mokkink et al., 2010). It can be assessed by comparing associations between the outcome measure and other variables with known relation to the construct, in the exercise example the correlation with other similar measures of physical exercise (Vitolins et al., 2000). Criterion validity describes the degree to which the score on an outcome measure reflects a gold standard. It can be further subdivided into concurrent validity (considers both the score for the outcome measure and the gold standard at the same time), or predictive validity (how well the measurement predicts the gold standard in the future) (De Vet et al., 2011; Mokkink et al., 2010). Available information about validity of the outcome measures used in this thesis will be reported in Table 2-4.

4.5 Summary of outcome measures (Paper 1 - 3)

Table 2-4 gives a description over the outcome measures used in this thesis, including purpose, description of the outcome variable (including equipment needed), as well as reliability and validity.

Table 2. Outcome measures paper 1 (Adherence to CIMT)

Outcome variable	Purpose	Description of outcome variable, testing procedure and equipment	Reliability	Validity
Adherence to CIMT	Assessment of time spent in various parts of CIMT treatment and time exclusively spent on activity during shaping tasks (pure activity).	Minutes spent in shaping tasks, standard task practice, transfer package were recorded by therapists during CIMT sessions. Systematic breaks and activities not directly related to treatment were excluded. Participants recorded duration of home exercises and mitt-use. Results were reviewed (day after participants were given exercises) together with therapist and modified if necessary. Treatment intensity: challenging. **Intended duration:** Total treatment time 180 min Shaping 120 min Standard task practice 30 min Transfer package 30 min Home exercise 30 min Mitt use (90% of waking time) 864 min **Pure activity:** Sum of duration of each of the 60-70 individual shaping tasks, i.e. only task performance. Remaining time of shaping session was used for rest, feedback, documentation and task set-up. Equipment: Treatment schedules (Appendix A and D). Home exercise schedule. Home diary and treatment schedules (mitt use).	**Test-retest reliability:** not available **Inter-rater reliability:** 2 raters judged treatment time (7 defined activities) by viewing videotaped treatment sessions. Significant correlations between raters score were found for upper limb activities (ρ = 0.88) (Wittwer et al., 2000).	**Criterion validity**: high correlation (ρ = 0.79) between video recordings of treatment time (upper limb) and time recorded by therapists on record forms. No systematic error (Wittwer, Goldie, Matyas, & Galea, 2000). Therapist estimated (after session) vs. video-recorded total treatment time and active time (ICC = 0.90 and 0.83). Systematic over-estimation of total and active treatment time by therapist. Inactive time (ICC = 0.62). Systematic underestimation of inactive time by therapist (Kaur, English, & Hillier, 2013)

Table 2. Continued

Outcome variable	Purpose	Description of outcome variable, testing procedure and equipment	Reliability	Validity
Treatment components	*Progression parameter*: assessment of adaptation of task difficulty during shaping. *Shaping Quality of movement* (QOM): Assessment of movement quality.	Therapist regularly evaluated degree of task difficulty together with patient. When a task was no longer perceived as difficult, one element of task execution was adapted, i.e. a progression parameter was applied. Shaping QOM scale (Appendix B), 6-point ordinal scale: 0 (no movement) to 5 (normal movement). Used as feedback on performance after each shaping task, 0.5 increments allowed to fine-tune feedback. Equipment: Shaping schedules (Appendix D).	**Inter-rater and test-retest reliability:** not available for both progression parameter and shaping QOM scale. Shaping QOM scale and QOM scale of Motor Activity Log (MAL) are very similar. MAL is a semi-structured interview to assess how well (QOM) and how often the arm is used in ADL. MAL (QOM) test-retest reliability: $ICC_{3,1} = 0.82$ (Uswatte et al., 2006).	**Validity**: not available for both progression parameter and shaping QOM scale. **Construct validity** for MAL (QOM): high correlation between MAL-28 (QOM) and Stroke Impact Scale - hand function scores (r = 0.72) and adequate correlation between MAL-28 (QOM) and accelerometery (r = 0.52) (Uswatte, Taub, Morris, Light, & Thompson, 2006).
Borg Scale Borg Rating Scale of Perceived Exertion (Borg, 1970)	Measures intensity level of physical activity (used to record perceived exertion after shaping session).	15-point scale ranging from 6 (no exertion) to 20 (maximal exertion). Participants were asked to assess perceived exertion on a copy of the scale where level of exertion is indicated in both numbers and words. Equipment: Printed copy of scale.	**Test-retest reliability:** $ICC_{2,1} = 0.82$, Borg Scale after 6-minute gait test in stroke patients (Gjellesvik, Brurok, Tjonna, Torhaug, & Askim, 2017)	**Criterion validity**: strong correlation (r = 0.8) between Borg Scale and Visual Analogue Fatigue Scale (Tseng, Gajewski, & Kluding, 2010). **Content validity**: Borg Scale is an appropriate indicator of exercise intensity for moderate (60-70% of peak aerobic capacity) but not for high-intensity exercise (Sage et al., 2013).

Table 3. Outcome measures paper 2 (Early vs delayed CIMT)

Outcome variable	Purpose	Description of outcome variable, testing procedure and equipment	Reliability	Validity
Wolf Motor Function Test (WMFT) (Wolf et al., 2001)	To assess arm motor function.	Consists of 17 items: 15 tasks measuring time to perform a task and quality of movement, 2 tasks measuring strength. Video recordings of movement tasks were used to assess performance time (WMFT-PT) and functional ability (WMFT-FA). Two blinded examiners assessed the tasks independently. WMFT-FA: 6-point ordinal scale ranging from 0 (does not attempt with upper extremity being tested) to 5 (arm does participate – movement appears to be normal). Equipment: standardized table and chair; standardized test template; test items such as note cards, can, pencil, paper clip, towel etc; and wrist weights, dynamometer, height-adjustable bedside table.	**Test-retest reliability:** *Chronic stroke:* r = 0.90 (WMFT-PT) and 0.95 (WMFT-FA) (Morris, Uswatte, Crago, Cook, & Taub, 2001). $ICC_{2,1}$ = 0.99 (WMFT-PT) and 0.97 (WMFT-FA) (Whitall, Savin, Harris-Love, & Waller, 2006). **Inter-rater reliability:** *Chronic stroke:* $ICC_{2,1}$ = 0.97 (WMFT-PT) and 0.88 (WMFT-FA) (Morris et al., 2001). *Late sub-acute to chronic stroke:* ICC = 0.94 (Nijland et al., 2010).	**Construct validity:** high correlations between WMFT-PT/FA and Fugl-Meyer Assessment (Upper-extremity) (ρ = 0.76/0.71) and Action Research Arm Test (ARAT) (ρ = 0.63/0.77) (Hsieh et al., 2009). **Criterion validity:** high correlations between WMFT-FA with ARAT (r = 0.75 - 0.86) and WMFT-PT (r = -0.64 to -0.83) at day 0/14/90 post-stroke support concurrent validity of WMFT (Edwards, Lang, Wagner, Birkenmeier, & Dromerick, 2012). WMFT-PT scores showed moderate predictive validity with the Functional Independence Measure scores (ρ = 0.47), while WMFT-FA had low (ρ = 0.26) predictive validity (Hsieh et al., 2009).

Table 3. Continued

Outcome variable	Purpose	Description of outcome variable, testing procedure and equipment	Reliability	Validity
Fugl-Meyer Assessment (Upper-extremity) (FMA-UE) (Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975)	To measure motor impairment following stroke. Developed for assessing sensorimotor recovery after stroke.	Includes 5 domains: motor function upper and lower extremity, sensory function, balance, joint range of motion and joint pain. Only motor function part for upper extremity was used in NORCIMT. Includes measuring movement, coordination and reflex action (shoulder, elbow, forearm, wrist and hand/finger). Score for the FMA-UE ranged from 0 - 66. Equipment: tennis ball, cylindrical container, tool for reflex testing.	**Inter-rater reliability:** ICC = 0.97 - 0.99 (Platz et al., 2005; Sanford, Moreland, Swanson, Stratford, & Gowland, 1993). **Test-retest reliability**: ICC = 0.97 for total motor score (Platz et al., 2005).	**Criterion validity**: motor and sensory scores of FMA 5 days after stroke were strong predictor of motor recovery 6 months after stroke (Duncan, Goldstein, Matchar, Divine, & Feussner, 1992). **Construct validity**: FMA-UE and Barthel Index r = 0.75, FMA-UE and Functional independence measure self-care r = 0.61, FMA-UE and Action Research Arm Test ρ = 0.91 - 0.94 (Gladstone, Danells, & Black, 2002).
Nine Hole Peg Test (NHPT) (Mathiowetz, Weber, Kashman, & Volland, 1985)	Measures finger dexterity in the upper extremities.	The participants were asked to take wooden pegs as quickly as possible from a container and place them one by one into the holes of the pegboard. Using only the hand tested. Pegs/sec placed into the holes were tested for the more affected side. Equipment: wooden, 9-hole pegboard (Weston Home Health/Medical Equipment, West Sussex, UK) and stopwatch.	**Test-retest reliability**: $ICC_{2,1}$ = 0.85 - 0.99 (Chen, Chen, Hsueh, Huang, & Hsieh, 2009; Ekstrand, Lexell, & Brogardh, 2016b). **Inter-rater reliability**: acute and chronic stroke ρ = 0.75 - 0.99 (Heller et al., 1987).	**Criterion validity**: correlation between NHPT and Stroke Impact Scale (hand function domain) ρ = -0.58 to -0.66; NHPT and Box and Block Test ρ = -0.71 to -0.80; NHPT and Action Research Arm test ρ = -0.55 to -0.57. Low to fair correlations with FMA and Motor Activity Log ρ = 0.16 - 0.33 (Lin, Chuang, Wu, Hsieh, & Chang, 2010).

Table 3. Continued

Outcome variable	Purpose	Description of outcome variable, testing procedure and equipment	Reliability	Validity
Stroke Impact Scale (SIS) (Duncan et al., 1999)	Assesses the impact of stroke on health status and quality of life.	Assesses multidimensional stroke outcomes. 8 domains (59 items) were assessed: strength (4), hand function (5), activities of daily living (ADL) and instrumented activities of daily living (IADL) (10), mobility (9), communication (7), emotion (9), memory and thinking (7), participation/role function (8). The patients rated questions about how stroke has affected each item on a 5-point Likert scale. Equipment: questionnaire.	**Test-retest reliability**: ICC = 0.67 - 0.96 (highest value hand function, lowest social participation) (Chou, Ou, & Chiang, 2015). **Inter-rater reliability**: patients vs. proxy for strength, hand function, mobility and ADL/ IADL (ICC = 0.61 - 0.82) (Carod-Artal, Ferreira Coral, Stieven Trizotto, & Menezes Moreira, 2009).	**Construct validity**: most SIS domain scores discriminate between patients with varying degree of stroke severity (Duncan et al., 1999). **Criterion validity**: concurrent validity SIS strength correlated with Motricity Index (r = 0.67); SIS ADL/IADL with Barthel Index (r = 0.72) (Duncan et al., 2002).
Modified Rankin Scale (mRS) (Van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988)	Categorizes the level of functional independence.	Global outcome measure. Single-item rating scale. The patients were asked about their ADL, including outdoor activities. Combines all aspects of a patient's performance (physical, mental and speech) into a single score. Score from 0 (no symptoms at all) to 6 (dead). Grading from 1-5: no significant, slight, moderate, moderately severe to severe disability. Equipment: structured interview guide was used (Wilson et al., 2002).	**Test-retest reliability:** strong test retest reliability (kappa = 0.81 - 0.95) (Banks & Marotta, 2007). **Inter-rater reliability:** moderate, improves with structured interviews (kappa 0.56 vs. 0.78) (Banks & Marotta, 2007).	**Criterion validity**: concurrent validity with Frenchay Activities Index (ρ = -0.80), Barthel Index (ρ = -0.81) (Cup, Scholte op Reimer, Thijssen, & van Kuyk-Minis, 2003). **Construct validity**: many studies have demonstrated a relationship between mRS and location, type and extent of stroke as well as neurological impairment (Banks & Marotta, 2007).

Table 4. Outcome measures paper 3 (Grip strength)

Outcome variable	Purpose	Description of outcome variable, testing procedure and equipment	Reliability	Validity
Grip strength Maximum voluntary contraction (MVC)	Assessment of the maximal grip strength.	Hand grip strength was assessed in 5 different handle positions of a hand dynamometer, pinch grip strength with a pinchmeter. The 3 pinch-grip positions were: key grip (holding the pinchmeter between the lateral side of the 2nd phalanx of the index finger and the tip of the thumb), 3-jaw grip (holding the pinchmeter between the fingertips of the index finger, middle finger and thumb) and pinch grip (between the fingertips of the index finger and thumb). Assessment was carried out according to the recommendations of the American Association of Hand Therapists: Subject seated with shoulder in neutral, elbow 90-degree position, neutral forearm and wrist position. The participants performed 3 trials with each hand with 60 sec rest between the trials. The mean of the 3 values was taken as the value for MVC. Instructions during testing were: "grip as hard as you can when I say go – go – grip as hard as you can". Equipment: Biometrics E-LINK EP99 evaluation system (Biometrics Ltd, Gwent, UK, 2006), with electronic hand dynamometer (G100) and pinchmeter (P100).	**Test-retest reliability** (patients without spasticity): hand grip, key and 3-jaw grip: $ICC_{2,1}$ = 0.96 - 0.98 (Chen et al., 2009). **Inter-rater reliability** (mean of 3 trials): hand grip $ICC_{2,3}$ = 0.98 - 0.99; key and 3-jaw grip $ICC_{2,3}$ = 0.94 - 0.95; tip-to-tip grip $ICC_{2,3}$ = 0.85 (non-affected hand) and 0.94 (affected hand) (Aguiar et al., 2016). **Intra-rater reliability** (mean of 3 trials): hand grip $ICC_{2,3}$ = 0.98 – 0.99; key and 3-jaw grip $ICC_{2,3}$ = 0.94 – 0.96; tip-to-tip grip $ICC_{2,3}$ = 0.85 (non-affected hand) and 0.90 (affected hand) (Aguiar et al., 2016).	**Criterion validity**: Jamar dynamometer is considered to be the gold standard to validate hydraulic and electronic dynamometers. Excellent concurrent validity between Jamar dynamometer and Biometrics E-Link system (r = 0.98) (Allen & Barnett, 2011). **Construct validity**: Hand grip strength is correlated with National Institutes of Health Stroke Scale (ρ = -0.82) and Stroke Impact Scale arm and hand (ρ = 0.70 and ρ = 0.85 respectively) (Bohannon, 2004).

Table 4. Continued

Outcome variable	Purpose	Description of outcome variable, testing procedure and equipment	Reliability	Validity
Rate of force development (RFD)	Assessment of the ability to generate muscle force explosively.	The same testing positions as for grip strength measurement were used. Each hand was tested once using position 2 of the dynamometer and key grip on the pinchmeter. Instructions were: "Grip as hard and as fast as you can when I say go – go – grip as hard as you can – grip as hard as you can (repeated)". A 0 - 500 ms time interval was used to calculate RFD. Onset of the force-time curve was detected visually. Equipment: same as for grip strength (sampling frequency 20 Hz).	**Test-retest reliability**: ICC = 0.78 for 0.5 sec interval (Demura, Yamaji, Nagasawa, Minami, & Kita, 2000).	Not available for rate of force development during grip strength measurements. **Criterion validity for detection of signal onset**: manual/visual approaches on detecting signal onset are considered as the gold standard for validation of other approaches (automated detection methods) (Maffiuletti et al., 2016).
Sustained grip strength	Assessment of the ability to sustain maximal grip strength for 12 sec (fatigue during prolonged gripping).	Same testing procedures as for RFD. Absolute degree of decreased force during 12 sec of sustained gripping (decrease of maximum voluntary contraction in kg). Decrease of maximal grip strength during 12 sec expressed as percentage of maximal recorded grip strength. Equipment: same as for grip strength.	**Test-retest reliability:** 6 sec test: stroke (ICC = 0.95) (Kamimura & Ikuta, 2002). **Inter-rater reliability:** not available.	Not available

4.6 Data analysis and statistics

The level of significance was set at $p < 0.05$ in paper 1 and 2. Due to the longitudinal design and multiple comparisons between the two treatment groups in paper 2, the Benjamini - Hochberg method was applied to correct for multiple comparisons (Benjamini & Hochberg, 1995). A conservative p-value was chosen in paper 3, due to multiple comparisons between the two hands during 5 time points and 5 grip positions. P-values <0.01 were regarded as representing a significant difference. Normal distribution was assessed by the Shapiro-Wilk test in paper 1 and by visual inspection of quantile-quantile (Q-Q) plots in paper 2 and 3. Normally distributed data were presented as mean and standard deviation, if data were non-normally distributed as median and interquartile range. Differences between groups were assessed by independent t-test for normally distributed data or Mann-Whitney U-test if data were non-normally distributed. Within-group differences between 2 time points were assessed by paired t-test or Wilcoxon signed-rank test if data were non-normally distributed. SPSS for Windows, version 18 (SPSS Inc, Chicago, IL), was used in paper 1, STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) was used in paper 2 and Stata Release 15 in paper 3.

4.6.1 Paper 1

Descriptive statistics was used to assess the adherence to the treatment protocol by the number of completed treatment sessions and the time (in minutes) spent in the various parts of the treatment protocol. Regression analysis was used to assess the associations between the treatment variables, i.e. time spent in treatment components, home exercise, and mitt use (dependent variables) and demographic as well as treatment parameters (independent variables). Age, gender and other independent variables that were possibly related to treatment time variables and were correlated with the dependent variables ($p < 0.1$) were included in a linear stepwise multiple regression model.

4.6.2 Paper 2

Power calculations showed that a power of 0.8 required 53 participants in each treatment group (Thrane et al., 2015). The primary outcome measure was the Wolf Motor Function Test (WMFT). Linear mixed models were used to assess differences in the primary and secondary outcome measures between early and later CIMT intervention across the 5 time points. Linear mixed models allow performing the analysis on all participants. To account for missing data, the maximum likelihood estimation was used. To better fit normal distribution,

the primary outcome variable, the WMFT time, was log-transformed using the LG10 function. FMA-UE values were not normally distributed, and were therefore analysed by a non-parametric test, the Friedman analysis of variance.

4.6.3 Paper 3

Descriptive statistics was used in the explorative evaluation of grip strength, RFD and sustained grip strength. Comparisons between the affected and non-affected hand were analysed by independent t-test. To assess RFD, the onset of the force-time curve, i.e. the point in time where the force-time curve starts to rise, had to be determined. Visual determination of signal onset, i.e. the examiner defines the onset point by inspecting the curve, is regarded as the reference for the validation of automated onset detection (Maffiuletti et al., 2016). The onset of the force-time curve was determined visually by two independent examiners. ICC (3,1) was used to assess the degree of agreement between the examiners.

4.7 Ethical considerations

The study was reviewed and approved by the Regional Committee of Medical Ethics and the Commission of Privacy Rights at the University Hospital of North Norway (REK NORD 39/2008). All participants had to be able and willing to sign an informed consent form before inclusion in the study. The evaluation of the participants' competence to consent was based on clinical judgement.

Possible harm of the study was mentioned in the informed consent form. The participants were informed that CIMT treatment is intensive and could be tiring for some people and that there is a possibility of increased pain in the affected arm due to the intensity of the treatment.

5 Results and summary of papers

The three papers included in this thesis address aspects that are important for rehabilitation of upper limb function early after stroke. The results showed that general adherence to intensive task-oriented CIMT is quite good; however, there was a substantial reduction of task practice time and time spent in pure activity. Early applied CIMT was as effective as delayed applied CIMT in the long run. Furthermore, grip strength, and especially fatigability during gripping, were substantially reduced during the first weeks after stroke.

5.1 Paper 1

The primary aim of this paper was to investigate the adherence to the treatment protocol in the patients included into the early intervention group of the NORCIMT study.

The intended supervised daily treatment time defined in the protocol was 180 min. Of these, 120 min were to be used for shaping tasks, 30 min each for both standard task practice and transfer package. In addition, the patients were to practice for 30 min at home. Therapy schedules were used to record the duration of each individual part of the treatment protocol. During the shaping exercise, performance time for each of the 60-70 sets of tasks was recorded, which made it possible to calculate how much of the time the participants spent in shaping sessions was used for pure physical activity.

Our study found that the participants tended to have a high adherence rate and spent a mean of 91.3 % of the intended time for treatment. Less time than intended was spent in shaping tasks (82%) and standard tasks practice (77%), and more time than intended in activities related to the transfer package (120%). The study found that a surprisingly low part of the time spent in shaping was devoted exclusively to motor activity (33%) compared to the time spent on documentation, feedback, task set up, and rests.

Regression analysis showed a positive association between the treatment progression parameter and time spent in treatment ($r = 0.74$). Standard task practice was negatively associated with age ($r = -0.65$). Women used the treatment mitt less compared to men ($r = -0.55$).

5.2 Paper 2

The main aim of this study was to compare the long-term effects of CIMT applied later with the early intervention.

A single-blinded, multicentre, randomized controlled trial with a crossover design was used to compare CIMT commenced in the early sub-acute phase with CIMT commenced in the chronic phase after stroke. Both groups received 3 hours of CIMT daily during a 2-week period and standard rehabilitation otherwise during the 12-month follow-up period. The early intervention group commenced CIMT within 28 days, the delayed intervention group 6 months after inclusion. Both groups were tested 5 times, at inclusion, 2, 26, 28 and 52 weeks after inclusion with WMFT, measuring motor function as the primary outcome measure. Secondary outcome measures were the Nine Hole Peg Test (NHPT), a measure of dexterity; Fugl-Meyer Assessment of the upper limb (FMA-UE) that measures motor impairment; the Stroke Impact Scale (SIS), an interviewer-administered assessment of self-reported health; and the modified Rankin Scale (mRS), a global measure to categorize the level of functional independence.

The study included 47 patients with mild to moderate stroke. Both groups improved significantly during the 12-month follow-up on both primary and secondary outcome measures. However, no significant difference between the groups was found before and after the delayed intervention group received CIMT and at 12-month follow-up. The patients randomized into the early intervention group initially showed a faster recovery curve on the WMFT, NHPT, and mRS scores. However, both groups recovered considerably and showed only minor impairment (median FMA-UE score 64/66) at 6 months. The results indicate that early intervention with CIMT is as good as delayed CIMT in this group of participants, which might have reached a ceiling during the first 6 months after stroke.

5.3 Paper 3

The primary aim was to assess the long-term development of grip strength in hand and finger muscles in both the affected and the non-affected hand during the first year after stroke. Grip strength was also assessed in the main study (paper 2), but only maximal grip strength in the affected hand. For paper 3, a subsample of the NORCIMT study, 11 patients with mild to moderate stroke were selected from the participants recruited from Trondheim University Hospital. Different aspects of grip strength were assessed: 1) maximal grip strength in five handle positions (narrow to wide grip) on a hand dynamometer and three different types of pinch grip, 2) rate of force development (RFD) in hand grip and key pinch grip, as well as 3) fatigability during sustained grip, i.e. the ability to maintain maximal grip strength over 12 seconds. The measurements were performed on both hands at inclusion into the study (mean 16 days post-stroke) and at four different time points during the one-year follow-up period, using an electronic hand dynamometer (Biometrics Ltd, Gwent, UK, 2006) and pinch meter. At inclusion, grip strength in the affected hand reached 37-43% of the values of the non-affected hand in the different handle positions on the dynamometer. The participants improved considerably and approached 74-80% of the values in the non-affected hand during the first year after stroke, with most improvement occurring during the first 6 months and less between 6 and 12 months. No evidence was found for selective weakness in the different grip positions.

Pinch meter recordings showed similar patterns, but with less improvement between 6 and 12 months compared to hand grip strength. Key grip strength was better preserved (showed a higher grip strength ratio) compared to three-jaw and tip-to-tip grip strength at inclusion. At 12-month follow-up, it was only 14% lower than the non-affected side, compared to 24% for three-jaw and tip-to-tip grip strength. RFD in the affected hand was less than half that of the non-affected side at inclusion for both dynamometer (position 2) and pinchmeter (key grip) and approached the values of the non-affected side at 6 months follow-up with little further progress during the one-year follow-up. Similarly, sustained grip strength showed 20-30% greater decline in the affected hand compared to the non-affected at inclusion and approached the values of the non-affected hand at 6-month follow-up.

5.4 Adverse effects

Three of the participants in the early CIMT group developed shoulder pain (two participants between week 2 and week 26 and one between week 28 and week 56). Three participants in the delayed CIMT group developed shoulder pain before the treatment started; however, all completed the treatment and follow-up assessment.

6 Discussion

This thesis reports results from the NORCIMT study. The overall aim was to gain new knowledge about processes important for intensive rehabilitation of motor function in the upper limb during the first year after stroke by addressing adherence and efficacy of CIMT as well as the development of grip strength.

The thesis revealed that patients with mild to moderate stroke showed a high adherence rate to a 3-hour intensive task-oriented CIMT treatment. However, only one-third of the treatment time was used exclusively for motor activity, indicating the need for rest during task performance. Furthermore, CIMT training applied in the early sub-acute phase after stroke was more effective than standard care in improving motor function when measured after the early intervention period. However, the differences between the groups became non-significant after 6 months, and remained non-significant after the delayed intervention period and at 12-month follow-up. Finally, the results from detailed measurements of grip strength showed that not only grip strength was reduced in the early sub-acute phase after stroke, but also the ability to generate force rapidly. In addition, the participants showed increased fatigability in the affected hand. However, all aspects of grip strength approached the values of the non-affected side at 6 months, with little further progress towards 1-year follow-up. The results from this thesis show that during the first weeks after stroke patients have decreased task practice time and substantially increased fatigability in the hand and finger muscles. Both of these indicate an increased need for rest during intensive training, and thereby a potential influence on the efficacy of the treatment.

In this chapter methodological issues of this thesis will be discussed, followed by a general discussion of the findings and how these findings may contribute to optimize the treatment of upper limb function.

6.1 Methodological considerations

6.1.1 Internal validity

Internal validity is the extent to which systematic error in a clinical trial is minimized and depends on having accounted for biases. Factors that influence internal validity in our study will be described in detail in the following sections such as the design of the study, detection bias, selection bias, attrition bias, performance bias, standardization of examination and

treatment and measurement errors that may threaten the internal validity of a study (Juni, Altman, & Egger, 2001; Skelly, Dettori, & Brodt, 2012).

6.1.1.1 Study design

The use of an RCT as a study design is a strength of the NORCIMT trial. Randomized controlled trials are considered the gold standard for assessing the efficacy of a study in clinical research because they minimize the effect of confounding factors (Spieth et al., 2016). The randomization process ensures that baseline characteristics like age, sex and level of impairment are equally distributed, i.e. systematic variation is minimized, and the influence of bias is minimized (Concato, 2013). There will always be some random variation in the treatment groups, which will decrease with increasing sample size. However, the estimated sample size of 53 participants in each group was not reached in the NORCIMT study (Thrane et al., 2015), leading to increased risk of type II error, i.e. the possibility of falsely accepting the null hypothesis. This means accepting that an intervention has no effect even if it in fact has an effect, that cannot be proved due to the low power of the study. Low power in our study could have influenced the 6-month results in particular.

The sample in paper 1 consisted of the participants randomized to the early intervention group, while the sample in paper 3 was based on the participants randomized in one of the centres. Only 11 patients were included in the exploratory study in paper 3, and the patients randomized both to the early and delayed intervention group were included.

6.1.1.2 Detection bias

Detection bias occurs if the knowledge of a participants' assignment influences the assessment of an outcome and can be avoided by blinding (Juni et al., 2001). Blinding is a procedure in which the assessor and/or the participant in an RCT is kept unaware of which treatment arm the participants have been assigned to. In a double blinded study, both staff and participants are blinded. In paper 2, only the research assistants responsible for the assessment in the RCT were blinded; blinding of the participant to the intervention was not possible.

In the adherence study (paper 1), the therapist in charge recorded the adherence to the treatment, therefore blinding was practically not possible for the adherence data. The examiner in paper 3 was not blinded, which could potentially have led to biased grip strength values, for example by favouring the experimental group or the therapist

unconsciously wishing that the patients would get better over time. No group comparison between the early and delayed intervention was performed, which reduces a possible bias in favour of the experimental group. However, it cannot be excluded that non-blinding could have biased the results towards better performance over time. The participants were blinded regarding previous performance, i.e. they were not informed about the results from the previous test, but it could not be excluded that patients remembered parts of their performance.

6.1.1.3 Selection bias

Selection bias might be introduced by the inclusion of the participants or the randomization process, for example when the persons responsible for the enrolment of participants selectively enrol participants based on what the next allocation to the treatment is likely to be (Juni et al., 2001; Kahan, Rehal, & Cro, 2015). A multicentre randomized controlled trial design was applied in paper 2. After the patients had consented to participate in the study, they were allocated to either early or delayed CIMT intervention using a computer-generated block scheme for randomization (Thrane et al., 2015). A block scheme for randomization leads to a slightly higher risk of predictability of the allocation and might introduce the possibility of selection bias. The possible selection bias in paper 2 will also apply to paper 1 and 3. Paper 1 has been based on the participants in the early intervention group and paper 3 on the subsample from one centre, the three papers showed similar patient characteristics (Table 1).

We do not know what characterized the eligible patients who declined to participate; however, the patients included in the NORCIMT trial were approximately 10 years younger compared to the patients registered in the Norwegian stroke registry (Fjærtoft et al., 2017). The overrepresentation of younger stroke patients might be due to the intensive nature of the treatment, which might not appeal to older patients to the same degree as younger patients and might have led to older patients tending to choose not to participate in the study. This might be partly confirmed by the finding in paper 1 that older age was associated with less adherence to parts of the treatment, as also reported in the study by Aartolahti et al. (2015).

Only 23% of the included participants in paper 2 were women, in contrast to 46% of the patients included in the Norwegian stroke registry in 2016 (Fjærtoft et al., 2017). However,

the fact that fewer women were recruited could partly be explained by substantially fewer women suffering from stroke up to the age categories of 55-64 (30%) and 65-74 years (38%). The number of women and men is about the same in the age group 75-84 years, and there are approximately 40% more women than men in the age group above 85 years (Fjærtoft et al., 2017). The lower numbers of women who were recruited to our study reflect, at least partly, the lower cardiovascular burden in women, which leads to a lower proportion of women with stroke in all age groups up to 75 years, indicating that the proportion of women in our study is not very dissimilar to the proportion of stroke patients in this age group.

6.1.1.4 Attrition bias

Attrition bias is caused by the loss of participants who withdraw or do not attend assessments, especially if drop-out is different between the groups (Juni et al., 2001). The loss of participants is common in long-term follow-up studies; Corbetta et al. (2015) found drop-out rates in CIMT trials of up to 20% at 6-month follow-up. In the NORCIMT study (paper 2), four participants withdrew during the CIMT intervention. Two participants withdrew during the early CIMT intervention and two during the delayed intervention. The reason for the withdrawal of one participant in the early CIMT group was frustration with the complexity and intensity of the treatment, and for one participant in the delayed CIMT group it was lack of motivation. The reason why two other participants, one in each group, did not finish the intervention is not known because the participants could quit the intervention without giving a reason. It is reasonable to assume that the intensity of the treatment could have influenced the drop-out rate in the early and delayed CIMT groups. However, it is unlikely that the treatment was the main reason for drop-out in CIMT group, as there were also three participants who dropped out from standard treatment, one at week 2 and two at week 28. The drop-out rate increased, especially between week 28 and 56, where 16/24 (33%) patients were assessed in the early intervention group and 18/23 (22%) in the delayed intervention group. However, the different drop-out rates between the groups were not significant. The high drop-out rates might bias the results, i.e. they might further increase the risk of type II error, especially at week 52.

High drop-out rates have also been reported from other intervention studies with long-term (1-year) follow-up (Taub et al., 2013; Wolf et al., 2006) and might be due to a high number of repeated assessments. This may especially apply to the early intervention group, which had

to attend four assessments after they got the intervention. An alternative explanation is that procedures for calling in participants to assessments were not optimal.

A strength of our study is that adherence data (paper 1) were available for 23/24 patients, and that all 11 patients participated in all five assessments in the grip strength study (paper 3), with the exception of three grip strength assessments on the non-affected side for one of the patients.

6.1.1.5 Performance bias (Diffusion of treatment effect)

A diffusion of treatment effect, i.e. the spread of some intervention effects from the experimental to the control group, could not be excluded in paper 2 because some patients could have been at the same ward at the same time. However, as the patients were continuously included at the five centres during the study period, there was negligible risk that the participants in the early group had direct contact with participants in the delayed group. Furthermore, it is not plausible that the participants received more information about the treatment as given by the written informed consent and during the communication with the person who recruited the participants. However, we cannot exclude the possibility that some participants were inspired by this information and trained more intensively than they would otherwise have done. In addition, it could not be excluded that the knowledge about CIMT might have influenced some therapists to adapt the standard treatment without being conscious about it.

6.1.1.6 Standardization of procedures for treatment

Therapy schedules have been used to assess adherence to the treatment protocol in paper 1. The registration of the patients' presence and participation during the treatment was of main interest. The treatment procedures contained a detailed description of the content and of the order in which parts of the treatment had to be performed for each treatment day. Detailed instructions were given on how to record the time spent in the various parts of the protocol. The therapists responsible for the intervention attended a 4-day training programme to ensure that the treatment was applied according to the treatment protocol of the NORCIMT trial. Although the therapists went through an extensive training programme and received detailed written procedures about all parts of the treatment, it could never be excluded that aspects of the examination had been changed unintentionally during the course of the long follow-up, or that therapists did not adhere to the protocol. A detailed

description of which activities should have been performed on every treatment day was given to minimize this risk. Furthermore, there seems to be little systematic error when an activity is directly recorded during a treatment session (Wittwer et al., 2000). However, as Kaur et al. (2013) showed, therapists tended to overestimate the amount of time spent in therapy when the activity is recorded after a treatment session. Overestimating of adherence might apply especially for registration outside the therapy setting (home exercise and mitt use). In addition, there might be a risk that the participants' self-reported duration of home exercise was prone to overreporting (Troiano et al., 2008). As the tendency towards overreporting of self-reported physical activity is a known phenomenon, the home registration forms were reviewed by the therapist and the participant each day. Discussing the records may oblige the participants and therapists not to exaggerate the results and may help to strengthen the accuracy of the records. Alternatively, accelerometers could have been used to monitor activity both during the sessions and at home to reduce the probability of overreporting adherence.

For an intervention which claims to be intensive it is crucial that not only treatment intensity is described in the protocol, but also what has been done to ensure that the intended intensity has been applied according to the protocol. Intensity of training has been defined differently in studies of upper limb function, often by either minutes or hours spent in treatment, by the number of repetitions, by how vigorous the treatment is or the level of perceived difficulty. Many CIMT trials have no transparent treatment protocol for CIMT, and most often only information about the intended duration (number of hours, duration in days/weeks) is given (Kwakkel et al., 2015). Further details about intensity are rarely reported in RCTs on upper limb function.

In our protocol, the intensity of the treatment was defined by the number of repetitions (60-70 during shaping) and duration of task training (150 min); the difficulty of the tasks was intended to be challenging. Furthermore, the Borg Scale provided information about perceived exertion after the shaping sessions. Progression parameters, which were used to adapt the level of difficulty, depended on the therapist's continuous monitoring of the participant's performance and suggesting adaptations when the participant showed progress. There is some possibility for interpretation by the therapist in charge of the treatment regarding when and how progression parameters should be applied. To ensure

uniform application of progression parameters, substantial time in the training programme for the therapist was dedicated to how and when the tasks should be modified. The Borg Scale was applied at the end of the shaping session and might have been influenced by the last sets of tasks. A less biased score of perceived exertion could possibly have been achieved, if the Borg Scale had been applied repeatedly directly during a set of tasks instead of after the session.

6.1.1.7 Standardization of procedures for examination

The examiners at the respective treatment sites also completed a 4-day training programme on the study procedures to improve their adherence to the assessment protocol and thereby the reliability and validity of the assessment. The outcome measures used in paper 2 are reliable and valid, as Table 3 shows, with the exception of some domains of the SIS. Video recordings were used in the assessment of the WMFT and two blinded raters assessed the tasks independently to increase the reliability of the WMFT.

All grip strength assessments were performed according to the recommendations of the American society of hand therapists (Roberts et al., 2011). Grip strength testing and the equipment used in paper 3 show high reliability and good validity (Table 4), with the exception of RFD, which showed lower test-retest reliability compared to MVC and sustained grip force measurements. Differences in test set-up and instruction could potentially have biased the results. However, the relative stable values on the non-affected side during most measurement do not give any indications that this might be the case. Only the RFD values showed some fluctuation on the non-affected side; however, an explanation for this could be that RFD generally is a less reliable measure compared to MVC.

6.1.2 External validity

External validity is defined by the extent to which results from a trial can be generalized to other circumstances (Juni et al., 2001). The fact that mainly younger participants were recruited to this study together with the inclusion and exclusion criteria in the study, which restricted the recruitment to patients with mild to moderate stroke, indicate that CIMT is not an intervention applicable for the general stroke population, but only for a selected group of persons with stroke. The high intensity of CIMT is probably a reason that the interest in participating in CIMT declines with age. Older age is accompanied by more comorbidities, leading to an increased possibility for exclusion from taking part in the trial.

The results from the NORCIMT study may be not representative for the general stroke population and apply therefore mainly to younger patients with mild to moderate stroke.

Only 4% of our patients experienced a haemorrhagic stroke in contrast to approximately 13% in the Norwegian population as reported by the Norwegian stroke registry (Fjærtoft et al., 2017). This makes it unsure if the results from this study also apply to patients with haemorrhagic stroke.

A limitation of our study was that we did not assess cognitive impairment thoroughly. The Mini Mental Test used in our study does not give a comprehensive picture of cognitive function like executive function, attention, apraxia or memory; neither did the line bisection test regarding neglect. Due to the inclusion criteria, it is probable that the participants in our study had less cognitive impairment compared to the general stroke population and the results from this thesis will probably not apply to patients with more obvious cognitive impairment.

6.2 Discussion of results

In the following chapters, the results of this thesis will be discussed in the context of other literature in this field.

6.2.1 Adherence

As CIMT is very complex and time-consuming, reduced adherence to the treatment might be expected, especially early after stroke. However, our study (paper 1) showed good overall adherence. The overall time spent on CIMT activities in the early intervention group was only 9% below the intended 180 min treatment time (including task practice and transfer package). However, the 20% reduction in task practice time in our study is a marked deviation from the 150 min intended task practice time (120 min shaping and 30 min standard task practice) defined in our protocol. Apart from our study, there are only a few studies reporting adherence to CIMT, most of them are forced-use or home based CIMT studies (Brunner, Skouen, & Strand, 2012; Hammer & Lindmark, 2009; Kaplon et al., 2007; McNulty et al., 2015; Ploughman & Corbett, 2004); only the EXCITE study has a design that is comparable to our study. The overall adherence in our study is slightly lower compared to the EXCITE trial. The EXCITE study showed that approximately only 4 of the 6 hours of treatment were spent in task practice, while 2 hours were used for rest, task set-up, education, lunch and other activities (Kaplon et al., 2007). Details about rest and activities were not reported, and we do not know how much of the 4 hours task practice time was spent in pure activity, i.e. exclusively practising tasks, therefore it is difficult to compare the results with our study.

The importance of reporting adherence to treatment is emphasized in systematic reviews (Bonaiuti et al., 2007; Krekeler et al., 2018). To be able to comprehensively compare the efficacy of stroke trials, especially if trials claim to be intensive, it is essential to get information about the different aspects of the treatment protocol and the degree to which the studies followed the protocol, such as the time the participants actually spent in the different activities. Reduced adherence to a treatment may influence the results of a treatment and may help to explain why a potentially effective treatment did not show any effect.

The transfer package might facilitate adherence because it focuses on self-efficacy and involvement in the treatment. The participants in our study spent more than the intended 30 min per day for the transfer package, reflecting the importance of the transfer package.

6.2.2 Pure activity

A surprising result of our study was that only 33% of the time spent in shaping exercises was pure activity, meaning that the remaining time was spent in task set-up, documentation, feedback and rest. None of the other CIMT studies reported pure activity, and it remains unclear if this high proportion of non-practice elements is a feature of shaping or if it is due to reduced training capacity early after stroke.

As we have no comparison, we do not know if the reason for the low amount of pure activity is that CIMT was commenced very early after stroke or if a similar amount of pure activity would have been found in the chronic phase. Unfortunately, we have no information about pure activity in our delayed CIMT group. On the other hand, due to the design of the study and the expected spontaneous recovery between early and delayed intervention, the delayed group would have had a much higher functional level, which would have made direct comparison difficult.

Possibly, pure activity was also substantially reduced in the EXCITE trial. Since the trial used a protocol similar to our study (Morris et al., 2006), it is very likely that time was needed for activities not related to actively practising tasks during the 4 hours task practice time (Kaplon et al., 2007), such as task set-up and feedback, and that the participants needed some rest between the tasks. This probably applies, at least partly, to most of the other CIMT studies and possibly also to other intensive interventions for the upper limb, especially if commenced early after stroke. It seems to be plausible that the low pure activity during task practice is due to a considerable amount of rest needed to recover between the repetition of tasks.

6.2.3 Need for rest and fatigability

The need for rest will depend on multiple factors, like the duration, complexity and difficulty of the task, participants' capacity and how closely they work to the limit of their performance, as well as their fatigability. Task duration during shaping tasks was 30-120 sec, which made it possible to include more complex tasks compared to other studies on repetitive task training. For example, in the study by Birkenmeier, Prager, and Lang (2010),

more than 300 repetitions of a task per hour were achieved in patients in the chronic phase after stroke. This implies that the participants had less than 12 sec to perform one task, including short rests between the repetitions. A duration of less than 12 sec will be too short to perform complex tasks and to work at the limit of the participant's performance. Even if the number of repetitions is high, the tasks might be less tiring and thus require less need for rest between the repetitions.

An explanation for the probable high need for rest in our study could also be that the participants performed at the limit of their capacity. However, the Borg Scale, measured after the shaping exercises, remained on a stable moderately high level, while the QOM increased steadily during the 10 treatment days. The number of progression parameters did not decrease, which might have been expected if the intensity had been too high.

The low pure activity during shaping in our study might also to a substantial degree be due to commencement of the treatment early after stroke and the patients might have had a higher need for rest, due to fatigability after stroke. The results from the sustained grip strength testing confirm the fatigability in the first weeks after stroke, with a marked decline in grip strength during the first 2 sec after the patients reached maximal grip strength. As the patients were challenged to perform close to their limit during shaping, the fatigability observed in paper 3 could play a significant role in explaining the need for rests.

It has been shown that reduced ability to sustain maximum grip strength is also negatively related to the ability to squeeze objects during ADL (Kamimura & Ikuta, 2002). Many of the activities during shaping, such as opening a jar, wringing a wash cloth or lifting heavy objects demand near to maximal grip strength and will lead to increased fatigability and probably also increased need for rest. Force-time curve measurements could be used to assess fatigability in the hand muscles objectively and to adapt treatment intensity. Patients with a high degree of fatigability may possibly benefit from tasks of shorter duration, especially if the tasks demand high levels of grip strength, or from tasks that demand a less powerful grip. Probably longer rest periods between the tasks are needed to "recharge the batteries". Minimizing the effects of fatigability may help to increase both adherence and efficacy of CIMT treatment and is probably more important in the early sub-acute phase than in the late sub-acute and the chronic phase.

6.2.4 Efficacy of CIMT

A beneficial effect in the early CIMT group compared to standard care was observed directly after the intervention. However, it was no longer significant at 6 months, neither after the delayed CIMT group received treatment after 6 months, nor at one-year follow-up. It is difficult to know if this lack of significant effect means that there was no effect or if we were not able to detect an effect, for example due to the reduced power in our study. The differences between the groups were small after the 6 month-follow-up and it is not known whether a larger sample might have revealed significant results. A possible explanation for the early CIMT group not maintaining its initial positive effect over time is that 2 weeks of therapy might be not enough to change training behaviour after the intervention.

Reduced adherence to task practice and reduced pure activity (paper 1) might be possible explanations for the lack of a long-term effect in the early intervention group. However, it is not a likely explanation for the lack of effect in the delayed intervention group. The EXCITE trial showed beneficial effects despite less than intended task practice (Kaplon et al., 2007). The delayed group in our study and the EXCITE trial were comparable with regard to time after stroke and total adherence time. As a similar protocol has been used (Morris et al., 2006), it is reasonable that they also had similar pure activity time, and reduced adherence might not be a plausible explanation for the missing effect of the delayed intervention. Also, most other CIMT studies have shown effect, at least in the short run, if they were applied in the late sub-acute and chronic phase after stroke (Corbetta et al., 2015; Etoom et al., 2016; Kwakkel et al., 2015).

A more plausible explanation for the lack of treatment effect in our delayed CIMT group is a ceiling effect. Both groups improved substantially during the first 6 months and reached a high level of performance. This can be explained by spontaneous recovery, which occurs especially in the first months after stroke and makes it difficult to compare the effect of rehabilitation interventions (Langhorne et al., 2011; Nudo & McNeal, 2013). The patients in the delayed group reached a median FMA-UE score of 64/66, meaning that most of them only had minor impairment, and would not have been included in most CIMT studies because they were functioning fairly well. For example, the participants in the EXCITE trial had an FMA-UE score of 43 at inclusion (Wolf et al., 2006).

Goal attainment scaling might have been able to detect progress in the delayed group, but unfortunately it was only used to guide standard task practice and not as an outcome measure in paper 2. As the participants in the delayed group only had minor motor impairments and a high ADL score assessed by SIS, it seems likely that the chosen activities were mainly related to complex ADL activities and participation in social activities, for example related to hobbies or work. In contrast, the activities in the early intervention group were mostly less complex, basic ADL activities.

There is a possibility that the outcome measures used in our study were not able to detect an effect on complex activities. If the delayed treatment group did not feel any benefit of the treatment, a high drop-out rate would be probable because they most likely would not bother to train 3 hours a day for 2 weeks and follow a demanding protocol. However, drop-out rate and adherence were similar to the early intervention group. Probably the aims of most of the participants in the delayed group were related to complex activities, like playing an instrument, improving handwriting, knitting, hammering or advanced use of tools. As the effect of interventions seem to be mostly restricted to the functions and activities that were actually trained (Veerbeek et al., 2014), it is unlikely that we were able to detect any change with our outcome measures, which included mainly less complex tasks. Goal attainment scaling could have possibly revealed changes related to complex meaningful activities and attainment of discrete goals (Grant & Ponsford, 2014).

A recent study from Abdullahi (2018) suggests that CIMT interventions based on numbers of repetitions rather than number of hours spent in treatment could be used as an alternative CIMT protocol. However, measuring repetitions alone does not give a comprehensive picture unless combined with measuring the actual amount of time spent in repetitions. It is possible that repetitive training of tasks of short duration is less prone to fatigability and demands less rest between the performance of tasks. However, it will probably be at the expense of the participant's active participation. During treatment with a high number of repetitions, it is most likely harder to find tasks which are goal-directed and meaningful for the participant due to the short duration of the task. With a task duration of 12 sec or less as in the study from Birkenmeier et al. (2010), there is some risk that tasks are not practised in their natural context and not necessarily with real objects, which seems to be important for

motor learning and may influence transfer to ADL activities (Winstein & Kay, 2015). Repetition alone will probably be not enough to facilitate transfer to daily life.

CIMT is a complex intervention compared with repetitive training, mirror therapy and virtual reality training, which mainly target motor function. Compared to CIMT, these interventions have less focus on the participants' awareness of increasing use of the affected arm in real life situations. The behavioural and motivational aspects used in the transfer package help to increase awareness of using the arm and may also influence self-efficacy. Self-efficacy is important for both adherence and motor learning (Levin, 2016). The disadvantage of complex interventions may be that it is more difficult to achieve adherence to treatment (Bourbeau & Bartlett, 2008; Krekeler et al., 2018). On the other hand, as CIMT targets all levels of the ICF and intends to address self-efficacy, the potential for efficacy beyond improved motor function, such as transfer to ADL and increased participation, might be higher.

6.2.5 Grip strength during the first year after stroke

The main finding of paper 3, that most aspects of grip strength showed fast improvement during the first 6 months after stroke with less improvement later, are in line with general reported pattern of recovery after stroke (Langhorne et al., 2011). Only grip strength measured with a dynamometer, especially in the narrow positions, showed further progression between 6 and 12-month follow-up. Key grip strength in the affected hand was less impaired compared to three-jaw and tip-to-tip grip at baseline and was no longer significantly different from the non-affected side at 12-month follow-up. This finding might be explained by the less demanding mechanics of the key grip compared to the two other grips, which demand a higher degree of coordination between the fingers. All three types of grip are very important during ADL and may be crucial in holding small objects with high force, as required for example when holding a key while turning it in a lock.

In contrast to the study by Ada et al. (2003), we could not find evidence for position-dependent weakness in our sample in either of the phases after stroke. Possibly, position-dependent weakness applies to patients with more severe impairment or only to mono and biarticular muscles which pass one or two joints as in most elbow muscles and not to hand muscles which span several joints.

In our study, RFD was considerably decreased early after stroke, while RFD approached values of the non-affected side after 6 months. These findings might be especially relevant for task training if CIMT is applied early after stroke. Specific training of RFD during this phase might help to improve the efficacy of early applied CIMT. Many ADL activities, such as opening a jar or hammering, demand a rapid change in force. As DeJong et al. (2012) have shown, stroke patients were able to move faster if they were asked to do so and increased velocity during reaching and grasping as well as QOM. On the other hand, we do not know if and how this possible positive effect of the instruction will increase fatigability and the need for rest in the affected hand, especially early after stroke.

6.2.6 The relevance of grip strength and adherence for CIMT

Neither maximal grip strength nor other aspects of grip strength are usually explicitly part of CIMT protocols (Morris et al., 2006; Nijland et al., 2013), the main focus is on task-specific training. However, persons with stroke will probably often work close to their maximum grip strength during ADL activities and some activities will in addition demand rapid increase and adaptation of grip strength, for example cutting hard vegetables. Such activities could easily be included in standard task training, during shaping exercises, as well as during home exercise. Especially if the participants' goals are dependent on rapid force production and/or sustaining grip strength, the tasks or activities should be trained in a progressive manner with velocity (RFD) or fatigability as the progression parameter, with the intention of increasing the participant's performance during ADL. The results of paper 3 indicate that this might be especially important early after stroke.

Information from the time-force curve about sustained grip strength could probably be used to adapt treatment intensity. People who do not show any substantial drop in the normalized sustained force curve might be less prone to fatigability and will probably have less need for rest during task training. In contrast, people with marked initial decline in the sustained grip force might need more rest during task training or benefit from task training that does not demand close to maximal grip strength. Values from the force-time curve might be an additional objective measure useful for adapting treatment intensity together with subjectively rated perceived exertion in the Borg Scale. This might especially apply to shaping exercises demanding prolonged gripping or standard practice tasks like carrying heavy objects in the affected hand. Furthermore, it might be beneficial to ask the participant

about subjectively perceived exertion during each shaping set of shaping tasks and not at the end of the shaping session, because the degree of muscular fatigability will depend on the type of task.

The finding that progression parameters are positively associated with adherence to the treatment (paper 1) indicates that the perception of progress during CIMT is motivating. Progression parameters could be used more explicitly to fine-tune treatment progression with the intention of increasing participants' motivation.

7 Conclusions

The overall aim of this thesis was to increase knowledge about aspects that are important in intensive treatment of upper limb function in the first year after stroke by addressing adherence to and efficacy of CIMT as well as the development of grip strength.

Our study confirmed that overall adherence to CIMT applied early after stroke is fairly good, and persons with stroke are able to adhere to 3 hours intensive CIMT training. However, time spent in task-oriented training as well as the time exclusively spent in activity during the task training sessions, i.e. pure activity, was reduced, indicating the participants' need for rest. The findings in paper 1 showed that reporting adherence to a treatment protocol is important to better understand the content of interventions. Knowing what actually has been done during the intervention period will also be important when comparing interventions.

Furthermore, CIMT applied in the early sub-acute phase after stroke was more effective than standard care to improve motor function, dexterity and functional independence after the early intervention period. However, the differences between the groups were no longer significant after 6 months. Both groups recovered considerably during the first 6 months and the lack of effect in the delayed group is most likely explained by a ceiling effect.

Finally, the results of the grip strength assessment showed that not only grip strength was reduced during the first weeks after stroke, but also the ability to generate force rapidly and to sustain maximum grip strength over 12 sec, the latter indicating increased fatigability in the affected hand. However, all components of grip strength in the affected hand approached the values of the non-affected hand at 6 months, with little further progress during the 1-year follow-up.

Decreased adherence to task practice and decreased time spent in pure activity as well as the substantially increased fatigability in hand and finger muscles indicate that the participants early after stroke have increased need for rest during intensive training, which might have a potential influence on the efficacy of the treatment.

8 Future research

Investigating and reporting adherence is important to compare interventions and may contribute to explain the efficacy or inefficacy of treatments. This might be especially important in complex interventions with long daily treatment duration. Future studies should provide information about how the treatment protocol is realized in clinical practice. The assessment of training intensity should include duration, number of repetitions and how vigorous the training is, objectively and/or perceived by the participant, to get a comprehensive understanding of a treatment. Furthermore, we need to know more about the patients' need for rest and how it is related to aspects of the treatment such as intensity and complexity as well as patients' characteristics such as phase after stroke, functional level, fatigability and demographic factors. Together, this might provide more specific knowledge about how to increase adherence and to provide optimal treatment for persons in different phases after stroke.

More research is necessary to increase knowledge about the long-term efficacy of CIMT, how the treatment is best adapted to the individual needs of the participants and for which patients it is most effective. Future studies could investigate if machine learning approaches could be used to classify type of tasks and activities, as well as their intensity and duration by interpreting accelerometer data from wearable sensors. This would also make it possible to examine the amount of rest during the treatment and how this may be associated with stroke severity and background variables such as age or time since stroke, as well as progression during the rehabilitation process. The results from such research have the potential to provide a comprehensive picture of the participants' adherence and to adapt the treatment in accordance with the participants' needs. Future research should also examine if CIMT could be supplemented with training apps, which in combination with accelerometery might follow up the participants' training at home, how this could influence motivation and adherence, and increase communication with peers and health care providers.

The potential importance of RFD and sustained grip strength as progression parameters during shaping exercises should be further investigated in future studies. Furthermore, it should be evaluated if sustained force curve measurements could be used in clinical practice to guide CIMT interventions regarding the need for rest, i.e. if people with a marked

decrease in sustained force would benefit from longer rest periods, while people with close to normal sustained force curve measurements might need less rest.

9 Clinical implications of the findings

- CIMT can be implemented in rehabilitation early after stroke. However, the need for rest during CIMT early after stroke should be taken into account and treatment intensity should be adapted. It seems to be important to ensure that rest periods are included between the repetition of shaping tasks.
- Sustained grip strength measurement may give an indication of the fatigability of a patient and may help to adapt treatment intensity during CIMT.
- Especially if CIMT is applied early after stroke, less intensive treatment periods might be needed to enhance adherence to task training and to increase time spent in pure activity and thereby the efficacy of the treatment.
- Older participants may probably benefit from treatment of shorter duration or lower intensity.
- Feedback about progression should be used more explicitly to increase motivation and thereby adherence during task-oriented training.
- Tasks demanding maximum grip strength, as well as tasks that focus on gripping rapidly and/or on maintaining a high level of strength should be more intentionally included as part of task training in CIMT. These different aspects of grip strength could be used to guide treatment progression during shaping exercises.

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Paper 1

J Rehabil Med 2015; 47: 816–823

ORIGINAL REPORT

NORWEGIAN CONSTRAINT-INDUCED THERAPY MULTISITE TRIAL: ADHERENCE TO TREATMENT PROTOCOL APPLIED EARLY AFTER STROKE

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Objective: **To investigate to what degree patients adhered to a modified constraint-induced movement therapy protocol, and to explore factors associated with the results.**
Design: **Prospective follow-up of the intervention arm in a randomized controlled trial.**
Subjects: **Twenty-four patients within 28 days after stroke.**
Methods: **The protocol specified 180 min of treatment/day for 10 days. Therapy schedules were used to calculate the time spent in shaping, task practice and transfer package, as well as movement quality, perceived exertion and treatment progression.**
Results: **The participants spent a mean of 91.3% of the intended time for treatment. Time spent practicing tasks was 30 min less than the intended 150 min, whereas slightly more time than intended was spent on the transfer package. Of the time spent in shaping, 33% was spent in pure activity. The remainder was used on feedback, task set-up, and rests. Adherence was positively associated with treatment progression (r=0.74) and negatively associated with age (r=–0.65). Women were less likely to use the mitt (r=–0.55).**
Conclusion: **Overall adherence was good; however, time spent in motor activity was only one-third of total treatment time. The parameters in the constraint-induced movement therapy protocol should be individually adjusted early after stroke.**

Key words: stroke; constraint-induced movement therapy; adherence; rehabilitation.

J Rehabil Med 2015; 47: 816–823

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Accepted May 20, 2015; Epub ahead of print Aug 24, 2015

INTRODUCTION

During the last 20 years, constraint-induced movement therapy (CIMT) has evolved as a treatment aiming to improve upper-limb function in patients after a stroke (1). The feasibility of the high-intensity treatment has been questioned by patients and therapists (2–5). Although several meta-analyses (6–9) have found evidence that CIMT applied during the chronic phase is effective, the effect in the early phase after stroke is uncertain (10), and there is limited information about adherence to the treatment (11, 12).

The standard protocol, developed by Taub (1), defines CIMT as 6 h/day of task-specific training during 10 consecutive work-days, and wearing a constraint on the less impaired upper extremity for 90% of waking hours. The protocol distinguishes between adaptive task practice (shaping) and standard task practice (13, 14). An additional component, the transfer package, was added later to transfer activities learned in the therapy to daily life at home (14–17). Adherence to the treatment protocol has been assessed in a sample of patients from the Extremity Constraint Induced Therapy Evaluation (EXCITE) study. The results showed that patients attended a daily supervised therapy session for 6.4 h, but spent only 4 h practising. The training included both shaping and standard task practices of equal duration; however, the investigators did not provide further information (11, 12).

Many modified versions of the treatment (mCIMT) have been developed. These vary in training intensity, the use of constraints, and/or other aspects of the standard protocol (18–27); however, only a few studies have assessed the effect of mCIMT in the early phase after stroke (18, 19, 21, 22, 24). The different results in the trials lead to an uncertainty with regard to the effect of mCIMT in the early phase (10). To better understand the variations in the results and to assess the feasibility of mCIMT applied early after stroke, adherence to the treatment protocol, and the intensity of training (e.g. the amount of pure activity) should be thoroughly assessed. It is also possible that certain baseline characteristics, such as age or sex, can contribute to the understanding of adherence.

The results from the Norwegian constraint-induced therapy multisite trial (NORCIMT) were published recently. The NORCIMT study assessed the effect of a modified CIMT protocol for patients in the early phase, i.e. less than 28 days after stroke. The intervention showed a beneficial effect on arm motor activity and dexterity immediately after the intervention, which was no longer significant after 6 months (28).

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More knowledge about the adherence to the treatment protocol applied in this study will probably give a better understanding of the temporary effect.

The primary aim of the present study was to investigate to what degree the patients included in the intervention group of the NORCIMT study adhered to the treatment protocol. The secondary aims were to investigate: (*i*) the associations between treatment time variables and perceived exertion after the training sessions, treatment progression, and quality of movement (QOM); and (*ii*) whether patients' age, sex, time since stroke, or motor function influenced adherence to components in the protocol.

METHODS

Design overview

This prospective study assessed patient adherence to the treatment applied in the intervention group of the NORCIMT trial. Details about this single-blinded, multi-centre, randomized controlled trial have been reported previously (28).

Setting and participants

The participants were recruited from 5 Norwegian hospitals: the University Hospital of North Norway, Trondheim University Hospital, Oslo University Hospital, Vestfold Hospital, and Telemark Hospital. Inclusion criteria were: stroke more than 5 days and less than 26 days before enrolment, less than 28 days since stroke at the start of the treatment, either first stroke or second stroke without detectable arm weakness after the first stroke, modified Rankin Scale 0–2 points before admission, persistent unilateral arm or hand paresis (Scandinavian Stroke Scale arm motor function 2–5 points or hand motor function 2–4 points), the ability to lift 2 fingers with the forearm pronated on the table or to extend the wrist at least 10° from fully flexed position, Mini-Mental State Examination score of more than 20 points (or more than 16 points in combination with expressive aphasia), and ability and willingness to sign informed consent. Exclusion criteria were modified Rankin Scale more than 4 points, large hemi-spatial neglect (more than 2 cm on the Line Bisection Test), life expectancy less than 1 year due to other illnesses (e.g. cardiac, malignancy), prior injury or condition in the affected upper extremity that limited use before the stroke, and other neurological conditions affecting motor function. The North Norway Regional Committee of Medical Ethics and the Commission of Privacy Rights at the University Hospital of North Norway reviewed and approved the study (REK NORD 39/2008).

Intervention

The participants who were randomly assigned to the intervention group underwent a modified CIMT programme within 28 days post-stroke. Patients received treatment in 4 rehabilitation centres. In this study, the training records of the patients assigned to the modified CIMT group were used to evaluate patient adherence to the treatment protocol, which was based on the protocol described by Morris et al. (14, 29). Table I summarizes the different treatment components and the adjustments made for the NORCIMT trial. The patients took part in a daily 3 h programme over 10 consecutive working days. Up to 150 min of the treatment was allocated to task training, i.e. shaping (120 min) and standard task practice (30 min). Shaping tasks were characterized by short duration, high number of repetitions, systematic feedback on performance, and successively increasing task difficulty. At least 6 shaping tasks, each consisting of 10 repetitions, were conducted each day. Unlike in the original protocol (14), the therapists were allowed to introduce new exercises if an appropriate exercise could not be found in the bank of shaping tasks. The selected tasks had to be challenging, and, where possible, the difficulty of the shaping tasks was adjusted to a score of 3 (movements were slow or were only made with some effort) on the shaping QOM scale (29). The intended time for standard task practice (more continuously performed activities of longer duration with less frequent feedback, such as writing, ironing clothes, playing the piano, etc.) was 30 min. As part of the transfer package and treatment planning, patients' usual daily activity patterns were assessed to obtain an overview of daily living activities, interests, hobbies, and habits. We used Goal Attainment Scaling (GAS) to encourage patients to formulate 3 goals related to daily activities (30). The goals set during this procedure formed the basis for choosing activities during task practice and home skill assignment.

In addition, a modified version of the behavioural contract was developed and named "Agreement to participation in treatment". The contract included a list of activities with and without use of a constraining mitt (up to 90% of waking hours). The daily application of the other parts of the transfer package, i.e. Motor Activity Log, home diary, home skill assignment, and daily schedule, was performed according to the principles of Morris et al. (14). The therapists responsible for the intervention attended a 4-day training programme to familiarize themselves with the study procedures.

Measure of adherence

The therapist in charge of the CIMT therapy recorded the starting and stopping time of each shaping/standard task practice session and other

Table I. *Components of constraint-induced movement therapy used in the Norwegian constraint-induced therapy multisite trial (NORCIMT) and modifications from the protocol described by Morris et al. (14)*

Component	Modifications in NORCIMT	Intended duration in NORCIMT
Task practice		150 min
Shaping	At least 6 shaping tasks per session. New shaping tasks adjusted to functional level allowed. Preferred level of difficulty (quality of movement = 3)	120 min
Standard task practice	Goal Attainment Scaling was the basis for choosing tasks	30 min
Transfer package		30 min in treatment setting
Motor Activity Log	All 30 questions on the first and last day, alternating 15 questions on the other days	
Home diary	None	
Behavioural contract	Shorter text, less formal	
Home skill assignment/ home practice	None	30 min outside the treatment setting
Daily schedule	None	
Constraint		
Mitt restraint	No fingers with firm plastic material on the volar side. One size fits both right and left hands	90% of 16 waking h (14.4 h or 864 min)

treatment components in the daily schedules and used the values to calculate the duration of total treatment time and time spent in shaping exercises, standard task practice, transfer package, and other activities. Longer systematic rest breaks and other activities not directly related to the treatment were excluded from the calculation of total treatment time. For each shaping task, a journal was created that specified the QOM, number of trials, and duration (in s) of each trial. Based on this information, pure shaping activity time (time spent exclusively on activity without rest, feedback, documentation, and set-up) was calculated. The QOM was rated by the therapists, in 0.25 intervals from 0 (no movement) to 5 (normal movement) (29). Task set-up, such as the placement and types of objects used, was recorded in the shaping journal. To facilitate feedback on treatment performance, feedback parameters (e.g. performance time, number of repetitions during a specified time, or reaching distance) was chosen for each set of shaping tasks. After repetition of each task, patients immediately received feedback on their performance. The results were recorded in the shaping journal. Progression parameters were applied, i.e. if performance had increased during the last 5 tasks compared with the preceding 5 tasks, difficulty level was increased. When choosing progression parameters, only one aspect (placement, size, weight, or form of a manipulated object) of the task set-up could be changed. The patients recorded the time spent each day on the home skill assignment, using a separate form. Deviations from mitt use during the treatment were recorded, and the home diary was used to calculate the self-reported mitt use outside the therapy setting. Both home skill assignments and the home diary were reviewed jointly by the therapist and the patient each day to strengthen the accuracy of reporting. When the type of activities during home skill assignments, but not the duration, was recorded by the patient, the time was estimated based on the expected minimum number of minutes to carry out the activity. The Borg Scale (31) was used to record perceived exertion after the shaping activities (score 6–20), with a higher score indicating a higher degree of exertion.

Patient characteristics

Age, sex, time since stroke, and the Fugl-Meyer Motor Assessment Score (FMA) were recorded prior to treatment. The FMA measured motor function of the upper extremity (score 0–66), with a higher score indicating better motor function (32).

Statistical analysis

Normally distributed data were presented as mean and standard deviation; non-normally distributed data as median and interquartile range; categorical variables as proportions and percentage. The Shapiro–Wilk test was used to test normality for all treatment variables. Change in treatment duration between days was assessed using paired t-test. To analyse the associations between treatment time variables and patient characteristics as well as treatment parameters, several linear regression analyses were performed with the mean value of total treatment time as well as individual treatment time components, time spent in home exercise, and mitt use as dependent variables. The independent variables that were possibly related to treatment time variables were patient characteristics (age, sex, days post-stroke, and FMA upper extremity score), and treatment parameters (Borg Scale, QOM score, and progression parameters). The association between these variables and the dependent variables were first examined using correlation analyses. Next, for each dependent variable age and sex, as well as possible associations with p-values <0.1 were included in a linear stepwise multiple regression model. Because of the small sample size, a maximum of 3 independent variables could be included in the model at the same time, and predictors were entered into the model using the forward method. The variable with the lowest p-value was entered first. The next variables were entered singly; only variables with a p-value below 0.05 were included in the final model. Variance inflation factor was used to examine multi-collinearity (a value ≤ 10 was regarded as acceptable) of the independent variables. The residuals were examined to check the model assumptions. SPSS for Windows, version 18, was used to perform all analyses. The level of significance was set at $p \leq 0.05$.

RESULTS

The characteristics of the 24 included patients are shown in Table II. Time from onset of stroke to commencement of treatment ranged from 7 to 32 days, with one patient exceeding the 28 days prescribed in the inclusion criteria. The results for the FMA score of the upper extremity ranged from 21 to 62 points.

Completed treatment sessions

In total, 2 patients withdrew from the study: one on the second day of treatment and another after 8 days (Fig. 1). The data from the first patient were excluded from further analysis, because the patient withdrew before all parts of the treatment were introduced. This patient expressed frustration with the complexity and intensity of the treatment. The second patient withdrew for unknown reasons. Two patients finished their treatment early (1 and 3 days) due to public holidays. Another patient dropped out for 1 treatment day for unknown reasons. These 3 patients missed 5 treatment days in total. When combined with the 12 days from the patients who withdrew, a total of 223 possible treatment days were included, which corresponded to 92.9% (223/240) of the possible sessions completed (the data were based on participating patients, varying from 20 to 23 during the 10 treatment days). Additional missing values from these possible sessions for the other parts of the treatment were 4.5% for the QOM scale, 2.7% for the Borg Scale, 2.4% for mitt use, and 7.3% for home skill assignment. Three patients reported only which home exercises they performed, without specifying how much time they spent on the exercises each day.

Duration of the constraint-induced movement therapy treatment

Fig. 2 illustrates the duration of the different CIMT activities as a percentage of 180 min treatment time during the course of the 10 treatment days. The mean daily treatment time was 164.4 min (SD 18.8) or 91.3% of the intended 3 h total treatment time. The range of daily treatment time was 131–186 min. Total daily treatment time did not change significantly ($p = 0.08$) from the first to the last treatment day. The patients spent 82.2% (mean 98.6 min; SD 15.8 min) of the intended

Table II. *Participant characteristics (*n = *24)*

Characteristics	
Age, years, mean (SD)	65.3 (8.0)
Female, *n* (%)	5 (21)
Ischaemic stroke, *n* (%)	23 (96)
Right hand affected, *n* (%)	10 (42)
Dominant hand affected, *n* (%)	16 (67)
Fugl-Meyer Motor Assessment Score upper extremity, median [IQR]	53.5 [43–59]
Days since stroke, mean (SD)	16.6 (7.2)

SD: standard deviation; IQR: interquartile range.

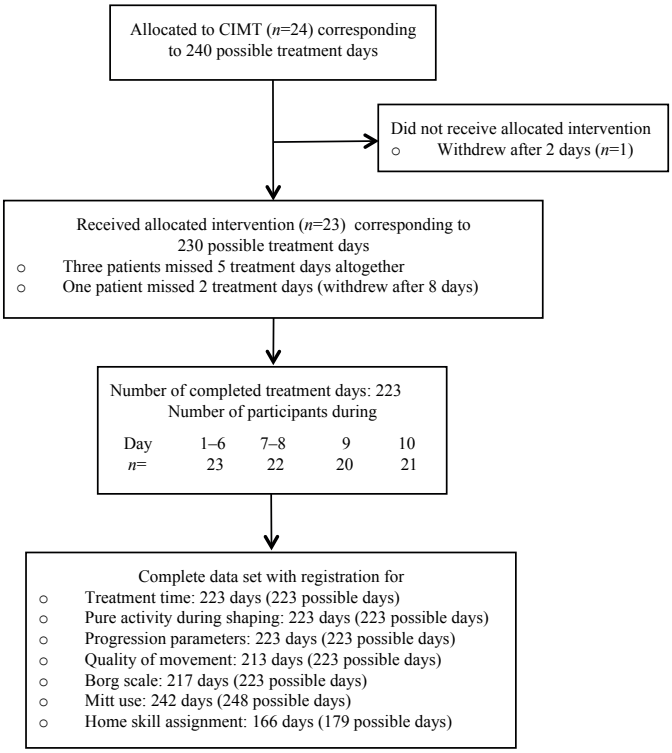

Fig. 1. Completed treatment sessions and missing treatment component and parameter values. Mitt use: 12 days (including weekend), last day excluded because no mitt use after treatment session. Home skill assignment: 8 days (day 2–9).

time in shaping activities (120 min intended), 77.3% (mean 23.3 min; SD 11.3 min) in standard task training (30 min intended), and 120.3% (mean 36.1 min; SD 13.0 min) on the transfer package (30 min intended). A mean of 6.4 min (SD 9.5) were spent on activities such as administration of GAS and the Borg Scale. More minutes were devoted to the transfer package during the first treatment day (mean 55.7 min; SD 16.6 min; $p < 0.001$) and last treatment day (mean 41.4 min; SD 11.0 min; $p < 0.001$) compared with days 2–9 (mean 32.9 min; SD 6.8 min).

Details of treatment parameters during the 10 treatment days are presented in Fig. 3. Mean Borg score was 13.5 (SD 1.6). Mean mitt use was 12.1 h/day (SD 2.4 h), which made up 75.6% of waking hours. During the treatment days, the patients wore the mitt for 13.0 h/day (81.3% of waking hours), and 8.4 h/day (52.5% of waking hours) during the weekend. Mean mitt use for women was 10.7 h/day (SD 1.9 h), compared with 13.7 h/day for men (SD 2.0 h). One patient was unable to use the mitt during the last 6 days because of eczema. A mean of 32.5 min (SD 8.4 min) were spent on pure activity during shaping, which comprised 33.0% of the total time spent in shaping. Time spent exclusively in motor activity, i.e. pure shaping activity and continuously performed standard task practice, was 55.8 min of 180 intended min (34% of total treatment time). The mean QOM score during the treatment period was 3.4 (SD 0.6), and the mean number of progression parameters changed per day was 1.6 (SD 1.6). The median time spent on home exercise was 39.0 min (interquartile range (IQR) 22–72), ranging from 12 to 155 min.

Regression analyses

In the correlation analyses, the following relationships were noted ($p < 0.1$), with 1 of the treatment time variables: age was negatively associated with standard task practice ($r = –0.65$; $p < 0.001$); female sex was positively associated with transfer package ($r = 0.42$; $p = 0.047$) and negatively with mitt use ($r = –0.55$; $p = 0.007$); FMA was negatively associated with total treatment time ($r = –0.40$; $p = 0.057$) and transfer package ($r = –0.45$; $p = 0.03$); QOM ($r = –0.47$; $p = 0.023$) was negatively associated with total treatment time; and number progression parameters changed per day was positively associated with total treatment time ($r = 0.74$; $p < 0.001$), shaping time ($r = 0.41$; $p = 0.049$), and transfer package ($r = 0.52$; $p = 0.011$). The results of multiple regression analyses are shown in Table III. Treatment time was positively associated with treatment progression and negatively associated with age, and women were less likely to use the mitt. The models explain 13–52% of the variability in the dependent variables.

DISCUSSION

The main finding from the present study was that patients who attended a 3-h CIMT programme within 4 weeks of stroke tended to have a high adherence rate with only some deviations from the treatment protocol. Notably, only about one-third of the treatment time was spent exclusively in motor activity. Furthermore, older age was associated with less time spent in standard task practice. While women spent significantly less time using the mitt than men, they spent significantly more time on transfer package. Treatment progression was positively associated with total treatment time.

Adherence to shaping

A surprising finding was that pure activity during shaping was only 33% of total shaping time. However, the EXCITE trial also acknowledged that their estimate of daily practice time was inflated, because they included non-practice components such as set-up, feedback and brief rests (11). We do not know if the results in our study reflect the nature of shaping, or if

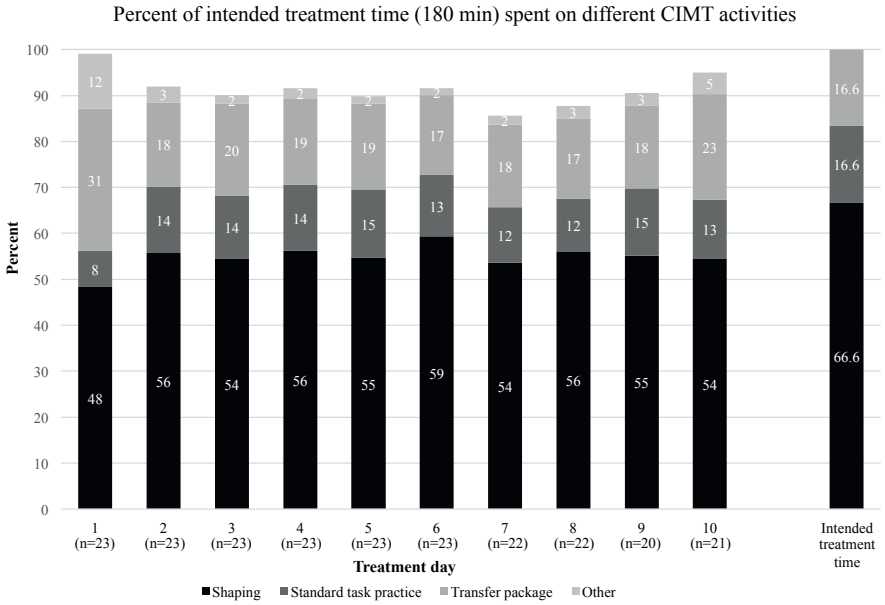

Fig. 2. Duration of the different treatment components as a percentage of the total intended treatment time during the 10 treatment days. Shaping: including rest, feedback, documentation, rearrangement of task set-up. Standard task practice: continuously performed tasks related to patients' goals. Transfer package: Motor Activity Log, behavioural contract, home diary, and home exercises. Other: administration of the Goal Attainment Scale (mainly days 1 and 10) and the Borg Scale (all days).

the low values are due to the fact that patients need more rest early after stroke than in the chronic phase (11).

The high variation in the patients' pure activity may indicate that some patients did not tolerate the training intensity well. Birkenmeier et al. (33) showed that subjects with chronic stroke were able to achieve more than 300 repetitions (3 tasks × 100 repetitions) during a 1-h session with high repetition training. The duration of treatment was 78% of the scheduled time. Although this initially seems more efficient than our study's reports of pure activity during shaping, different methods of calculating activity during training make it difficult to compare pure activity during shaping in our study with Birkenmeier's reports of activity during high-repetitive training. Nevertheless, it is reasonable to assume that the chronic patients in the high-repetitive training had a higher amount of pure activity and more repetitions compared with the shaping part of our treatment. On the other hand, our patients were encouraged to improve their performance and work as hard as they could during each set of shaping tasks. The high intensity of each set of tasks may have increased the need for rests between the 60–70 sets of shaping tasks, usually consisting of several repetitions. The mean change of 1.6 progression parameters per day, the successive improvements in QOM during the course of the treatment, and the simultaneously stable Borg values measured after shaping exercises reflect the progressive and demanding nature of our tasks.

It is possible that a more distributed application of CIMT (e.g. fewer hours of training per day over a longer period (18) or splitting up the training into 2–3 sessions per day interspersed

Table III. *Final models of multiple regression analyses for predicting treatment time (min)*

	Total treatment time Beta (95% CI)	Shaping Beta (95% CI)	Standard task practice Beta (95% CI)	Transfer package Beta (95% CI)	Mitt use Beta (95% CI)
Demographics					
Age (years)	ns	ns	–0.6 (–0.96 to –0.30)	ns	ns
Sex (female)	ns	ns	ns	6.7 (0.97–12.5)	–178.2 (–301.8 to –54.6)
Treatment parameters					
Progression parameter	12.4 (7.2–17.5)	4.0 (0.01–8.0)	ns	4.6 (1.46–7.74)	ns
Adjusted R-squared	0.52	0.13	0.40	0.38	0.27

Beta: linear regression coefficient; CI: confidence interval; ns: non-significant. Home exercises showed no significant associations with any of the independent variables and therefore were not included in the table.

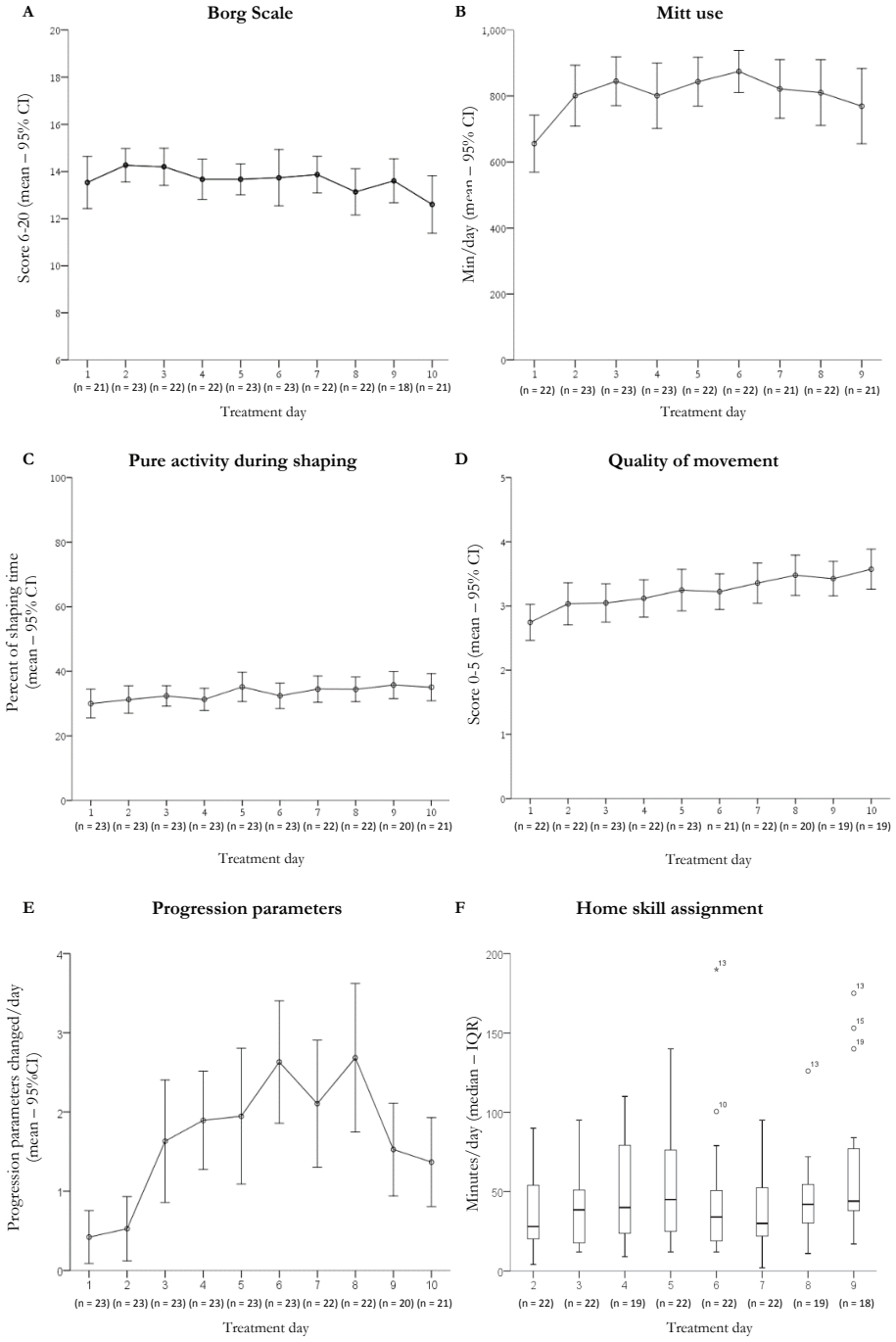

Fig. 3. Details of the different treatment components and parameters during the 10 treatment days. Graphs A–E show means per group and error bars of 95% confidence intervals plotted with connecting lines for Borg Scale, mitt use, pure activity during shaping, Quality of Movement Scale, and progression parameter. Graph F shows median and lower/upper quartiles of home exercise. Symbols: °outlier more than 1.5 × interquartile range; *outlier more than 3 × interquartile range.

with longer rest periods) could increase the pure activity time and might be a more effective therapy.

Other aspects of adherence

The number of withdrawals from our study seems to be comparable to studies in both the chronic (34) and the early phase after stroke (19, 22). As other comparable studies (11, 12) did not provide information about all included patients, this makes it difficult to compare data about completed treatment sessions. In contrast to our study, the EXCITE trial reported that patients spent more than the intended time in treatment; however, since they included activities not related to the treatment, accurate comparison is difficult. Regarding mitt use, another study conducted in patients early after stroke (mean 38 days) reported that a constraint was used during nearly 90% of waking hours, as intended (22). A possible explanation for our lower compliance might be that patients in our study began training earlier after stroke. A possible explanation of the hitherto unobserved sex difference in mitt use could be that women spend more time in bimanual housekeeping activities and removed the mitt during these activities. One patient withdrew from our study due to frustration with the treatment. Myint et al. (22) also reported that patients withdrew from their study owing to frustration with using the mitt. Some patients may consider the strict protocol involving mitt use, treatment contract, and home exercise assignments to be "too constraining". Surveys (2, 4) have confirmed patients' concerns about mitt use and treatment intensity. Providing detailed information to patients before treatment initiation about the demanding nature of the treatment seems to be crucial to avoid unnecessary frustration and withdrawal.

There was considerable variation among participants with regard to the total task practice time. However, the variability may not be due to the fact that our patients were training early after stroke; the EXCITE trial also reported considerable variations in daily training times in the sub-acute and chronic post-stroke phases (11).

Clinical implications of age and treatment progression

The negative association between standard task practice and age may indicate that older patients need more time for shaping exercises and have less time left for the subsequent standard task practice. The results imply that older patients may benefit more from shorter training durations. The positive association between total treatment time and the number of progression parameters changed per day could be explained by the perception of success and motivational aspects. Progression parameters make treatment progression more obvious and more explicit than verbal feedback alone. Giving feedback on treatment progression and structuring the training so that progression will be more obvious to both patient and therapist may help increase patient motivation and adherence to CIMT training.

Study limitations and strengths

Although we believe our sample was sufficient to highlight the important features of CIMT, a larger sample would permit wider generalization of the results. Another limitation of our study is that several parts of the transfer package were based on self-reported data and may have been swayed by over-reporting. The Borg Scale is frequently used to measure perceived exertion, especially in relation to strength and endurance training; however, there is some doubt as to whether it accurately captures exertion during high-intensity exercise after stroke (35). Additional information about the patients' subjective experiences with the treatment would have strengthened our results. The study setting required some additional time spent on data registration to be able to give a detailed description of the therapy; however, our impression is that this additional registration did not appreciably bias the registered treatment times. On the contrary, we consider the thorough description of all details and the inclusion of all patients treated with CIMT in an early post-stroke setting to be a strong point for this study. Another important point of the present study is the accurate recording of the time spent in pure activity. Typically, information about the intensity of training in CIMT studies is the intended treatment time, and only 2 studies have reported the actual duration of the treatment (11, 12).

Conclusion

This study showed good overall adherence to a modified CIMT programme; however, the time spent in task practice was less than intended. Pure activity time comprised only one-third of the intended total treatment time. Future CIMT research should focus on which organization or structuring of training yields the best adherence and functional benefit. In particular, the impact of shaping vs standard task practice and the role of the transfer package should be further investigated. Lastly, consideration should be given to whether treatment protocols should be modified according to patients' age, sex, and stage after stroke. In addition, the impact of adherence and motivation on outcome should be further investigated.

ACKNOWLEDGEMENTS

The authors would like to thank all the co-workers who contributed to this trial: Bent Indredavik for giving critical advice on planning and designing the study; Martin Vatshaug for collating the data for the study and for being responsible for ensuring the quality of data; all therapists and other hospital staff for taking part in providing the treatment, recruitment, and baseline examinations; and all the patients who participated in the study. The study was supported by the Northern Norway Regional Health Authority. The funding sources had no influence on the analysis.

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Paper 2

Received: 30 January 2017 | Revised: 26 March 2017 | Accepted: 6 May 2017

DOI: 10.1002/pri.1689

WILEY

RESEARCH ARTICLE

Early versus late-applied constraint-induced movement therapy: A multisite, randomized controlled trial with a 12-month follow-up

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Funding information
Northern Norway Regional Health Authority, Grant/Award Number: SAT 544-06; Landsforening for Slagrammede

Abstract

Background and Purpose: A direct comparison between the effects of constraint-induced movement therapy (CIMT) applied early after stroke and that of CIMT applied in the chronic phase has not been conducted. This study aimed to compare the long-term effects of CIMT applied 6 months after stroke with the results of CIMT applied within 28 days post-stroke.

Methods: This study was a single-blinded, multicentre, randomized controlled trial with a crossover design. Forty-seven patients received CIMT either early (within 28 days) or 6 months after stroke. Both groups received standard rehabilitation and were tested at 5 time points. The primary outcome measure was Wolf Motor Function Test (WMFT); the secondary measures were Nine-Hole Peg Test (NHPT), the Fugl-Meyer Assessment (FMA) of the upper extremity, Stroke Impact Scale, and Modified Rankin Scale (MRS).

Results: Compared with baseline data, both groups showed significant improvements in the primary and secondary outcome measures after 12 months. No significant differences between the 2 treatment groups were found before and after the delayed intervention group received CIMT at 6 months and during the 12-month follow-up. Both groups recovered considerably and showed only minor impairment (median FMA score of 64) after 6 months. The early intervention group showed an initially faster recovery curve of WMFT, NHPT, and MRS scores.

Discussion: In contrast to most CIMT studies, our study could not find an effect of CIMT applied 6 months after stroke. Our results indicate that commencing CIMT early is as good as delayed intervention in the long term, specifically in this group of patients who might have reached a ceiling effect during the first 6 months after stroke. Nevertheless, the early CIMT intervention group showed a faster recovery curve than the delayed intervention group, which can be a clinically important finding for patients in the acute phase.

KEYWORDS

physiotherapy, rehabilitation services, stroke, upper limb function

1 | INTRODUCTION

Constraint-induced movement therapy (CIMT) has been developed to improve arm motor function in patients with stroke. Several meta-analyses have shown that CIMT applied in the subacute and chronic phases is beneficial in the short term; however, conflicting evidence for the long-term effect exists, and information on the optimal dose of CIMT and time to start is limited (Corbetta, Sirtori, Castellini, Moja, & Gatti, 2015; Etoom et al., 2016; Fleet, Page, MacKay-Lyons, & Boe, 2014; Hatem et al., 2016; Kwakkel, Veerbeek, van Wegen, & Wolf, 2015; Thrane, Friborg, Anke, & Indredavik, 2014).

Evidence from animal research suggests that the greatest gains in recovery occur during the first weeks after a stroke (Murphy & Corbett, 2009). This time-limited window of neuroplasticity also applies to humans (Verheyden et al., 2008) and could be a basis for starting CIMT early after stroke (Kwakkel et al., 2015).

A number of randomized controlled trials have investigated the effect of CIMT applied in the early phase after stroke (≤45 days; Boake

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et al., 2007; Dromerick et al., 2009; Kwakkel et al., 2016; Page, Levine, & Leonard, 2005; Singh & Pradhan, 2013; Thrane et al., 2015; Yoon et al., 2014). A recent systematic review showed a trend towards a positive effect for early applied CIMT (Etoom et al., 2016). However, none of these studies followed the participants for >6 months (Etoom et al., 2016). One of the included studies, the Norwegian constraint-induced therapy multisite trial (NORCIMT), was conducted to assess the effect of CIMT applied at 7–28 days after stroke (Thrane et al., 2015). Compared with patients receiving standard rehabilitation, the patients who received CIMT early showed a significantly improved motor capacity at the end of the intervention; however, this difference was no longer significant at the 6-month follow-up (Thrane et al., 2015). Kwakkel et al. (2016) also confirmed this improvement in motor capacity at the end of the intervention and lack of long-term effect in early applied CIMT. The results from both trials indicate that CIMT applied in the early phase may result in faster recovery; however, the standard rehabilitation group also reached a high level of motor capacity at 6 months post-stroke. Moreover, the Extremity Constraint-Induced Therapy Evaluation (EXCITE) trial, the largest randomized controlled trial (with 222 participants) on CIMT in the subacute and chronic phases after stroke, showed clinically relevant improvements in arm motor capacity that persisted for at least 1 year (Wolf et al., 2006). Thus, it would also be of interest to investigate whether further improvements will occur if CIMT was administered to patients who received standard rehabilitation initially.

In the NORCIMT study, patients who were randomized to standard care in the early phase were offered CIMT at the 6-month follow-up. This study is part of the NORCIMT study, and the main aim was to compare the long-term effects of CIMT applied in the chronic phase, that is, 6 months after stroke with those of CIMT applied in the early phase, that is, within 28 days post-stroke. The secondary aims were to evaluate the short-term effects of CIMT applied in the chronic phase and to compare the time course of early versus late-applied CIMT.

2 | METHODS

2.1 | Study design and participants

This study was a single-blinded, multicentre, randomized controlled crossover trial. The participants were recruited from five Norwegian hospitals: University Hospital of North Norway, Trondheim University Hospital, Oslo University Hospital, Vestfold Hospital, and Telemark Hospital. The inclusion criteria were as follows: diagnosis of stroke, persistent unilateral arm or hand paresis within 5–26 days after stroke, and modified Rankin Scale (MRS) score between 0 and 2 prior to stroke. Furthermore, a Mini-Mental State Examination score of >20, ability to extend two fingers or the wrist, and ability to follow a two-step command were also required. The exclusion criteria included MRS > 4 after stroke, large hemispatial neglect, life expectancy of <1 year due to other illness, injury in the affected upper limb prior to stroke, and other conditions affecting motor function. All participants signed a written informed consent.

Using a computer-generated block scheme for randomization, we randomized the participants either to the early intervention group (CIMT within 28 days post-stroke) or to the delayed intervention group (CIMT at 6 months after stroke).

This study was approved by the Regional Committee of Medical Ethics and the Commission of Privacy Rights at the University Hospital of North Norway (REK NORD 39/2008), clinical trial registration number (ClinicalTrials.gov): NCT00906477.

2.2 | Study interventions

2.2.1 | Constraint-induced movement therapy

The participants in the intervention groups received CIMT in the rehabilitation departments of their corresponding treatment sites. Both the early and delayed intervention groups had an equal dose of CIMT, that is, 10 consecutive workdays with a 3-hr daily treatment. The intended daily duration of the different parts of the treatment was as follows: 2 hr shaping tasks, 0.5 hr standard task practice, and 0.5 hr adherence-enhancing behavioural strategies. Shaping tasks consisted of a high number of structured exercises of short duration where task difficulty was successively increased according to the patients' performance. Standard task practice consisted of continuously performed activities. Behavioural strategies (Morris, Taub, & Mark, 2006) consisted of a treatment contract, daily use of the motor activity log, home skill assignment, and home diary. To increase the use of the more affected arm, the participants wore a mitt on the less affected arm for up to 90% of their waking hours. The therapist responsible for the intervention attended a 4-day training programme on the study procedures. Further details of the treatment protocol have been described elsewhere (Stock et al., 2015).

2.2.2 | Standard care

Both groups received individually adjusted physical and occupational therapy according to the Norwegian guidelines for treatment after stroke during follow-up, except during the CIMT (Indredavik, Salvesen, Ness, & Thorsvik, 2010).

2.3 | Outcome measures

The participants were assessed by blinded assessors prior to randomization (T1), 2 weeks after randomization (T2), 6 months after randomization (T3), 6 months + 2 weeks after randomization (T4), and after 12 months (T5). The primary outcome measure was the Wolf Motor Function Test (WMFT) at 12 months (Morris, Uswatte, Crago, Cook, & Taub, 2001). The secondary outcome measures were the Fugl-Meyer Assessment (FMA) of the upper extremity (Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975), the Nine-Hole Peg Test (NHPT; Heller et al., 1987; Mathiowetz, Weber, Kashman, & Volland, 1985), and MRS (van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988) measured at all five time points. Additionally, the Stroke Impact Scale (SIS) was used at T3 and T5 (Duncan et al., 1999). Treatment schedules were used to calculate the time spent in the different parts of the treatment. Adverse events were recorded during the intervention periods.

The WMFT consists of 17 items to assess arm motor capacity: 15 tasks measuring speed and quality of movement and 2 tasks measuring strength. The median time for the 15 tasks was used in the analysis.

Video recordings of all movement tasks were used to calculate performance time and quality of movement, following a 6-point functional ability scale (ranging from 0 = *does not attempt* to 5 = *normal movement*). The WMFT has high validity and reliability in stroke patients (Morris et al., 2001).

The FMA measures motor impairment. The FMA upper extremity score ranges from 0 to 66, where a higher score indicates better motor function. The FMA has excellent reliability and good construct validity (Gladstone, Danells, & Black, 2002). In the NHPT (Weston Home Health/Medical Equipment, West Sussex, UK), the number of pegs placed per second was used to measure dexterity in the more affected arm. The NHPT has adequate to excellent reliability in acute stroke patients (Croarkin, Danoff, & Barnes, 2004; Heller et al., 1987).

The SIS is an interviewer-administered assessment of self-reported health status. SIS has adequate to excellent reliability and is regarded valid and sensitive to change in stroke patients (Duncan et al., 1999). MRS is a global outcome measure used to categorize the level of functional independence (Huybrechts & Caro, 2007).

2.4 | Statistical analysis

STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) was used for the statistical analyses. Group differences were considered significant when $p < .05$. Baseline characteristics are reported as means and standard deviation (*SD*). Differences between groups were assessed by independent *t* test or Mann–Whitney *U*-test (for nonnormally distributed data) and by chi-square test (for dichotomous variables) and within-group differences between two time points by paired *t* test or Wilcoxon signed-rank test (for nonnormally distributed data). A detailed description of the power calculation has been reported earlier (Thrane et al., 2015). A power of 0.8 required 53 participants in each group. Linear mixed models were

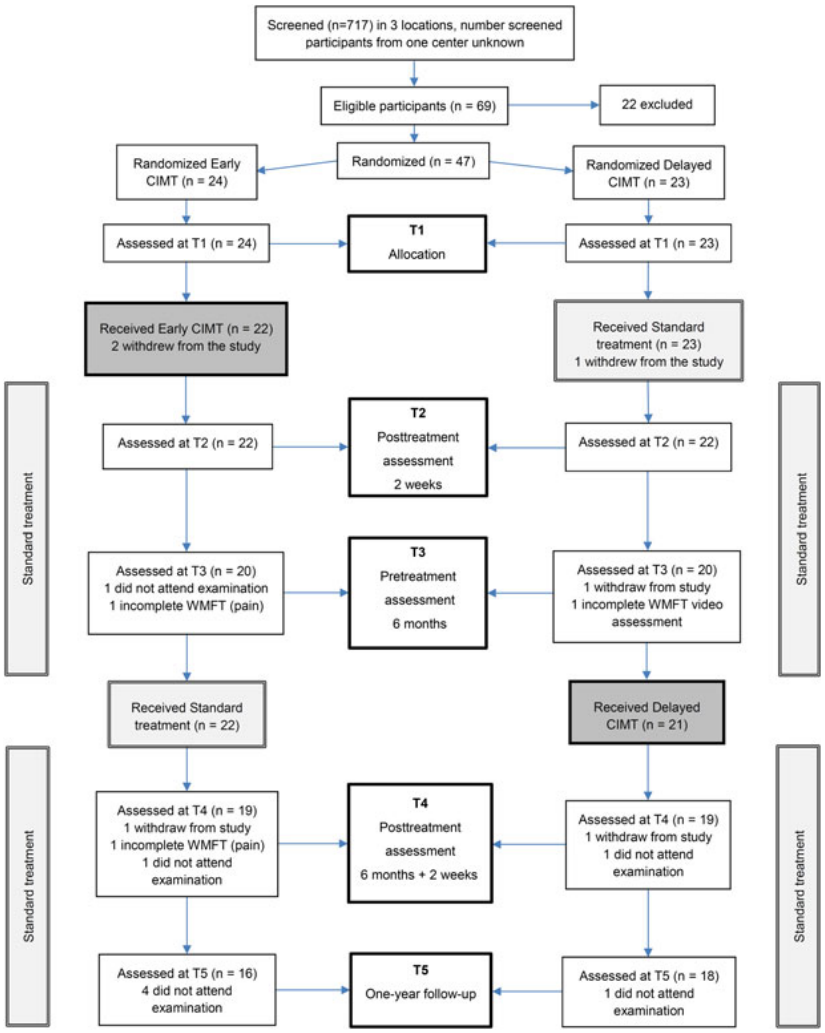

FIGURE 1 Study flow chart, including the recruitment, allocation, and withdrawal of participants. CIMT = constraint-induced movement therapy; WMFT = Wolf Motor Function Test

used to evaluate differences in the primary and secondary outcome measures across the time points between the treatment groups, with group, time, and interaction between group and time entered into the model. The analysis was performed on all participants. Maximum likelihood estimation was used to account for missing data. The model was adjusted for baseline values of the outcome variables as well as for age, sex, affected side, and time since stroke onset. In case of a significant time effect, pairwise comparisons between the 12-month follow-up assessment and the other time points were analysed separately for the two treatment groups. Differences between the treatment groups at each time point were assessed by linear contrasts of the estimated parameters. The Benjamini–Hochberg method was applied to correct for multiple comparisons (Benjamini & Hochberg, 1995). The WMFT time variable was log-transformed (logWMFT) using the LG10 function to better fit normal distribution. Nonnormally distributed data were analysed by Friedman analysis of variance.

3 | RESULTS

Figure 1 shows a CONSORT flow diagram, including screening, eligibility, consent, and dropout. Forty-seven patients were included in this study; 24 were randomized into the early CIMT group and 23 into the delayed CIMT group.

The dropout rate increased at the end of 1-year follow-up period, especially between T4 and T5. At the 1-year follow-up, 16/24 patients were assessed in the early intervention group and 18/23 in the delayed intervention group; no significant difference in the dropout rates was found (p = .37). Two participants from the early intervention group withdrew their participation. In the delayed intervention group, one participant withdrew after 4 days because of lack of motivation and another terminated treatment after 3 days. One participant in the early intervention group had a new minor stroke approximately 6 months after the treatment but participated in all assessments.

At baseline, no significant differences between the groups regarding age, sex, time since stroke onset, affected side, type of stroke, FMA upper extremity score, National Institutes of Health Stroke Scale score, and Mini-Mental State Examination score were found (Table 1).

No significant differences in the primary outcome measure between the early and delayed CIMT groups (p = .91) were found at T5 as well as in the subitems of the WMFT (Figure 2). Furthermore, no significant differences in the logWMFT or in other WMFT items between the groups were noted at T3 and T4.

The FMA of the upper extremity, NHPT, and MRS showed recovery curves similar to those of logWMFT; no significant differences between the groups at T3–T5 were found (Figure 3). At the 6-month follow-up, 10/42 participants reached the maximum FMA upper extremity score. The early CIMT group showed significantly better results in the MRS (p = .02) at T2 than the delayed intervention group; no differences were found during subsequent assessments. As previously reported, the early intervention group showed significantly better results in the logWMFT and NHPT at T2, and all other secondary variables showed no significant differences at T2 (Thrane et al., 2015).

Both the early and delayed CIMT groups showed significant improvements in the primary outcome measure logWMFT (p < .004) and in the secondary outcome measures from T1 to T5 (Figures 2 and 3). Visual inspection of the recovery curve of the logWMFT revealed that the early intervention group recovered faster and apparently reached a plateau at T3 without further improvements at T5, whereas the delayed intervention group seemed to improve during the intervention until T5. However, the within-group differences were similar in the two groups, and significant differences between T2 and T5 in both the early (p = .05) and delayed (p = .001) intervention groups, but not between T3 and T5 (p = .993 and p = .172, respectively) were observed. NHPT showed recovery curves similar to those of logWMFT. The SIS (Figure 4) showed no significant difference between the 6-month and 12-month follow-up and between the two groups.

TABLE 1 Baseline characteristics of participants

	Early CIMT (n = 24)	Delayed CIMT (n = 23)
Age (years), mean (*SD*)	65.3 (8.9)	61.0 (14.8)
Females, *n* (%)	5 (21%)	6 (26%)
Days post-stroke, mean (*SD*)	16.6 (7.2)	18.0 (6.5)
Range	7–32	7–29
NIHSS, mean (*SD*)	1.7 (1.9)	1.8 (1.8)
NIHSS affected arm, *n* (%)		
0	16 (67%)	16 (70%)
1	5 (21%)	6 (26%)
2	2 (8%)	1 (4%)
3	1 (4%)	0 (0%)
4	0 (0%)	0 (0%)
Modified Rankin Scale, mean (*SD*)	2.5 (0.7)	2.7 (0.9)
Affected side, right, *n* (%)	10 (42%)	12 (52%)
Dominant side affected, *n* (%)	16 (67%)	10 (45%)
Ischaemic stroke, *n* (%)	23 (96%)	20 (95%)
Prior stroke, *n* (%)	6 (25%)	4 (19%)
Days in hospital, mean (*SD*)	38.7 (14.1)	35.0 (18.5)
New stroke after inclusion, *n* (%)	1 (4%)	0 (0%)

Note. CIMT = constraint-induced movement therapy; *SD* = standard deviation; NIHSS = National Institutes of Health Stroke Scale.

The mean daily adherence in the early intervention group was 164.4 min (*SD* 18.8) or 91.3% of the intended treatment time (Stock et al., 2015), whereas that in the delayed intervention group was 157.8 min (*SD* 13.6) or 87.7% of the intended treatment time.

Adverse events

Three participants in the early intervention group developed shoulder pain (two between T2 and T3 and one between T4 and T5). Three participants in the delayed intervention group developed shoulder pain before the treatment started; nevertheless, all completed the treatment and follow-up assessment.

4 | DISCUSSION

This single-blinded, multicentre, randomized controlled trial compared the effect of CIMT applied early after stroke with that of CIMT applied in the chronic phase. Compared with baseline data, both groups

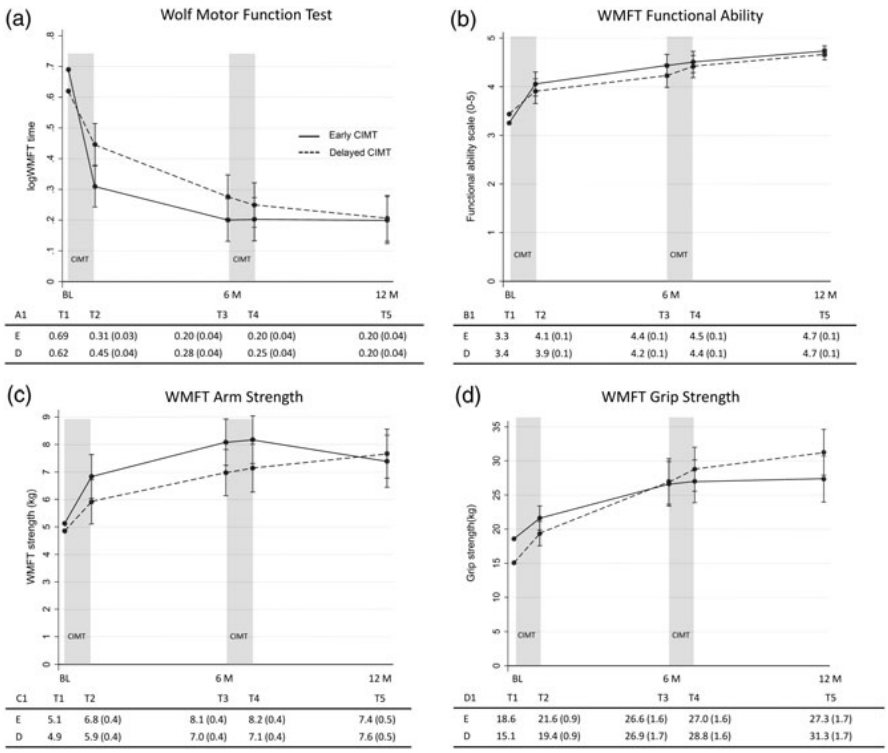

FIGURE 2 Comparison between early and late-applied constraint-induced movement therapy (CIMT). (a) The mean values and standard errors of Wolf Motor Function Test (logWMFT), (b) WMFT functional ability, (c) WMFT arm strength, and (d) WMFT grip strength scores from enrolment to the 12-month follow-up. The early intervention group received CIMT treatment between 8 and 28 days after stroke for 2 weeks and the delayed intervention group at 6 months after stroke. Note that the treatment intervals are upscaled to improve readability. Numbers below the figure are the mean and standard error (A1–D1) for the early CIMT (E) and delayed CIMT (D) groups from T1 to T5. No significant differences between the groups were found except for logWMFT at T2, as earlier reported (Thrane et al., 2015)

showed significant improvements in the outcome measures at the 12-month follow-up, recovered considerably, and had only mild impairment after 6 months. No significant differences in any of the outcome measures between the two treatment groups were found before and after the delayed intervention group received CIMT at 6 months and at the 12-month follow-up. However, the early intervention group had a faster recovery and showed significantly better logWMFT and NHPT results than the delayed intervention group immediately after the early group finished treatment as reported by Thrane et al. (2015).

Comparing our study's results on CIMT early after stroke with those from other studies is difficult, because our study is the first crossover study in the early phase after stroke that followed the participants for 1 year and compared early with delayed intervention. Most studies in the early phase after stroke followed the participants for only 1–3 months (Boake et al., 2007; Dromerick et al., 2009; Myint et al., 2008; Singh & Pradhan, 2013) or presented only posttest results (Page et al., 2005; Yoon et al., 2014). Only a recent study by Kwakkel et al. (2016) followed the participants for 6 months. Similar to our study, clinically relevant differences in arm motor function were found after treatment; however, the results were no longer significant at the 6-month follow-up. The additional benefit of CIMT to spontaneous recovery seems to decrease over time (Kwakkel et al., 2016). We cannot exclude that any other intensive training would have achieved similar results.

The lack of long-term effects of early applied CIMT may be attributed to the possibility that the intervention resulted in increased use of the affected arm during the intervention, followed by decreased use thereafter. The participants may have not utilized the function they achieved during the intervention when they were no longer encouraged to use their arm. Repeated CIMT interventions or other interventions that focus on increased use of the arm over longer periods, for example, training apps, could lead to better utilization of the functional gain. Reaching a higher level of motor function faster may be positive for the participants and thus could lead to earlier functional independence, which might be reflected by the MRS results.

We could not find a positive effect of late-applied CIMT on any of the outcome measures, which is in contrast to the EXCITE study (Wolf et al., 2006). The EXCITE study reported statistically and clinically significant improvements in arm motor capacity that persisted for at least 1 year in patients who received CIMT in the subacute and chronic phases (3–9 months after stroke). In the EXCITE trial, the participants had a mean FMA score of 43 before they started CIMT, whereas the participants in our delayed CIMT group had a score of 60. Hence,

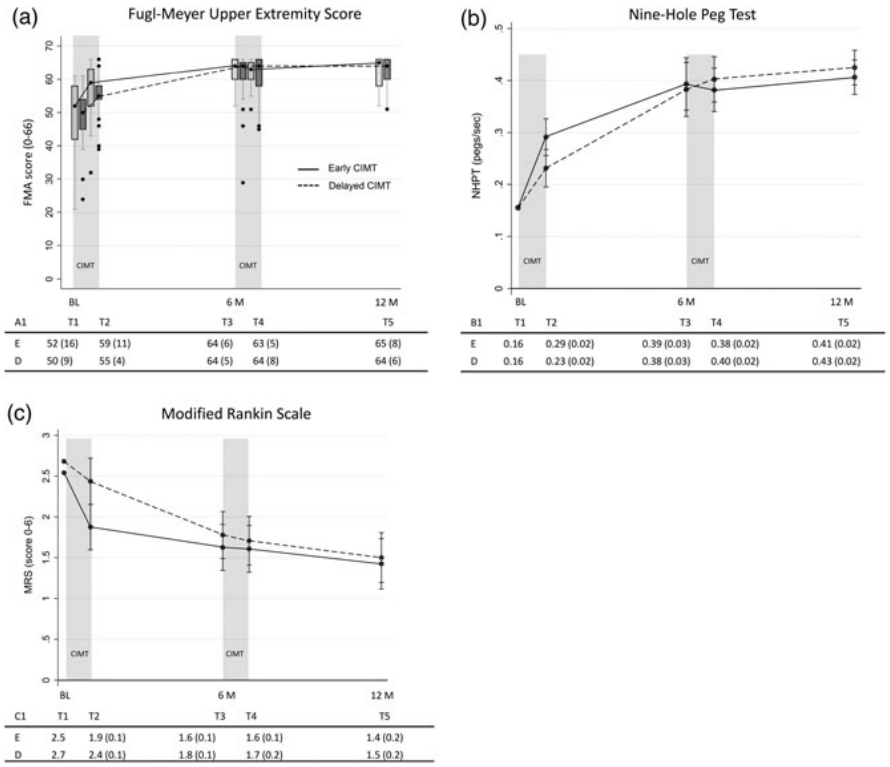

FIGURE 3 Comparison between early and late-applied constraint-induced movement therapy (CIMT). (a) The median values and interquartile range for Fugl-Meyer Assessment (FMA; upper extremity) score. (b) The mean values and standard errors for Nine-Hole Peg Test (NHPT). (c) The mean values and standard errors for modified Rankin Scale (MRS). Scores are presented from enrolment to the 12-month follow-up. The early intervention group received CIMT between 8 and 28 days after stroke for 2 weeks and the delayed group at 6 months after stroke. Note that the treatment intervals are upscaled to improve readability. Numbers below the figure are the median and interquartile range (A1) and mean and standard error (B1–C1) for the early CIMT (E) and delayed CIMT (D) groups from T1 to T5. No significant differences between the groups were found except for MRS at T2 and, as earlier reported, for NHPT at T2 (Thrane et al., 2015)

our participants had a high functional level before they started CIMT, where further progress was difficult to detect with standardized tests.

Similar to the majority of CIMT studies, especially the studies conducted early after stroke (Etoom et al., 2016; Thrane et al., 2014), our study was underpowered. However, the differences at T5 are negligible for most outcome measures, and it is unlikely for a larger sample to have different conclusions regarding differences between two treatment groups. Nevertheless, a nondetected improvement after the intervention in the delayed treatment group is possible. Another limitation of our study was the high dropout rate, especially at the 12-month follow-up, which is similar to the dropout rate in the EXCITE study (Wolf et al., 2006). This indicates that a long-term follow-up period with repeated assessments might lead to bother and consequently disinterest among the participants, especially among patients with mild to moderate impairment, as those included in our study. Patients with more severe impairment might have considered CIMT as too demanding and therefore decided not to participate. Furthermore, most of the participants in the delayed CIMT group showed good recovery at 6 months; thus, most likely they would not be included in a CIMT study; in addition, it was difficult to detect further progress on the outcome measures because of a ceiling effect. However, despite a high level of functioning, most of the participants in the delayed intervention group completed the CIMT, indicating that they still experience functional problems and see potential benefits from the treatment. Several participants had goals on a high functional level, including playing the piano, handwriting, and hammering. Meaningful progress during these activities is possibly difficult to determine by standardized motor tests but could be captured by goal assessment. Furthermore, because of the already reached high level of motor function, it is likely that other intensive treatments would have shown similar results during the delayed intervention.

5 | IMPLICATIONS FOR PHYSIOTHERAPY PRACTICE

This study showed that both early and delayed CIMT significantly improved outcomes; however, no differences between the groups were found at the 12-month follow-up. This result indicates that commencing therapy early is as good as delayed intervention in the long term. Nevertheless, the early CIMT intervention group showed faster recovery with less dependency in activities of daily living than the

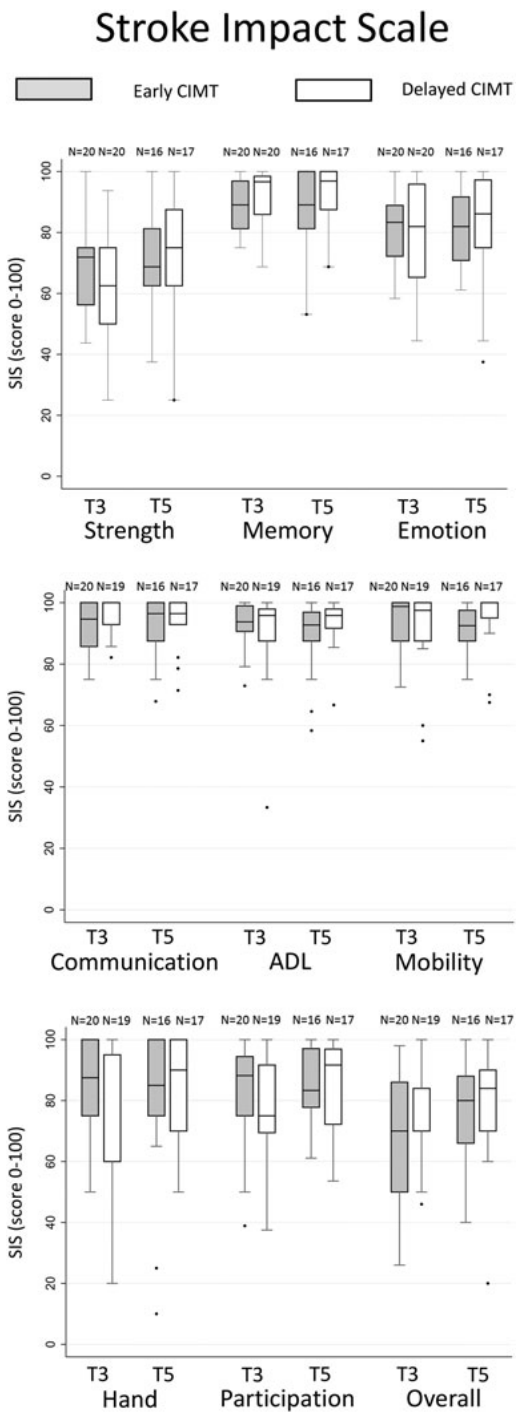

FIGURE 4 Comparison between early and late-applied constraint-induced movement therapy (CIMT). A boxplot showing the median and interquartile range of eight domains as well as the overall recovery in the Stroke Impact Scale (SIS) at T3 (6-month follow-up) and T5 (12-month follow-up). No significant differences between the groups were found at any point in time

delayed intervention group, which can be a clinically important finding for patients in the acute phase. Further large-scale studies are needed to determine the dose and optimal time point for commencing CIMT. Excluding higher functioning participants may be advantageous to minimize the influence of spontaneous recovery.

ACKNOWLEDGEMENTS

We would like to thank the research participants and all therapists and other hospital staff involved in the study. We thank the following therapists for their contribution to the development of the treatment protocol, data collection, and recruitment of participants: Gunn Marte Karlsen, Eli Langørgen, Grethe Jakobsen, Martin Vatshaug, and Anne Erichsen. We would like to thank Turid Follestad for statistical advice. This study was supported by the Northern Norway Regional Health Authority (SAT 544-06). The authors would like to thank "Landsforening for Slagrammede" (Slagrammedes Minne og Forskningsfond) for the support in writing this article.

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How to cite this article: Stock R, Thrane G, Anke A, Gjone R, Askim T. Early versus late-applied constraint-induced movement therapy: A multisite, randomized controlled trial with a 12-month follow-up. *Physiother Res Int*. 2017;e1689. https://doi.org/10.1002/pri.1689

Paper 3

Development of grip strength during the first year after stroke

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Short title: Grip strength after stroke

Abstract

Objective: To assess progress in grip strength during the first year post-stroke.

Design: Exploratory study on a subsample of patients participating in the Norwegian Constraint-Induced Movement Therapy trial.

Subjects: Eleven patients (mean age 59.1 years; 3 women) with mild to moderate stroke were recruited 7-29 days post-stroke.

Methods: An electronic dynamometer (Biometrics Ltd, Gwent, UK, 2006) was used to assess maximal grip strength in 5 hand positions, rate of force development and fatigability during sustained grip. Similar assessments were performed to assess pinch strength. The participants were assessed 5 times during a one-year period.

Results: Grip strength in the affected hand increased in all handle positions during the one-year follow-up, mostly during the first 6 months. At baseline and after 2 weeks, rate of force development was less than half, and relative sustained grip strength showed 20-30% greater decline than for the non-affected hand. The affected hand approached the values of the non-affected hand after 6 months with little further progress until one-year follow-up.

Conclusion: Grip strength in the affected hand improved considerably in the first year post-stroke. Patterns of improvement were similar across tests, i.e., rapid during the first weeks, slower until 6 months, and minimal 6-12 months post-stroke.

Keywords: Stroke, rehabilitation, hand strength, pinch strength, muscle fatigue

Journal of Rehabilitation Medicine

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Introduction

Stroke often leads to muscle weakness and less effective and coordinated movements in the affected upper limb during activities of daily living (ADL) (1). Most improvements in overall motor function occur during the first year after the stroke, with less progress after 6 months and a fairly stable motor function from 12 months post-stroke (2).

Grip strength of both the whole palm and the fingers are important for upper limb function (3) and several studies have shown that grip strength is positively correlated with motor function and ADL performance (4, 5). However, few studies have measured grip strength with follow-up beyond 3 months (6, 7) and a detailed description of the long-term progress of hand muscle function is currently lacking. Furthermore, it has been shown that the elbow flexor and extensor muscles in the affected arm in persons with stroke are relatively weaker in their shortened range (8); however, it is unclear if such selective weakness also applies to hand muscles.

In addition to a reduction in muscle strength, the force-time characteristics (i.e., rate of force development [RFD] and fatigability) are altered in persons with stroke. Canning et al. (9) found that persons with stroke have reduced RFD capacity in the elbow flexor and extensor muscles compared to healthy controls. Similar results have been found for ankle plantar flexor muscles (10). However, little is known about RFD in the hand muscles in persons with stroke and how RFD evolves during the first year post-stroke. Furthermore, some studies indicate increased muscle fatigability in person with stroke. Kamimura & Ikuta (11) assessed the decline in maximal sustained grip force as the percentage of maximal voluntary contraction (MVC) force and found that the affected hand reached values below 80% faster than the non-affected hand. However, there is limited knowledge about the progress of fatigability during the first year after stroke.

The main aim of this exploratory study was to assess progress of muscle function in hand and fingers during the first year post-stroke. We assessed i) maximal grip strength in different hand positions (wide to narrow grip) and different modalities of pinch strength, ii) rate of force development in hand grip and key pinch grip, and iii) fatigability during sustained hand and key pinch grip. To assess progress, we compared the performance by the affected versus the non-affected side at inclusion into the study and at 4 different time points during the one-year follow-up period.

Methods

Participants and design

The participants in the current study were a subsample of the Norwegian Constraint-Induced Therapy Multisite Trial (NORCIMT) (12, 13). NORCIMT is a multicentre, randomised controlled trial, investigating the effect of early versus late implementation of constraint-induced movement therapy (CIMT).

The inclusion criteria for the NORCIMT study were: more than 5 days and less than 26 days after stroke, persistent unilateral paresis (arm function 2-5 or hand motor function 2-4 on the Scandinavian Stroke Scale), ability to extend the wrist or 2 fingers, modified Rankin Scale (MRS) score 0-2 prior to stroke, a Mini-Mental State Examination (MMSE) score of less than 20 and the ability to follow a 2-step command and to sign informed consent. Exclusion criteria were: MRS post-stroke > 4, hemispatial neglect (line bisection test more than 2 cm deviation), life expectancy less than 1 year, injury or other conditions affecting motor function. The North Norway Regional Committee of Medical Ethics and the Commission of Privacy Rights at the University Hospital of North Norway reviewed and approved the study (reference no. 39/2008).

Additional criteria for this study were recruitment at Trondheim University Hospital and available data on grip strength, RFD and fatigability of the affected and non-affected hand (only grip strength in the affected hand was tested in the main study). The participants were assessed 5 times: at inclusion (baseline) as well as after 2, 26, 28 and 52 weeks; hereafter referred to as W2, W26, W28 and W52. The NORCIMT intervention groups were not compared in the current subsample, because the results from the main study showed no group differences in grip strength in the affected hand (13).

Outcome measures

All participants were examined by the same non-blinded examiner at all 5 time points. The outcome measures were detailed isometric measurements of grip strength including MVC in 5 different hand and finger positions and force-time curves. MVC during grip strength measurements and strength ratios (affected/non-affected hand) can be used to reliably examine strength impairments in chronic stroke patients (14). Excellent test-retest reliability for maximal grip strength measurements has also been shown < 12 weeks post-stroke (15).

A Biometrics E-LINK EP9 evaluation system (Biometrics Ltd, Gwent, UK, 2006), with an electronic hand dynamometer (G100) and pinchmeter (P100) were used to assess grip strength. The dynamometer has 5 adjustable handle positions ranging from narrow grip (position 1 – muscles are in a shortened range) to wide grip (position 5 – muscles are in a lengthened position). Force-time curves were generated with a sampling frequency of 20 Hz. Allen et al. (16) demonstrated that the Biometrics electronic dynamometer is valid (intra-class correlation [ICC] 0.98-0.99) compared with the Jamar hydraulic dynamometer and has excellent test-retest reliability (ICC 0.98-0.99). The advantage of electronic dynamometers is the sensitivity to record low grip strength and the possibility to assess force-time characteristics. Pinchmeters can be used to obtain a reliable assessment of pinch strength in stroke patients (17, 18).

All grip strength measurements were performed according to the recommendations of the American Society of Hand Therapists (ASHT) (19). The patients were seated with their shoulder in a neutral position, the elbow flexed to 90 degrees, the wrist in a neutral position; the same chair was used for all measurements. The examiner explained and demonstrated the testing procedure. First, 2 trials with submaximal isometric contractions were performed to familiarize the participant with the equipment. Each MVC was performed 3 times in the 5 handle positions. The hands were tested alternately with 30 sec rest between the trials, i.e., 60 sec rest before the same hand was tested again, as recommended by Watanabe et al. (20).

Pinchmeter recordings were performed in the same manner in 3 different grip positions: key grip (holding the pinchmeter between the lateral side of the 2nd phalanx of the index finger and the tip of the thumb), three-jaw grip (holding the pinchmeter between the fingertips of the index finger, middle finger and thumb) and pinch grip (between the fingertips of the index finger and thumb). If the patient was not able to hold the instrument in a stable position, it was placed and gently held by the examiner in the correct position. During the actual testing, the participants were instructed to grip as hard as possible, and were encouraged verbally “Harder...Harder...Relax” (21).

Rate of force development and sustained grip strength

A 0-0.5 sec time interval was chosen to evaluate RFD (22). Sustained grip strength can be measured in absolute values (23) or as the percentage or ratio of the momentary force value relative to MVC (24, 25), which makes it possible to express how much the individual force curves drop during a given period. Both absolute and relative values are reported in the current study. The measurements of RFD and sustained grip strength were performed once in both the affected and the non-affected hand with a hand dynamometer (position 2) and pinchmeter (key grip). The participants were instructed to increase grip force as fast as possible, followed by the instruction “hold as hard as you can” for 15 sec.

Statistics

Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) was used for the statistical analyses. Background variables were reported as mean (standard deviation [SD]) or median (range) when non-normally distributed. Differences between the affected and non-affected hand were analysed by independent t-test, or by the Mann-Whitney U test when the data were non-normally distributed. The onset of the force-time curve was visually determined by 2 independent raters as the point where the curve starts to rise after stable baseline measurements. In case of disagreement on the onset point, the raters reached consensus through discussion. ICC (3,1) was used to determine the degree of agreement between the 2 raters. Last observation carried forward was applied where observations were missing in the non-affected hand. Normal distribution was assessed by visual inspection of quantile-quantile (Q-Q) plots. Due to multiple comparisons between the 2 hands during 5 time points and 5 grip positions, the possibility for Type II error was high. P-values <0.05 were therefore regarded as indicating a possible difference between the hands, while p-values <0.01 were regarded as representing a significant difference.

Results

Of the 47 patients included in the NORCIMT study, 14 were recruited from Trondheim University Hospital. Of these, 11 participants had available data on grip strength, RFD and fatigability of the affected and non-affected hand. Table I presents the baseline characteristics of the 11 patients included in the study. The participants were middle-aged to elderly and mostly men. The Fugl-Meyer score for the upper extremity indicates that the patients had mild to moderate reduction in motor function. Disability (Modified Rankin Scale) ranged from slight disability to moderate disability.

Insert Table I

One patient missed the follow-up assessments at W26, W28, and W52 for the non-affected side because of pain due to overload of the non-affected hand during walking with walking aids. More than 3 sec were needed to reach MVC during some recordings. As a result, 7% (15/214) of the sustained curve recordings were shorter than 12 sec (mean 9.3 sec [SD 2.1]). One patient had an additional minor stroke after 26 weeks, which did not result in a pronounced difference in grip strength parameters except that the force curve dropped markedly faster during sustained grip on the non-affected side at W28, but no longer at W52. The assessment of the onset of the force-time curves by 2 independent raters showed excellent agreement: ICC (3,1)=0.98.

Hand grip strength

Patients reached the highest MVC values in hand grip position 2 for both the affected and non-affected hand (Figure 1). MVCs were lower on the affected side in all positions at baseline and W2 ($p \leq 0.003$ for all comparisons). However, MVCs on the affected side increased steadily during the follow-up period and approached the values of the non-affected side at W26 and W28 and were no longer different at W52 (p=0.09-0.25). At baseline, the median grip strength ratio (MVC affected/MVC non-affected hand) was least for position 1 (0.37, corresponding to 63% difference, Figure 1A) and largest for position 5 (0.43, corresponding to 57% difference, Figure 1E). At W52, the ratio between hands ranged from 0.74 to 0.80 for the various handgrip positions. There was no difference in grip strength ratio between position 1 (narrow) and position 5 (wide) at any time point ($p \geq 0.22$ for all comparisons).

Insert figure 1

Finger grip strength

Figure 2 shows the strength progress of the key grip, three-jaw grip, and tip-to-tip grip during the one-year follow-up. At baseline, key grip MVC was 45% lower in the affected hand compared to the non-affected hand ($p<0.001$, Figure 2A). Key grip MVC remained essentially unchanged for the non-affected hand during follow-up but increased steadily in the affected hand. At W52, MVC was 14% lower in the affected hand compared to the non-affected hand but the difference between hands was no longer significant ($p=0.25$).

At baseline, the MVC for the three-jaw grip was 55% lower for the affected hand than the non-affected hand ($p<0.001$, Figure 2B). This difference decreased to 24% at W52 but the MVC for the affected side remained lower than the MVC for the non-affected side ($p=0.02$). A similar pattern was observed for the progress of tip-to-tip strength. At baseline, MVC was 57% lower for the affected side compared to the non-affected side ($p<0.001$, Figure 2C). This difference decreased to 24% at W52 but MVC remained lower on the affected side compared to the non-affected side ($p=0.01$).

Insert figure 2

Rate of force development

Figure 3 shows the progress of RFD in hand grip MVC (position 2) during the one-year follow-up period. At baseline, RFD during the first 500 ms was 62% lower for the affected hand than for the non-affected hand ($p=0.001$, Figure 3A). RFD during the first 500 ms in the affected hand increased during the first 6 months and there was no difference between the hands at W26 and W28 ($p\geq0.19$ for all comparisons). At W52, RFD was 21% lower for the affected hand than for the non-affected ($p=0.30$).

Insert figure 3

The pinchmeter recordings for the 0-500 ms interval (figure 3B) showed a similar pattern, but lower RFD compared to the dynamometer recordings. RFD on the affected side was 46% of the non-affected side at baseline (p=0.001) and 88% at W52 (p=0.43). Most increase in RFD on the affected side occurred between baseline and W26.

Sustained grip strength

At baseline, there was a similar decrease in the ability to maintain hand grip MVC during the 12-sec sustained period when measured in absolute values (p=0.68). However, when the force curve was normalized to %MVC, the affected side decreased to 44% of MVC during the 12-sec interval at baseline, while the non-affected side decreased only to 74% of MVC (p<0.001, figure 4A). At W52, the ability to sustain relative hand grip MVC was still lower on the affected side (p=0.004).

Pinchmeter recording showed a similar pattern with no difference in decline between the affected and non-affected side when measured in absolute values at baseline (p=0.22). Figure 4B shows the normalized key pinchmeter values. At baseline, the affected side decreased to 47% of the MVC and the non-affected side to 67% (p=0.009). At W52, the ability to sustain relative key grip MVC no longer differed between the affected and non-affected hand (p=0.24). Furthermore, as figure 4A and 4B show, there was a marked drop in sustained grip force at baseline during the first 2-2.5 sec on the affected side compared to the non-affected side. This drop decreased during the one-year follow-up period but was still visible at W52.

Insert figure 4

Discussion

This study examined the progress of hand grip and pinch strength during the first year after stroke in patients with mild to moderate stroke. Maximal strength in the affected hand increased most during the first 6 months, with less improvement between 6 months and one year after stroke. Grip strength was highest in position 2 (second most narrow grip) on the hand dynamometer for both the affected and non-affected hand. No significant differences between the hands were found with respect to position-dependent weakness. The ability to generate grip force rapidly was lower on the affected side at baseline; however, this difference was no longer present at 6 months. At baseline, the ability to sustain maximal grip strength declined more rapidly on the affected side compared with the non-affected side (to 45% versus 75% of MVC, respectively) during the 12-sec sustained grip test. Notably, relative grip strength on the affected side decreased markedly during the first 2-3 sec of the sustained grip test, especially at baseline and at the 2-week follow-up measurement, indicating increased fatigability. However, the relative capacity to sustain maximal grip strength approached the values of the non-affected side at 6 months post-stroke.

Limitations

A limitation of this study is the low sample size, which makes it difficult to draw firm conclusions and to analyse the effect of gender and age. Moreover, the findings are limited to patients with mild to moderate stroke. Another potential limitation is missing values. One participant missed 3 assessments on the non-affected side. However, measurements on the non-affected side remained stable during the one-year follow-up and it seems unlikely that this has caused biased results. Furthermore, there are some missing values for the assessment of the sustained curve after the 7^{th} sec, which might bias the results for the last part of the

sustained curve. The last part of the sustained curve could also be biased, according to the findings by Kamimura & Ikuta (24), who showed that the first 6 sec of the sustained curve are more reliable than the 10 sec period. However, the force curves on the non-affected side seem to be similar during the one-year follow-up, both for hand grip and key pinch force, indicating stable values, except for week 28 which showed a similar pattern, but slightly lower values. The latter may in part be explained by lower values by the patient who suffered a second minor stroke at 6 months. Despite these limitations, the longitudinal data combined with the detailed assessment of various aspects of grip strength provide new knowledge with possible relevance for clinical practice.

Grip strength

The progress of grip strength in our study is generally comparable to the recovery curve described by Langhorne et al. (2), with most improvement in motor function occurring during the first 6 months after stroke. However, our study shows that hand grip strength continued to improve between 6 and 12 months, while we observed less improvement for the 3 types of pinch grip strength during this period. MVC and grip strength ratios (MVC affected/MVC non-affected hand) were similar to other studies with stroke patients with mild to moderate impairment (6). Key grip strength at baseline showed a higher strength ratio, i.e. strength on the affected side was relatively higher, compared to three-jaw grip and tip-to-tip grip. In addition, the difference in key grip strength between the affected and non-affected hand at one-year follow-up was less pronounced than for the three-jaw and tip-to-tip grip. A possible explanation for the better preserved key grip strength might be that the key grip demands less dexterity and coordination between the fingers.

There are no comparable longitudinal studies on the progress of hand grip strength in different positions. In contrast to Ada et al. (8), we found no evidence of selective weakness

in the affected compared to the non-affected side. Possibly, selective weakness may apply to patients with more severe impairment.

Rate of force development

In general, measurements of RFD have lower reliability than measurements of MVC (26), and the highest variation in muscle force usually occurs during the initial 0.2-0.3 sec period. Demura et al. (22) reported higher reliability for RFD with time intervals from 500 ms up to 2000 ms (ICC 0.77 and 0.93 respectively) compared to shorter intervals, as well as for peak RFD (ICC 0.67). Due to the high variation during shorter intervals and because longer intervals do not measure the ability to generate force quickly, we decided to use the 0-500 ms time interval in the current study.

RFD was markedly decreased in the affected hand at baseline but approached the values of non-affected hand during the first 6 months post-stroke. We are not aware of any comparable study on RFD of grip strength. Canning et al. (9) found that stroke patients have a decreased rate of torque development in elbow flexion and extension 6 weeks after stroke compared to healthy controls. This difference was no longer present at 25 weeks. In contrast, McCrea et al. (27) found that rate of torque development in elbow and shoulder muscles is reduced several years post-stroke. Similar results have been reported for the lower limb (10). Interestingly, it has been demonstrated that stroke patients are able to move faster if they are asked to do so during a reach-grip-lift task with a 3-finger grip without decreasing movement quality (28). Thus, the instruction to move faster may be effective in increasing training intensity and facilitating faster functional recovery (28). Our results indicate that this may be of particular importance during the first 6 months after stroke.

Sustained grip strength

Our measurements of sustained grip strength are comparable to the results reported by Kamimura & Ikuta (11). They showed that MVC and the time until the momentary sustained grip strength values dropped below 80% of MVC were lower in the affected versus the non-affected hand. MVC and sustained grip strength in the non-affected hand were not different from that of healthy controls. Especially the participants < 1 month post-stroke decreased to 80% of MVC during less than 3 sec. This is also shown by the initial marked drop in the sustained curve during the first 2-3 sec in our study at baseline and W2. In contrast to the cross-sectional data of Kamimura & Ikuta (11), the longitudinal data in our study allow a description of the progress of fatigability. In the current study, the drop in the sustained force curve in the affected hand was less marked after 6 months, indicating that fatigability is most prominent during the first weeks after stroke.

Kamimura & Ikuta (11) also found a significant relation between sustained grip strength and the ability to squeeze objects during ADL (wring a wet wash cloth, open a jar, lift a container, wash the non-paretic arm). They concluded that both MVC and the ability to sustain high grip force is essential in squeezing an object. The ability to sustain high grip force is important for many activities, such as carrying a suitcase or using tools. However, it is not clear if the sustained grip capacity can be modified by training and if it could be successfully included in strength interventions.

Possible clinical implications

Our findings may have some clinical implications. Several meta-analyses and guidelines for stroke rehabilitation stress the importance of task-specific training (29, 30). Even if strength training is common in stroke rehabilitation, there seems to be little focus on practising grip strength that is functional in different hand positions or grip strength capacity related to RFD

or sustained muscle activation. For example, high grip force in the narrow hand position is necessary for holding a knife while cutting hard vegetables while, in contrast, opening a jar demands high grip force in the wide hand position. Furthermore, being able to maintain grip force over time is important during ADL (e.g., carrying a shopping bag, squeezing objects) and requires task-specific training. The results of our study indicate that training of grip strength should target different modalities and not only focus on improving maximal grip strength.

In conclusion, grip strength in the affected hand increases steadily during the first year after stroke. The progress is most pronounced during the first 6 months and less between 6 and 12 months. Pinch strength shows less progress during 6 to 12 months compared to hand grip strength. We observed no clear evidence of selective weakness in the shortened range of the hand muscles. RFD and the ability to sustain maximal grip force is reduced in the affected hand early after stroke but approaches a level similar to the non-affected hand 6 months after stroke.

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Tables

Table I. Baseline characteristics of participants (n=11)

Characteristic	Values
Age, years, mean (SD), range	59.1 (10.5), 44-78
Females, n (%)	3 (27.3)
Days post-stroke, mean (SD), range	16.4 (7.1), 7-29
National Institutes of Health Stroke Scale, mean (SD), range	3 (1.9), 0-6
Fugl-Meyer Assessment of the upper extremity, mean (SD), range	48.7 (7.3), 32-61
Modified Rankin Scale, mean (SD), range	2.6 (0.8), 2-4
Affected side, right, n (%)	6 (54.5)
Dominant side affected, n (%)	7 (63.6)
Ischaemic stroke, n (%)	11 (100)
New stroke after inclusion, n (%)	1 (9)

Abbreviations: SD, standard deviation

Figure legends

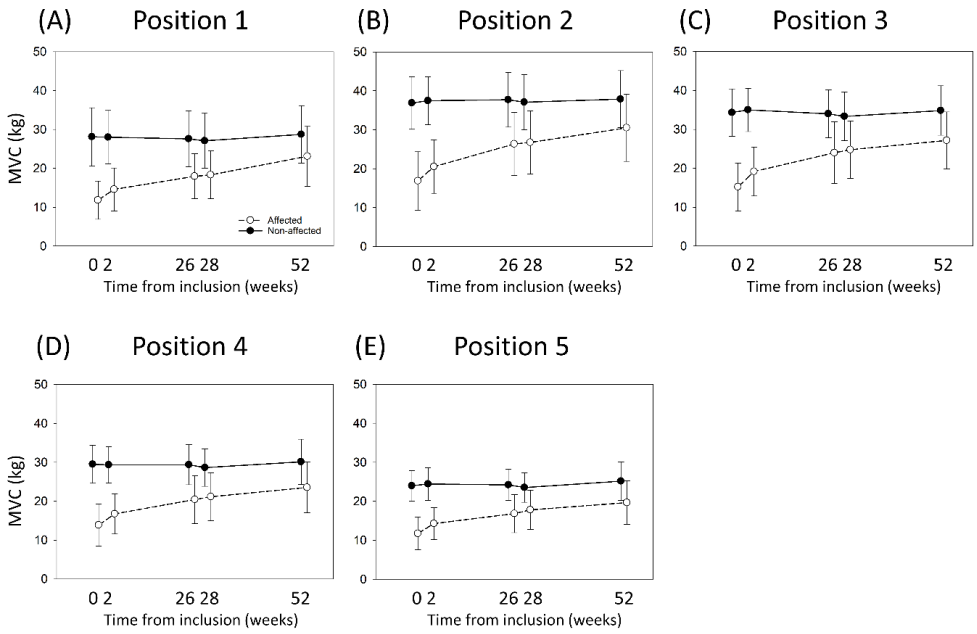
Fig 1. Progress of maximum voluntary contraction (MVC) of hand grip during the first year after stroke. MVC was measured with a hand dynamometer in 5 positions from (A) narrow grip (position 1) to (E) wide grip (position 5) at baseline (0), and at 2, 26, 28 and 52 weeks after inclusion. Values are mean and error bars 95% CI. Note that the assessment intervals are upscaled to improve readability.

Fig 2. Progress of maximum voluntary contraction (MVC) in key grip (A), three-jaw grip (B) and tip-to-tip grip (C) during the first year after stroke. MVC was measured with a pinchmeter at baseline (0), 2, 26, 28 and 52 weeks after inclusion. Values are mean and error bars 95% CI. Note that the assessment intervals are upscaled to improve readability.

Fig 3. Progress of rate of force development (RFD) for (A) dynamometer (position 2) and (B) pinchmeter (key grip) recordings during 0-500 ms during the first year after stroke. RFD was measured at baseline (0), and 2, 26, 28 and 52 weeks after inclusion. Values are mean and error bars 95% CI. Note the different scaling on the y-axis for dynamometer and pinchmeter recordings. The assessment intervals are upscaled to improve readability.

Fig 4. Progress of sustained grip force during 12 sec after maximum voluntary contraction (MVC) for dynamometer (A) and key grip pinchmeter (B) during the first year after stroke. Sustained grip force was measured at baseline (0), and 2, 26, 28 and 52 weeks after inclusion. Values are mean and error bars 95% CI. Sustained grip force is expressed as percentage of MVC.

JRMStock_Figure 1



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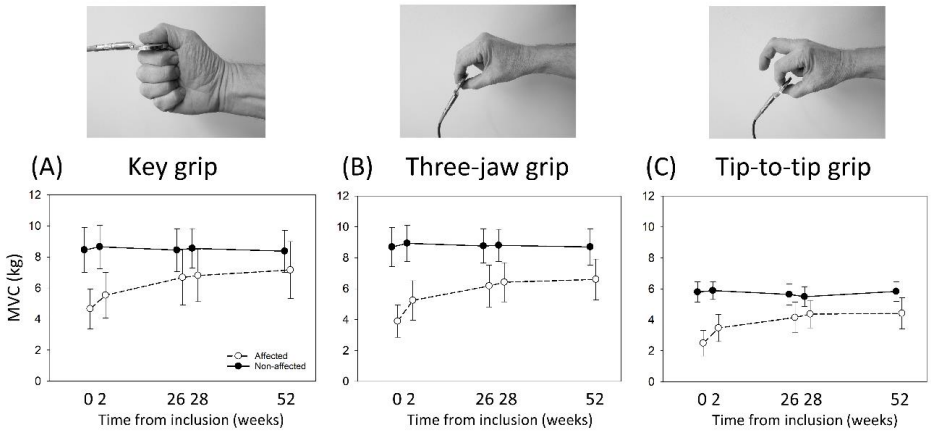

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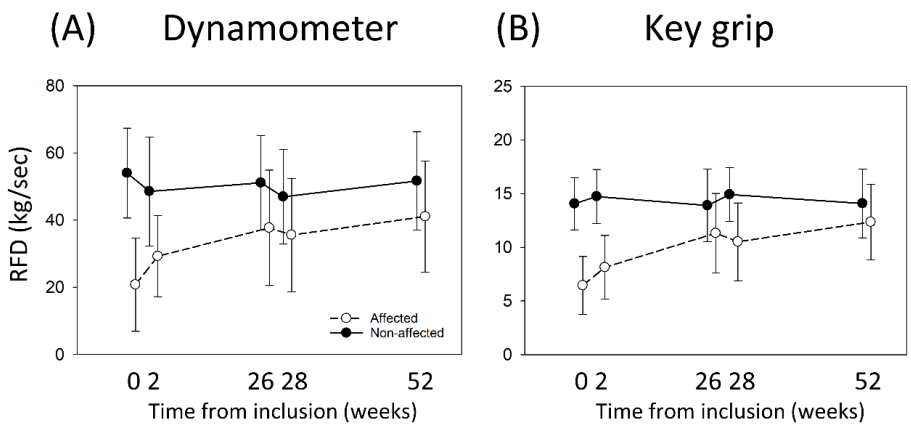

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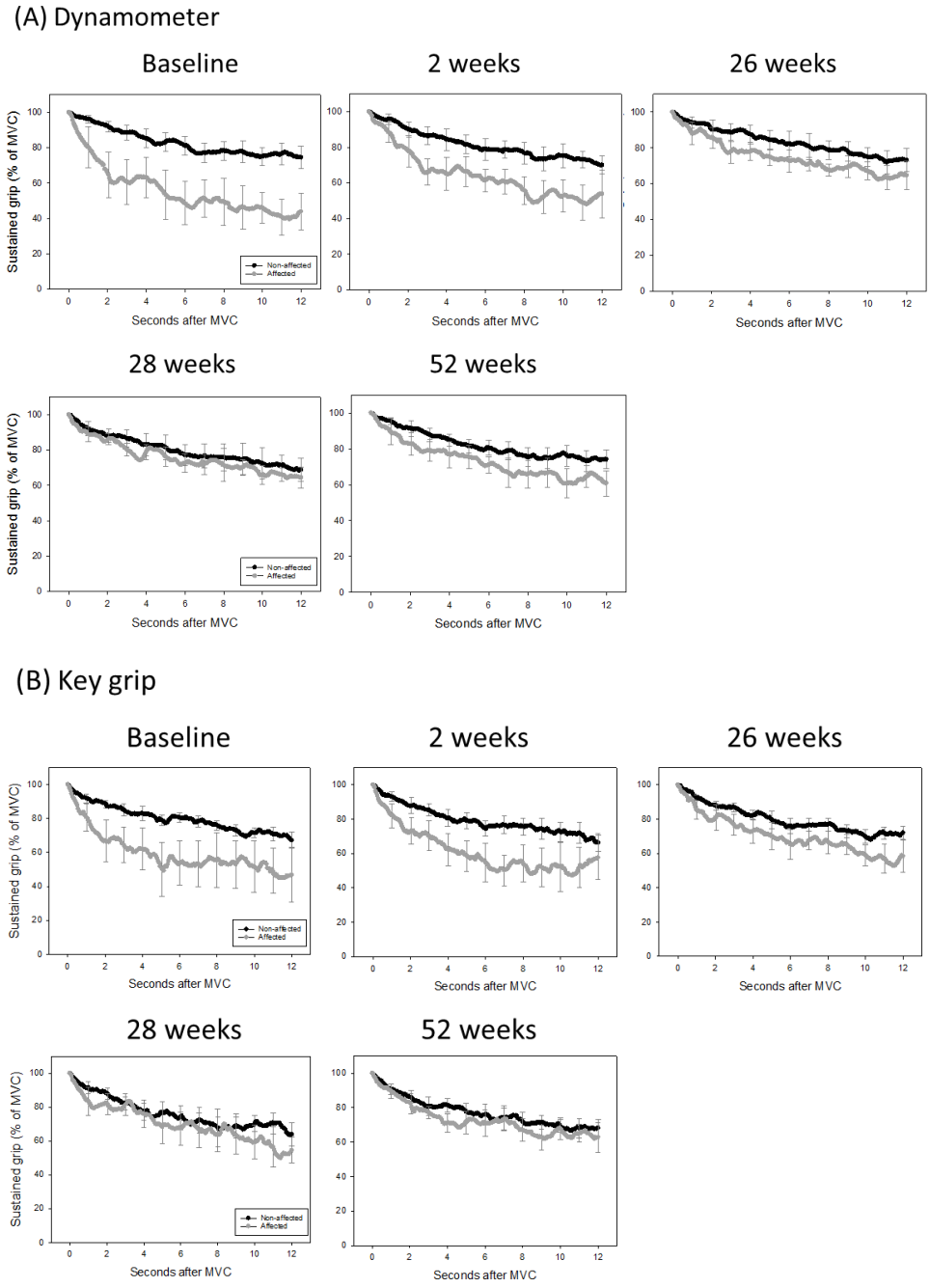

Acknowledgements

The authors would like to thank all the patients who participated in the study. The funding sources had no influence on the analysis.

Appendix

Appendix A-D

Appendix A: Therapy schedules 1. and 2. treatment day

Appendix B: Shaping Quality of Movement Scale

Appendix C: Shaping registration form

Appendix D: Shaping schedule

Appendix A: Therapy schedules 1. and 2. treatment day

Aktiviteter under CI-terapi BD1

Navn: _____ Dato:_____ Behandlingsdag: 1

Tid	Aktivitet	Kommentarer / Notater/ Gjennombevegelse(minutter)
	Gi ut votten	
	MAL (30 spørsmål)	
	ST1	
	ST2	
	ST3	
	ST4	
	ST5	
	ST6	
	ST7	
	Borgs skala	Resultat:
	Goal Attainment scaling	
	TP1	
	TP2	
	TP3	
	BORGS SKALA	Resultat:
	Adferdskontrakt	
	Hjemmeoppgaver	
	Hjemmedagbok	

Aktiviteter under CI-terapi BD2

Navn: _____ Dato:_____ Behandlingsdag: 2

Tid	Aktivitet	Kommentarer / Notater/ Gjennombevegelse(minutter)
	MAL (første 15 spørsmål)	
	Hjemmedagbok	
	Hjemmeoppgaver	
	ST8	
	ST9:	
	ST10	
	ST11	
	ST12	
	ST13	
	ST14	
	Borgs skala	Resultat:
	TP1	
	TP2	
	TP3	
	BORGS SKALA	Resultat:
	Hjemmeoppgaver	
	Hjemmedagbok	

Appendix B: Shaping Quality of Movement Scale

Bevegelseskvalitet (shaping øvelser)

0	**Ingen bevegelse intitiert**
1	**Delvis bevegelsesutslag oppnås,** men: bevegelsen er preget av synergier, eller det er stor inkoordinasjon mellom ekstremitetens segmenter.
2	**Bevegelsen kan gjennomføres,** men: er influert av synergier, eller gjøres med store kompensatoriske bevegelser i trunkus, hodet eller den kontralaterale overekstremiteten, eller mangler enten proksimal kontroll eller finmotoriske evner, eller bevegelsen gjøres svært sakte, eller bare minimal evne til å gjennomføre vektbærende aktiviteter.
3	**Noe isolert bevegelse,** men: påvirket av noe synergi, eller bevegelse med lite synergier som utføres sakte, eller moderat inkoordinasjon og manglende nøyaktighet, eller vektbærende aktiviteter som gjøres med vanskeligheter, eller primitive gripemønstre.
4	**Bevegelse nært det normale,** men: noe saktere, eller mangler presisjon, flyt eller presis koordinasjon, eller kan gjennomføre vektbærende aktiviteter men med noe nølende eller med små vanskeligheter.
5	**Normale bevegelser *:** God flyt og koordinasjon, hastighet innen for normale grenser.

* For å bestemme hva som er normalt kan den mindre affiserte armen brukes som referanse, dersom man samtidig tar premorbid dominans i betraktning.

Appendix C: Shaping registration form

Journal Shaping

Deltaker:_____ **Oppgave:** _____

Behandlingsdag: _____ Dato:_____ Tid: _____ Terapeut: _____

Plasser: _____ :	**Plasser:** _____ :
I forhold til pasienten (ett kryss):	I forhold til pasienten (ett kryss):
____ Foran ____ Til høyre ____ Til venstre	____ Foran ____ Til høyre ____ Til venstre
____ annet: _____	____ annet: _____
Avstander:	Avstander:
_____ cm fra bordkanten	_____ cm fra bordkanten
_____ cm fra midtlinjen	_____ cm fra midtlinjen
_____ annet: _____	_____ annet: _____
Høyde: _____ cm.	Høyde: _____ cm.

Instruksjon som blir gitt (hvis relevant): _____

Assistanse som blir gitt (hvis relevant: _____

Coaching som blir gitt (hvis relevant): _____

Feedback parameter (FPM): _____

Progresjonsparameter 1 (PPV1): _____

Progresjonsparameter 2 (PPV2): _____

Progresjonsparameter 3 (PPV3): _____

,

Appendix D: Shaping schedule

Deltaker:_____ **Oppgave:** _____

Behandlingsdag: _____ Dato:_____ Tid: _____ Terapeut: ____

Forsøk	FPM	QOM	PPV1	PPV2	PPV3	Kommentarer
Enhet cm / s						
1						
2						
3						
4						
5						Snitt:
6						
7						
8						
9						
10						Snitt:

Behandlingsdag: _____ Dato:_____ Tid: _____ Terapeut: ____

Forsøk	FPM	QOM	PPV1	PPV2	PPV3	Kommentarer
Enhet cm / s						
1						
2						
3						
4						
5						Snitt:
6						
7						
8						
9						
10						Snitt: