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Constraint-Induced Movement Therapy in Stroke Rehabilitation:

Impact on Shoulder Pain, Motor Function, Balance and Health-Related Quality of Life

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Till mina barn och barnbarn

Contents

Abstract

Background. Constraint-Induced Movement Therapy (CIMT) is a treatment modality originally intended for impaired arm and hand function following unilateral brain damage, such as stroke. Extensive research has shown that CIMT may effectively enhance upper-extremity motor function with a good carry-over effect to activity levels and the improvements sustained at long-term follow-up. However, the impact of CIMT on hemiplegic shoulder pain (HSP) and Health-related Quality of Life (HRQoL) has not been adequately investigated and clinical implementation of CIMT has thus far been limited. The CIMT concept has eventually been adapted to treat lower extremity deficits (LE-CIMT) focusing on gait and balance, however currently with limited evidence.

Aim. The overall aim of this thesis was to investigate treatment effects of CIMT in an outpatient clinical setting with focus on HSP, motor function, balance, leg muscle strength and HRQoL after stroke.

Methods. A longitudinal cohort study was conducted at a physiotherapy clinic in Stockholm between 2000 and 2018. The CIMT treatment was delivered to all participants and consisted of high-intensity, task-specific training, six hours per weekday for two consecutive weeks. Treatment focus was on either arm/hand or gait/balance. Assessments used were the Fugl-Meyer Assessment scale for scoring shoulder pain, goniometry for passive and active shoulder ROM and B. Lindmark Motor Assessment, Berg Balance Scale, Single-Leg-Stance, one Repetition Maximum in a leg press and Timed Up and Go. All assessments were carried out pre- and post-CIMT and at 3-month follow-up. Additionally, the short form-36 (SF-36) Health Survey was administered pre-CIMT and at 3-month follow-up to assess HRQoL.

Results. Study participants were middle-aged and in the subacute and chronic post-stroke phases. In the upper extremities cohort (221 participants, median age 56 years, 62% men) we found significantly reduced shoulder pain alongside improved motor function and active and passive range of motion. Additionally, positive impacts were found on HRQoL at 3-month follow-up post-CIMT. Results demonstrated overall improvements in physical domains, with women improving significantly more in physical domains and men in mental domains.

Regarding participants in lower extremity CIMT (147 participants, median age 53 years, 68% men), the intervention demonstrated enhanced balance, leg strength and dual-task ability. Leg strength improvements were greater in the affected leg, resulting in decreased leg strength asymmetry between affected and non-affected lower extremity. Furthermore, we showed positive impacts on HRQoL, revealing improvements in the Physical Function and Vitality domains after participation in lower extremity CIMT. Improvements after both CIMT and LE-CIMT were maintained at 3-month follow-up.

Conclusion. CIMT and LE-CIMT are clinically applicable treatment modalities in an outpatient clinical setting with positive impacts on HSP, motor function, balance and leg strength as well as improved self-assessed health-related quality of life among predominantly middle-aged individuals in a chronic stage post-stroke.

Sammanfattning på svenska

Bakgrund. Stroke är den vanligast orsaken till förvärvad funktionsnedsättning hos vuxna i Sverige och drabbar årligen närmare 25 000 personer, varav ungefär 20 % är under 65 år. Trots betydande forskningsframsteg och förbättrad vård, bedöms behovet av vård och omsorg för denna patientgrupp komma att öka framgent. Forskning och hälsovård står således inför en betydande utmaning att utveckla evidensbaserade och effektiva metoder för vård inklusive rehabilitering.

Constraint-Induced Movement Therapy (CIMT) är en behandlingsmodell som ursprungligen utvecklades för behandling av nedsatt arm/handfunktion efter halvsidig hjärnskada såsom stroke. Flera decenniers forskning har visat att CIMT har god effekt på nedsatt rörelseförmåga, att försökspersoner efter behandlingens slut använt sin svagare arm/hand i vardagssituationer och att behandlingseffekten kvarstått vid långtidsuppföljning. Studier har vidare kunnat påvisa att behandling med CIMT stimulerar hjärnans plastiska förmåga att reparera sig och att kunna ta nya områden i hjärnan i anspråk för att återfå funktion och förmåga. Med tiden har CIMT-konceptet kommit att utvecklas även för behandling av nedsatt gång- och balansförmåga (LE-CIMT) och även om CIMT för gång/balans är betydligt mindre beforskat, pekar befintlig forskning på likaledes goda resultat. Trots ett tydligt evidensläge, är implementeringen av CIMT i klinisk verksamhet begränsad.

Syfte. Det övergripande syftet med denna avhandling, som omfattar fyra delstudier, var att utvärdera behandlingseffekter av CIMT utförd i en klinisk verksamhet. Avhandlingens delarbeten utvärderar effekter av CIMT avseende skuldersmärta, rörelseförmåga, balans, benmuskelstyrka och självskattad hälsorelaterad livskvalité (HRQoL), områden som är relativt lite beforskade och där kunskapen således är begränsad.

Metod. Studien är en longitudinell studie, utan kontrollgrupp, med data insamlat vid en fysioterapeutisk öppenvårdsmottagning i Stockholm mellan åren 2000 och 2018. Behandlingsinterventionen omfattade, i enlighet med CIMT konceptet, högintensiv, uppgifts-specifik träning 6 tim/dag, varje vardag i två veckor inklusive hemträning på helgerna och ett individuellt utformat träningsprogram att träna efter på egen hand efter avslutad behandling. En behandlingsperiod omfattade träning med inriktning på endera arm/hand eller gång/balans.

Resultaten utvärderades med följande status; Fugl-Meyer Assessment för bedömning av skuldersmärta, goniometer för rörlighet i skuldran, B Lindmark Motor Assessment, Bergs balansskala, 1-bensstående, Timed-Up and Go och ett Repetition Maximum för benstyrka i benpress. Utvärderingar gjordes före och efter samt 3 månader efter CIMT. Dessutom fyllde deltagarna i Short Form-36 Health Survey för utvärdering av självskattad hälsorelaterad livskvalité före och 3 månader efter CIMT.

Resultat. Deltagarna var medelålders där ca 90% var under 65 år. Deltagarna var i subakut och kroniskt skede efter stroke, med majoriteten i kroniskt skede, vid tiden för deltagande i CIMT (mediantid 9 månader från stroke till CIMT).

Avseende deltagare i arm/hand CIMT (medianålder 56 år, 62% män) visade resultaten på minskad smärta eller smärtfrihet vid passiv rörlighet i skuldran och att motorik och rörelseförmåga samtidigt förbättrats. Vi fann vidare, vid 3-månaders uppföljning, att deltagande i CIMT haft en positiv inverkan på HRQoL avseende fysiska parametrar för hela gruppen samt sågs en könsskillnad där kvinnorna i högre grad förbättrades på fysiska domäner och män på mentala, samtidigt som ingen könsskillnad noterades avseende förbättringar av rörelseförmåga i arm/hand eller rörlighet i skuldran.

Avseende deltagare i gång/balans CIMT (medianålder 53 år, 68% män) visade resultaten på förbättrad balans, muskelstyrka i benen och förmåga att utföra två sysslor parallellt, sk dual-task-förmåga. Muskelstyrkan i det svagare benet förbättrades betydligt mer, varför asymmetrin i muskelstyrka mellan benen minskade. Resultaten visade vidare att HRQoL förbättrades avseende domänerna fysisk funktion och vitalitet. För samtliga delstudier kvarstod behandlingseffekten vid 3-månadersuppföljning.

Slutsats. CIMT och LE-CIMT är en tillämpbara behandlingsmodeller för verksamhet inom klinisk öppenvård, med positiva behandlings-effekter avseende skuldersmärta, aktiv rörelseförmåga, balans och benmuskelstyrka, liksom för förbättring av hälsorelaterad livskvalité bland medelålders individer i ett subakut och kroniskt skede efter stroke.

Abbreviations

ADL	Activities of Daily Living
BLMA	Birgitta Lindmark Motor Assessment
BBS	Berg Balance Scale
CIMT	Constraint-Induced Movement Therapy
CNS	Central Nervous System
CT	Computed Tomography
ES	Effect size
FMA	Fugl-Meyer Assessment Scale
fMRI	functional Magnetic Resonance Imaging
ICF	The International Classification of Function, Disability and Health
IQR	Inter Quartile Range
HRQoL	Health Related Quality of Life
LE-CIMT	Lower-Extremity Constraint-Induced Movement Therapy
MCID	Minimal Clinically Important Difference
MRI	Magnetic Resonance Imaging
HSP	Hemiplegic Shoulder Pain
ROM	Range of motion
SF-36	Short Form-36 Health Survey
SLS	Single Leg Stance

SPSS	Statistical Package for the Social Sciences
TUG	Timed Up and Go
WHO	World Health Organization
1RM	One-Repetition Maximum
6-MinWalk	Six-Minute Walk Test

Definitions (WHO 2001)

Activity - the execution of a task or action by the individual

Body functions - the physiological functions of the body systems

Body structures - the anatomical parts of the body such as organs, limbs and their components

Capacity - the ability to execute a task or an action in a standardized environment

Environmental factors - the physical, social and attitudinal environment in which people live their lives

Functioning - umbrella term of body functions, structures, activities and participation, positive aspects

Impairment - problems in body function or structure as a significant deviation or loss

Participation - the individual´s involvement in his/her life situation

Personal factors - the particular background of an individual´s life, comprise features that are not part of health condition or health state

List of original papers

This thesis is based on the following papers, referred to, in the text, by their roman numerals:

I. **Sefastsson A**, Brändström T, Littbrand H, Wester P, Sörlin A, Stålnacke BM, Liv P, Hu X. **Constraint-Induced Movement Therapy reduced shoulder pain and improved function in subacute and chronic stroke: A cohort study.** Frontiers in Neurology. 2025 Sep 4;16:1639840. doi: 10.3389/fneur.2025.1639840.

II. **Sefastsson A**, Brändström T, Littbrand H, Wester P, Stålnacke BM, Sörlin A, Hu X. **Improved health related quality of life after Constraint-Induced Movement Therapy in middle-aged adults with stroke - A Longitudinal Cohort Study.** *Manuscript*

III. **Sefastsson A**, Marklund I, Littbrand H, Wester P, Stålnacke BM, Sörlin A, Langhammer B and Hu X. **Positive effects of lower extremity constraint-induced movement therapy on balance, leg strength and dual-task ability in stroke patients: A longitudinal cohort study.** Journal of Rehabilitation Medicine. 2024 Oct 3:56:jrm24168. doi: 10.2340/jrm.v56.24168.

IV. Brändström T, **Sefastsson A**, Littbrand H, Wester P, Stålnacke BM, Sörlin A, Hu X. **Improved Health-Related Quality of Life among individuals with stroke Following Lower Extremity Constraint Induced Movement Therapy: A Longitudinal Cohort Study**. *Manuscript*

Published in conjunction with this thesis but not part of the thesis:

Ingela Marklund, **Sefastsson A**, Fure B, Klässbo M, Liv P, Ståhlnacke BM, Hu X. **Lower-extremity constraint-induced movement therapy improved motor function, mobility and walking after stroke.** European Journal of Physical and Rehabilitation Medicine 2023 Mar 09 DOI: 10.23736/S1973-9087.23.07683-9

My contributions

Description of my contribution to the different papers:

I: Actively involved at all stages, including the idea, the planning and statistical analyses. Responsible for recruiting participants, planning and performing the intervention, collecting data and writing the manuscript. *First author*.

II: Actively involved at all stages, including idea, planning, and statistical analyses. Responsible for recruiting participants, planning and performing the intervention, collecting data, writing the manuscript and submission. *First author*.

III: Actively involved at all stages, including the idea, planning and statistical analysis. Responsible for recruiting participants, planning and performing the intervention, collecting data and writing the manuscript. *First author*.

IV: Actively involved at all stages, including the idea, planning and statistical analysis. Responsible for recruiting participants, planning and performing the intervention, collecting data and support in writing the manuscript. *Second author*.

Article published in conjunction with the thesis but not part of the thesis:

Responsible for recruiting participants, planning and performing the intervention and collecting data. Involved in formulating the idea and planning. Support in writing the manuscript. *Second author*.

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Preface

In the mid 1990`s as I participated in a university class on stroke rehabilitation, my fellow classmates challenged me on whether it was relevant to be doing rehabilitation training with stroke patients who were past their acute and subacute phases, which I, at the time, was doing. If the challenge was adequate, I would have wanted to change the path of my clinical career and if, on the contrary, the criticism was not valid, I wanted to learn more about the current evidence situation.

On pursuing my search for evidence, I came across the first articles on CIMT, published by Edward Taub and Steven Wolf in the 1980´s. After visiting with Dr Wolf at Emory University Atlanta GA where he generously shared assessments, clinical treatment and insight into the Extremity Constraint Induced Therapy Evaluation trial (EXCITE), which was about to start, I began planning my own clinical work with CIMT at my clinic in Stockholm.

Based on results from treating my first two groups of stroke patients I wrote a master paper on CIMT and shared my experiences and treatment outcomes with the local health authorities. We eventually decided to embark on a mutual journey to evaluate CIMT in a clinical setting. The project started out on a small scale – we kept a close watch on outcomes and later on, what started out as a small project, was expanded and altogether some 600 CIMT treatments were performed before I closed my small private clinic in 2018.

Working clinically with CIMT for 20 years was incredibly inspiring and rewarding - both to be able to make a difference for many participants and to experience the participants´ drive and strive to achieve and succeed. I have often felt empowered and enlightened, after a long day of focused work, from being amid the atmosphere created by four random individuals struggling to recover.

With this thesis I hope to clarify that clinical implementation certainly is possible and to inspire further research in CIMT. Since the clinical cohort is fairly extensive, I hope that gathering and analyzing outcomes may be of general interest and will help shed light on less known effects of CIMT. Having been given the opportunity to scientifically analyze and evaluate two decades of clinical work has been a privilege and tremendously exciting and gratifying. Many a time have results been what I anticipated but at times I have also been surprised and even puzzled.

Burgsvik, september 2025

Annika Sefastsson

Background

Stroke

Definitions and risk factors

The World Health Organization (WHO) in 1970 defined stroke as "*rapidly developing clinical signs of focal (at times global) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin*" (1). Five decades later, with extended knowledge of the central nervous system (CNS) and development of diagnostic tools like computed tomography (CT) and magnetic resonance imaging (MRI) that help clarify the diagnosis, there was a call for an updated definition of stroke. In 2013 the American Heart Association published a scientific statement *"Stroke is a neurological dysfunction caused by focal cerebral, spinal, or retinal infarction confirmed by neuroimaging or pathology"* ***(2).*** The WHO has kept its definition despite the medically and technically somewhat limited accuracy.

There are a series of established risk factors for stroke such as hypertension, high cholesterol levels, diabetes and lifestyle factors such as smoking, unhealthy dietary habits and lack of physical activity (3). A study investigating risk factors for stroke among young European adults found the same risk factors valid for the young but additionally found migraine, specifically with aura, birth control pills, heavy alcohol consumption and the use of illicit drugs to be risk factors (3-5).

Epidemiology

Stroke is the second leading cause of death worldwide (6) and the third leading cause of death in Sweden (7). Stroke is also one of the leading causes of acquired adult disabilities worldwide (8) and the prime cause in Sweden (9). Close to 25.000 people/year suffer a stroke in Sweden, with approximately 20% being under the age of 65 years (9). Most participants included in the four studies of this thesis are part of the age group <65. Stroke is caused by disrupted blood supply to the Central Nervous System (CNS) by either infarction (85%) or hemorrhage (15%) (7).

During the last decades Sweden, as well as other high-income countries, has seen a considerable decrease in stroke incidence, stroke related death and stroke severity, likely due to more effective acute care and primary and secondary prevention routines stipulated in national clinical guidelines (8, 9). During the same period, in Sweden as well as in other high-income countries, there has been an increasing stroke incidence in younger age groups (5). Despite overall stroke incidence rates decreasing, we are likely to see an increase in prevalence in the future due to an aging population (O´Flaherty 2023) and Europe alone has been estimated to have a 27% increase in the demand for rehabilitation and long-time care over the coming few decades (10). Health care is obviously faced with an immense demand to establish effective evidence-based rehabilitation interventions.

Symptoms and consequences of stroke

The most common initial stroke symptom is different degrees of hemiparesis of the opposite side to the side of the brain damage which is reported to initially affect approximately 80% of stroke patients (11). Additional common symptoms are sensory deficits, speech disorders, cognitive and perceptual impairments, depression and fatigue. Prevalent consequences of stroke include muscle weakness, shoulder pain, reduced walking and balance capacity and impaired health-related quality of life (HRQoL). Depending on the site and extent of the brain damage the degree of hemiparesis and other symptoms vary substantially between individuals. Spontaneous recovery of function post stroke appears mostly within the first three to six months after stroke onset (6, 12) and thereafter spontaneous improvement has been shown to subside (13, 14) and the individual often to experience a feeling of having reached a plateau regarding improvements (12, 15). However, improvements have been experienced and seen up to several years after stroke, to a highly differing degree and specifically when enhanced by effective rehabilitation procedures (16, 17).

Upper extremity symptoms

Reduced upper extremity (UE) sensorimotor function is a most common post stroke impairment affecting stroke patients both initially and with effects remaining long term (18). Reduced arm and hand function negatively affects the ability to perform activities of daily living (ADL) independently (6, 8) and leads to the individual remaining in need of different levels of support to manage their everyday life (13, 14). Reduced

hand motor function is defined to be a major factor negatively affecting HRQoL (19-21).

Hemiplegic Shoulder Pain (HSP) is a common complication (22) known to hinder the patient´s ability to participate effectively in rehabilitation (23, 24) and followingly, to negatively affect activity and HRQoL (23, 25-27). Research indicates a peak of HSP incidence around 4 months post stroke, which is after rehabilitation interventions have normally waned (28). Premorbid shoulder pain, poor arm motor function, age, female sex and reduced passive shoulder range of motion (ROM) for flexion and abduction are among risk factors identified in research for developing HSP (22, 26, 29).

A series of possible relationships of peripheral origin have been identified such as subluxation, impingement and rotator cuff tear (26, 30) while impaired sensation, hemi-spatial neglect and spasticity are identified causes of central origin (30) and mixed etiology is not uncommon. Central post stroke pain (CPSP) is estimated to account for approx. 8% of cases and younger stroke victims are found to have an increased risk for CPSP (31). Despite extensive research, risk factors and causes of HSP are not fully understood, and the prevailing view is that etiology is multifactorial and unclear (32-35).

Lower extremity symptoms

Regaining the ability to walk independently is a highly prioritized goal for stroke patients (36, 37) and likewise a main goal for rehabilitation interventions. Most stroke victims regain their walking ability to some degree, while over 60% experience reduced walking speed (38). Normal walking speed for healthy adults is generally stated to be approximately 1,3 m/s (39). Research implies that some 30% of stroke victims reach a walking speed of 0.8 m/s or more, which is considered a lower speed limit for victims to be expected to be community ambulatory (40). This discrepancy in walking speed reveals a substantial walking handicap in the stroke population despite rehabilitation efforts and costs. Impaired balance, muscle weakness as well as asymmetric strength of lower extremities (41, 42) negatively affect walking speed (43, 44), functional mobility and dual-task capacity (45) and have also been identified as risk factors for falls (46). Simultaneously, walking endurance and balance have been identified as key factors leading to activity and participation limitations and thus to negatively affect HRQoL (47, 48). Hence, an important focus and immense challenge in stroke rehabilitation is to improve treatment interventions in balance, strength and functional

mobility to help prevent falls, enhance walking capacity and improve HRQoL.

Rehabilitation

The ICF classification

The World Health Organization´s International Classification of Functioning, Disability and Health (the ICF) provide a structured model for aspects of rehabilitation and health. The ICF framework includes the health condition, body functions and structures, activity and participation, which in turn are affected by environmental and personal factors (6, 49) (Figure 1). Examples of the different aspects of health for body function and structures are muscle strength, joint motion and pain, for activities walking, mobility and managing ADL and participation entails an individual's involvement with family, work and leisure activities. Environmental factors may involve housing, social support system and societal attitudes while examples of personal factors are age, gender, marital status and level of education. All aspects are intertwined in an adaptive and interactive manner. The ICF classification can be utilized on any health condition to document and describe the condition, to set rehabilitation goals, to decide on means of assessment and to evaluate rehabilitation outcomes.

A recent study on how the ICF framework is implemented in the physiotherapy profession, concluded that the ICF is broadly known and approved of within the profession and is experienced to be clinically relevant in the areas of communication, assessment, intervention, outcomes and additionally when establishing local clinical guidelines (50).

Furthermore, the ICF classification serves as a research tool to study health and health related conditions and its consequences. The health condition in this thesis is obviously stroke and the rehabilitation outcomes are assessed on function, activity and participation levels. It has been argued that the ICF framework ought to be expanded to include the concept of Quality of Life (51). In Studies II and IV, HRQoL was assessed measuring the effect of impaired health on the individual's quality of life (52) with aspects on activity and participation levels.

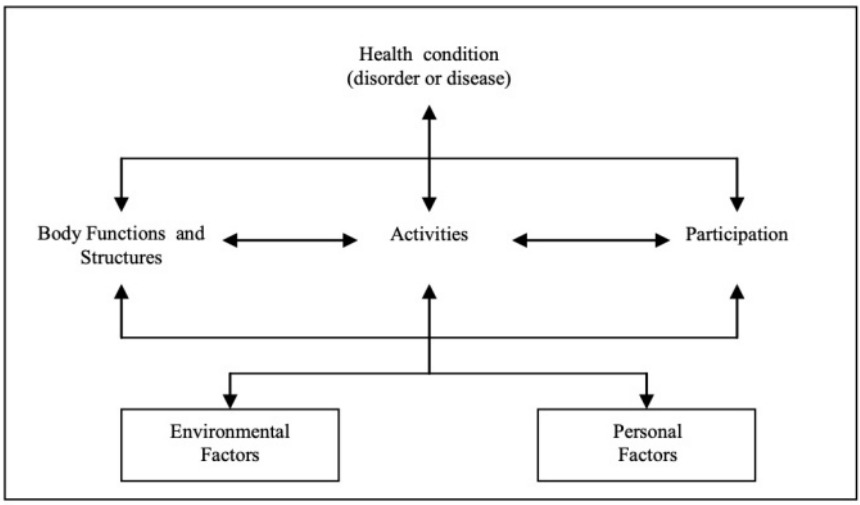

Figure 1. *The theoretical model of the International Classification of Functioning, Disability and Health (ICF)*

Brain plasticity

The brain´s capacity to modify and reorganize its structure and function as a reaction to brain damage caused by internal or external factors, enables an individual to regain function after stroke or other brain damage and is referred to as brain plasticity. The initial spontaneous recovery during the first weeks to months post stroke is enabled by means of plasticity. The effect of CIMT on brain plasticity was first demonstrated in the late 1990´s, when treatment induced motor improvements after CIMT was shown to correlate with both direct and 6 month changes in brain function in chronic stroke patients as assessed with fMRI (53, 54). The knowledge of the CNS plastic capacity forms the basis for current treatment modalities like CIMT and other task-oriented treatments.

Several other recent treatment strategies, both pharmacological and non-pharmacological, have been investigated and found to enhance and benefit from brain plasticity (55, 56). Research on the impact of physiotherapy interventions on brain plasticity has shown promising results with robot-assisted training improving lost motor function (57) while other results on robotics have been contradictory (58, 59). Research findings state that the plastic capacity of the brain is life-long (53, 60, 61), revealing the potential for improvements even in the subacute and chronic stages post stroke. The increasing knowledge and understanding of brain plasticity needs to be further incorporated effectively in developing treatment models that maximize the potential of brain plasticity (62).

Recovery and compensation

Physiotherapy in stroke rehabilitation focuses mainly on achieving recovery of impaired movement and its associated functions based on a seemingly direct relation between motor impairment and function where an example is the correlation between the function walking and impaired leg strength (11). The term recovery in neurorehabilitation is most often used to describe clinical improvements however, this is done without clarifying whether the improvement is based on actual restitution of damaged brain tissue or on compensational mechanisms (63). Outcome measures in physical therapy typically register function and activity as the ability to achieve a movement or task without analyzing how the task is performed, i.e. the quality of the movement. Consequently, a patient may receive a full score for accomplishing a task if the outcome measure does not specify how the task is to be performed. Other outcome

measures will deduct part of the score if a task is not fully completed or performed in a slow or uncoordinated manner indicating that a task may need compensatory motor strategies to be completed.

Compensatory strategies are utilized to enable performance of daily activities when normal function is lost and helpful or even crucial to the patient in the early phase post stroke and for the individual to achieve a desired task like dressing or eating. However, compensatory strategies may, in the long run, limit the individual´s ability to make additional improvements and contribute to the individual reaching a standstill regarding improvement in motor performance (63). This may in turn facilitate the development of learned-non-use (64).

Stroke Rehabilitation

The WHO definition of rehabilitation is "a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions, in interaction with their environment"(65). The main quest for stroke rehabilitation is to enhance function and activity leading to enhanced participation, while considering personal and environmental factors, to enable the stroke victim to return as much as possible to everyday life and to reach the highest possible level of independence and quality of life all according to the ICF framework.

The Swedish national guidelines for stroke emphasize the importance of interdisciplinary rehabilitation interventions and that the acute care is handled in a specialized stroke unit (9). Generally, in Sweden, stroke care facilities offer stroke rehabilitation in the early subacute phase (24 hrs until 3 months) while rehabilitation in the late subacute (3 - 6 months) and chronic phases (>6 months) is less commonly available despite the Swedish national guidelines suggesting that stroke survivors need lifelong recurrent rehabilitation measures (9). Early supported discharge (ESD) from stroke unit care with continued rehabilitation in one's home for patients with mild stroke has been thoroughly investigated and has demonstrated solid positive results and Swedish national guidelines conclude that ESD with specialized multidisciplinary rehabilitation in the home setting after mild stroke is an evidence based and recommended intervention. (9, 66-69).

With an increasing prevalence and more stroke survivors living at home the demands on outpatient rehabilitation facilities to deliver cost and time effective rehabilitation interventions impose an immense challenge. Several international clinical guidelines, based on substantial research

evidence emphasize the importance of high-intensity rehabilitation interventions (70, 71)

Physiotherapy in rehabilitation

Physiotherapy interventions

Physiotherapy is a key contributor to interdisciplinary stroke rehabilitation. During the last few decades, the field of stroke in neurological physiotherapy has seen an unprecedented increase in research output. Current consensus in the field of stroke motor rehabilitation includes focus on task-specificity, intensity and repetition (11, 71, 72). The importance of exercises being goal-oriented and meaningful to the patient and of rehabilitation taking place in an enriched environment (73) is emphasized. Despite high intensity and repetition being emphasized the definition thereof varies greatly. Research states the importance of massive doses of up to 6 hrs. of daily training to produce clinically meaningful improvements in the subacute and chronic stages (16, 70, 71)

Upper extremity physiotherapy interventions

A number of physical therapy interventions, enhancing UE function, as recommended by international clinical guidelines, include bilateral arm training (74) strength training (75, 76) and repetitive task-specific training (77). Different versions of electrical stimulation, mirror therapy, robotics and virtual reality are recommended mostly as an adjunct to conventional therapy (78).

Constraint-Induced Movement Therapy which was developed to overcome upper extremity impairments after CNS damage, including stroke, is to date the most investigated treatment intervention for stroke patients and it has the strongest and most comprehensive evidence base to date (11, 71, 79, 80).

With HSP etiology remaining unclear, consensus regarding treatment interventions has not been established. Both pharmacological and non-pharmacological interventions have demonstrated different degrees of effectiveness on HSP (24, 33, 81-83). Physiotherapy has been identified as a primary treatment choice for HSP often combined with oral analgesics. Swedish national guidelines recommend the use of a cuff sling to reduce shoulder pain (9, 24). Possible effects of different

electrical stimulation modalities have been subject to extensive research (33, 84, 85) with contradictory and uncertain results and the interventions are not explicitly recommended in Swedish national guidelines. Effects of local injections with different substances have been investigated (86, 87) as has injections with botulinum-toxin A with inconclusive effects (81, 88). HSP in the subacute and chronic phases is considered under-diagnosed (27, 89) and a substantial part of HSP patients do not receive pain treatment in the later phases (23, 90) indicating that HSP is also an under-treated diagnosis (89).

Lower extremity physiotherapy interventions

Various physical therapy strategies are being used to enhance walking capacity, balance and strength in stroke survivors (91, 92). Based on positive results from CIMT, the protocol was eventually modified into a Lower Extremity-CIMT (LE-CIMT) protocol (79, 93, 94) partially enhanced by various other physical therapy approaches, such as high-intensity training and task-specific-training shown to positively affect gait, balance and strength among persons with stroke (92, 95). Other lower extremity interventions include treadmill training with or without body weight support (96), balance training (97), aerobic and strength training (75, 98) are utilized to address walking and balance deficits with a growing evidence base. A recent review concluded that using a combination of different approaches would likely improve degree of recovery of function and mobility after stroke (99).

Constraint-Induced Movement Therapy

CIMT was initially developed to augment impaired upper extremity motor function after Central Nervous System (CNS) damage and is based on the knowledge from novel findings on brain plasticity (64, 79, 100). Extensive research has proven CIMT to be an effective treatment for improving arm and hand function in the acute and chronic phases post stroke and, importantly, with a transfer of treatment effects into everyday life and with effects remaining at long term follow-up (79).

The theory of CIMT is based on studies of primates by several research teams during the 19-hundreds and again during the 1960´s by Taub (64). The observation was made by Taub that deafferented monkeys refrained from using the insensate upper limb unless forced to do so by immobilization of the not impaired upper limb and the conclusion was drawn that not using the insensate forelimb was disuse rather than

inability – which Taub interpreted as a behavioral strategy that he labeled “learned-non-use”.

The original CIMT protocol consists of four main features: *(I)* highly intensive, task-specific supervised training of the upper extremity, six hours/day, for two consecutive weeks. *(II)* restraint of the intact upper extremity, usually a padded mitt or a sling, to be worn for 90% of waking hours. *(III)* training based on shaping strategy, where more complex activities are practiced in small steps with a gradually increasing level of difficulty to ensure that goals are achievable to the patient. The achieved skills are eventually assembled into a more complete activity, which could be expressed as “practicing parts” before “practicing tasks”. *(IV)* transfer package, a series of behavioral features intended to support the transfer of achieved skills from the treatment situation to everyday life – from “can do” to “actually does do”.

Several modified CIMT (m-CIMT) protocols have been investigated in a series of RCT studies with a varying number of weeks and hours of intervention and with or without behavioral aspects or restraint on stronger hand/arm. Different definitions have been stipulated such as high-intensity modified CIMT (3-6 h/day) and low-intensity mCIMT (<3 h training/day) and modifications have demonstrated similarly good results as the original protocol (79). CIMT and mCIMT are currently considered the most effective treatment regimens in physical therapy to improve upper extremity on function and activity levels (6, 72).

Lower extremity CIMT

In recent years, a protocol outlining LE-CIMT has been developed; however, its evidence base remains less robust than that of CIMT (101). Nevertheless, several RCT studies (102, 103) and systematic reviews (104, 105) have been published, mostly supporting the effectiveness of LE-CIMT on improving impaired gait, functional mobility and balance.

The LE-CIMT protocol is a modification of the original CIMT protocol and consists of: intensive supervised task-specific training, motor training based on shaping strategy, the application of a transfer package and, when considered appropriate, use of restraint on the stronger leg combined with exercises that focus mainly on the weaker leg. (106). LE-CIMT typically encompasses exercises that provoke balance and postural control, strength exercises, task specific walking exercises and stretching of short muscles when required.

Balance training

Balance deficit is a common post-stroke impairment that limits the individual on activity and participation levels and negatively affects quality of life (11). Reduced balance capacity is estimated to affect approximately 83% of stroke victims (107). Balance and postural control encompass the individual's ability to maintain, achieve or restore balance in each situation and is dependent on the CNS´s ability to integrate its sensory and motor systems (108). The ability to sustain balance is crucial to functional mobility, to walking and balance and apparently has among the strongest relations to walking capacity. Falls are common in the stroke population and are repeatedly related to balance deficits (109, 110). People with higher levels of balance control have been found to have fewer injuries after a fall, possibly because the impact of falling being reduced by intact balance reactions (91) which in turn is dependent on leg muscle strength.

These findings indicate a need to include balance training in treatment interventions aimed at improving walking and to simultaneously reduce the risk of falls (109). Research emphasizes that effective balance training is task-specific, intense and repetitive with a gradually increased level of difficulty. Systematic reviews conclude that further research is needed to establish best practices to improve balance capacity (75, 108).

Strength training

Stroke results in extensive loss of muscle strength, which is significantly related to functional mobility and walking as well as to ADL activities (41, 111, 112). Research has reported muscle strength in the affected leg to be around 50% of that of matched controls (42). Muscle strength has been identified as one of the stroke-related impairments most strongly associated with walking capacity. Furthermore, decreased muscle strength is related to increased risk of falls and has been identified as a significant predictor of reduced HRQoL (47). These findings highlight the need to include effective strength training in rehabilitation programs. Progressive resistance training is an established training modality to increase muscle strength. It entails exercise against a progressively increasing load and a small number of repetitions aimed at overloading a muscle. The muscle being overloaded stimulates neural and muscular changes resulting in increased muscle strength (76). Progressive resistance training has demonstrated increased muscle strength in lower as well as upper extremity post stroke with effects persisting at long-term follow-up (75, 98). Maximum strength is often trained with a load

of 80% of 1RM and with few repetitions while enduring strength is often trained with a load of 60% of 1RM and with a larger number of repetitions. A resent systematic review concluded that resistance training of different scopes positively affects walking capacity and speed as well as HRQoL post stroke (113).

Health related quality of life'

Health-related quality of life (HRQoL) is a broad concept that reflects how people perceive their physical, mental, and social well-being as being affected by their health status, disease, or treatment**.** In stroke rehabilitation, assessing HRQoL provides insight into how individuals experience the impact of stroke and complement traditional measures that mainly focus on impairment and activity. HRQoL is often reduced after stroke, with studies showing up to a 35% decrease compared to the general population. Assessing HRQoL is thus essential for evaluating rehabilitation outcomes from the patient's perspective.

Rationale for this project

Constraint-Induced Movement Therapy (CIMT) for the upper extremity has strong evidence for improving arm and hand function after stroke, with lasting effects. Despite numerous RCTs and systematic reviews, its clinical use remains limited—likely due to lack of awareness, confidence and organizational barriers. This project aims to evaluate the effects of CIMT in routine clinical settings, using broader inclusion criteria than in most research, among middle-aged individuals in subacute and chronic post-stroke phases.

Hemiplegic shoulder pain (HSP) is common after stroke but rarely studied in relation to CIMT. Patients with HSP are often excluded from trials due to concerns of the treatment causing increased pain. In this thesis the effects of CIMT on HSP will be investigated.

LE-CIMT, a modified protocol targeting the lower limb, has shown promising results but remains less investigated. The effects of CIMT on functional mobility, balance, leg strength, and dual-task ability will be investigated. Effects on dual-task ability is scarcely studied despite its importance for fall prevention.

Finally, possible effects of CIMT on health-related quality of life (HRQoL) from pre-intervention to 3-month follow-up will be evaluated. HRQoL provides a vital patient-centered perspective beyond functional outcomes, yet few studies have explored its response to CIMT or LE-CIMT.

Aims

The overall aim of this thesis was to investigate the effects of CIMT and LE-CIMT delivered in an outpatient clinical setting with broader recruitment criteria than traditional RCTs. Especially, the thesis aimed to determine whether these interventions improve motor function for upper and lower extremities, reduce shoulder pain and enhance Health-Related Quality of Life in middle-aged individuals during the subacute and chronic stages post stroke.

Study I

To investigate the effects of CIMT on HSP, passive and active ROM and upper extremity motor function by comparing data from pre- to post CIMT and if eventual effects persist at follow-up. An additional aim explored in this thesis was to assess whether participants with HSP achieved improvements on par with participants without HSP.

Study II

To evaluate effects of CIMT on HRQoL and to investigate effects on HRQoL from pre-CIMT to 3-month follow-up.

Study III

To explore whether LE-CIMT can improve balance, leg muscle strength and dual-task ability by comparing data from pre- to post CIMT and if eventual effects persist at follow-up. A second aim was to examine whether any observed effects correlated with descriptive characteristics.

Study IV

To investigate the effect of LE-CIMT on HRQoL from pre-CIMT to follow-up and to examine whether any observed effects correlated with descriptive characteristics.

Material and methods

Study setting and design

The present thesis is based on a longitudinal cohort study with data gathered between 2000 and 2018 from an outpatient physiotherapy clinic in Stockholm, Sweden. The private outpatient clinic specialized in CIMT and LE-CIMT which was offered to patients with hemiplegia after CNS damage. Data from the years 2000 to 2014 were collected retrospectively from medical records and thereafter prospectively until 2018. All included participants were followed with an identical study protocol. Patients were mostly referred to CIMT from regional hospitals after having undergone standard rehabilitation routines of differing scope.

Ethical approval

Ethical approval was obtained from the regional Ethical Review Board in Umeå and, as of 2019, The Swedish Ethical Review Authority, Sweden (Dnr. 2013-327-31 M).

Participants provided written informed consent prior to study inclusion. This study conformed to the Helsinki declaration.

Participants

Study participants were recruited from patients who had or were going to participate in CIMT and/or LE-CIMT at the outpatient clinic and who met the following inclusion criteria: motivation to participate defined as an expressed wish to participate after receiving written and oral information about the treatment, minimum 1 month since acquired brain injury, ability to understand written or oral instructions, ability to walk indoors without an assistive device or using a wheelchair and minimum wrist extension 20 degrees and finger extension 10 degrees. The motor criteria for wrist and fingers were to be performed three times in maximum one minute (16). Patients with unstable medical conditions, as assessed by a physician, were not referred to CIMT. Between the years 2000 and 2008 the Mini Mental State Examination (MMSE) was performed with a limit for inclusion set at 23 points out of a maximum of

30 points with the ambition to ensure sufficiently good cognitive function. Efforts were made to contact all patients who participated in CIMT between 2000 and 2014 to invite them to participate in the study. Regarding the prospective part of the study, patients were invited to participate in the study on their first visit to the clinic.

Study participants were recruited from patients who had or were going to participate in CIMT and/or LE-CIMT at the outpatient clinic and who met the following additional inclusion criteria: written informed consent and participating in first ever CIMT or LE-CIMT. Exclusion criteria were brain injury other than stroke and age <18 years at time of stroke.

CIMT intervention

The treatment intervention in the included studies was mainly performed in accordance with the original CIMT protocol as described above (64, 79) with the exceptions of treatment being performed in groups of four participants and one physiotherapist (PT) and enhanced emphasis on muscle strength and joint motion exercises. Strength and mobility training of the shoulder exceeding the individuals pain limit in Studies I and III is also a modification of the original protocol. The treatment protocol for both CIMT and LE-CIMT encompassed:

At the initial visit to the CIMT clinic patients received oral and written information on CIMT including emphasis on CIMT being demanding, a conversation on personal rehabilitation goals and a general overview of motor function according to minimum motor inclusion criteria. Additional time for making the decision on whether to participate in CIMT was suggested.

On a second visit to the CIMT-clinic a 90 min assessment procedure was performed, where parts of the assessments are included in this thesis. Personal rehabilitation goals were discussed and a time plan for treatment participation was set.

The treatment intervention entailed:

I) Intensive supervised training. Six hours of daily training for 10 consecutive weekdays, supervised by a physiotherapist (PT) with extensive experience from working with CIMT. Individual exercise programs, based on pretreatment assessments and the patient´s individually set goals. A daily revision of the training programs was done

to ensure that exercises were adequately challenging and diverse. Utmost care was taken to avoid compensatory movements when performing motor- and activity enhancing exercises. Daily strength and joint motion exercises were performed. Participants were given personalized home exercises to do on weekends. Frequent feedback was given by the PT throughout sessions to ensure intervention fidelity.

For participants with HSP, strength exercises were performed even when initially provoking pain. Any painful exercise was discontinued if causing increased pain after several repetitions but then tried again with adequate alteration to prevent further pain.

(II) Motor training based on shaping strategy. The shaping strategy encompasses more complex motor tasks being practiced in small steps with a gradually increasing level of difficulty to ensure that exercises were achievable. The skills achieved were eventually assembled into the more complex and complete activity. The shaping strategy requires a comprehensive analysis of patient impairments by the physiotherapist. to enhance the ability to eventually practice the activity itself in a normalized manner.

(III) Application of a transfer package. A series of behavioral aspects were implicated to enhance real life use of the affected limb. A written agreement, mutually signed by the participant and the PT with personalized instructions to follow at home was utilized including a daily, informal follow-up on compliance with the agreement.

Participants were given personalized home exercises to do in the home environment during the two weekends included in the treatment period. Examples could be to pick door key out of a pocket, place key in door lock, turn the key, reverse and repeat, turning pages in the newspaper with weaker hand, emptying books from bookshelf, wiping off kitchen counter or back splash with a dishcloth with the weaker hand or standing up/sitting down without the support of hands a vast number of repetitions/day with feet positions specified.

After completing CIMT, participants received a training program which they were recommended to do 4 -7 days/week until the 3-month follow-up. The content and frequency with which to perform the program was decided in collaboration with the individual to enhance the feeling of responsibility and commitment. Participants were encouraged to keep a simple diary of the extent of training performed. There was merely an oral inquiry on compliance with the home exercise program at follow-up.

Patients could contact the PT for consultation if needed from the end of treatment until follow-up.

(IV) Constraining mitt. Participants in Studies I and II consented to wearing a padded mitt on the less affected hand for at least 90 % of waking hours. A written agreement was signed, stating situations constituting the individual exceptions from the agreement specified in detail. The equivalent of the constraining mitt for participants in LE-CIMT, Studies III and IV, was the use of an immobilizing orthosis on the non-affected leg during part of the training sessions.

Outcome measures

Assessments for the four studies were performed before and after treatment and at 3-month follow-up except for the SF-36 in Studies II and IV which were performed before treatment and at 3-month follow-up. (Table 1). Assessments were performed by an experienced PT who was well acquainted with all included assessments and who also planned and performed treatments and is the author of this thesis.

B Lindmark Motor Assessment. The studies I and II, subscale A of the full version of the B Lindmark Motor Assessment (BLMA) (114) was used. The BLMA is a 4-point scale (0-3) and has a maximum score of 57 points. The assessment has proven to be valid and reliable (115).

Fugl-Meyer Assessment, shoulder pain score. The FMA score was used to assess shoulder pain during passive flexion, abduction, external and internal rotation. The FMA was developed to evaluate recovery from hemiplegic stroke (116). The assessment records pain on a 3-point ordinal scale 0-2, where 2 indicates no pain, 1 some pain and 0 pronounced pain and followingly a total FMA shoulder pain score of 8 points indicates no pain. The maximum pain intensity was recorded as the highest FMA shoulder pain score in any one of the assessed directions of motion.

Goniometry. Passive and active ROM were assessed using goniometry (117) and recorded as the sum of ROM for flexion and abduction (normal range 0-180° respectively). Tests were performed in a sitting position.

Berg Balance Scale. The BBS was used to assess functional balance capacity and is widely used in both research and clinical settings. The

scale has a maximum score of 56 points. The minimal detectable change (MDC) for BBS has been calculated to 2,7 points for chronic stroke (118).

One Repetition Maximum in a leg-press. Lower-limb strength was measured bilaterally as one repetition maximum (1RM) for leg extension in a leg press machine (119). 1RM is defined as the maximum weight a person can lift once before becoming fatigued. The difference in leg strength between the affected and nonaffected leg (Diff-1RM) illustrates the degree of leg strength symmetry.

Single leg stance. SLS was tested bilaterally, twice for each leg for a maximum of 30. The test assesses static postural control (120).

Timed Up and Go and TUG Manual. The TUG assesses functional mobility and balance. It is a commonly used test in the stroke population and has shown good reliability (45). The TUG manual is a development of the TUG. A manual task, in this case carrying a glass of water, is added to the TUG procedure (121). An inability to perform dual tasks may be an indicator of an increased risk of falls (122). MDC for TUG is calculated to be 3.2 s in the chronic stage post stroke (118).

Short-Form Health Survey SF-36. The Short Form - 36 Health Survey (SF- 36), Swedish standard version was used to assess Health Related Quality of Life (@ref). The SF-36 is a generic, patient-reported health survey covering 8 domains of health: physical functioning (PF), physical role (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role (RE) and mental health (MH). The SF-36 is widely used in research and clinical settings. Results were analyzed for the eight domains separately as well as for Physical Component Score (PCS) and Mental Component Score (MCS).

Table 1. *Assessments utilized for upper and lower extremity CIMT respectively, categorized into ICF levels. ICF-International Classification of Functioning, Disability and Health.*

ICF domain	Upper Extremity	Lower extremity
Function	B Lindmark Motor Assessment	Berg Balance Scale
	Fugl-Meyer Assessment shoulder pain score	Leg strength, One Repetition Maximum in a leg press
	Goniometry, active and passive shoulder flexion and abduction	Single leg stance
Activity	B Lindmark Motor Assessment	Berg Balance Scale
		Timed Up and Go
	Short Form-36	Short Form-36
Participation	Short Form-36	Short Form-36

Statistical analyses

All data analysis in this thesis were performed using the IBM SPSS Statistics software, version 29.0.1.0. Figures were generated using the GraphPad Prism 10, version 10.3.0.

Table 2. *Statistical analysis performed in studies I, II, III and IV.*

Statistical test	Study I	Study II	Study III	Study IV
Tests for normality				
QQ-Plots	X	X	X	X
Shapiro-Wilks Test	X	X		X
Histograms	X	X		X
Between-group comparisons				
Chi-Square Test	X	X		X
Mann-Whitney U Test	X	X		X
Within-group comparisons				
Sign Test for Matched -Pairs	X			
Wilcoxon Matched-Pairs Signed-Rank Test		X		X
Linear Mixed Model			X	
Post hoc test (correction for multiple comparisons)				
Bonferroni Correction	X		X	
Correlation				
Spearman´s Rank Correlation				X
Effect Sizes				
PS_{dep} (Probability of Superiority for Dependent Samples)	X			
$r\ (Z / \lvert \sqrt{N} \rvert)$		X		X
Cohen´s d			X	

Study I

Descriptive statistics for baseline characteristics, including motor function and active/passive ROM, were summarized and reported as frequencies and percentages or as medians and interquartile ranges for the total cohort and for HSP and no HSP groups separately.

Group comparisons between HSP and no HSP groups were conducted using Chi-square- or Mann-Whitney U-tests, as appropriate. Outcome variables are presented as medians and interquartile ranges. Maximum pain intensity is also presented as percentages.

To assess whether participants with lower baseline motor function improved to the same extent as those with higher baseline motor function, BLMA scores were stratified (≤ 29 vs. >29 points) and compared using the Kruskal-Wallis test.

Study III

Demographic characteristics are presented as median and IQR. A linear mixed model (LMM) was used to evaluate mean differences between measurements pre- and post-treatment and follow-up. Q–Q plots were used to verify the normal distribution assumption for model residuals. To examine heterogeneity regarding effect on BBS, we fitted additional corresponding LMMs by including age, gender, type of stroke, affected side, or time to intervention as main fixed effects as well as their interactions with time.

Studies II and IV

Raw data from the SF-36 questionnaire were transformed into percentages of full HRQoL for the eight domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health, according to the SF-36 Swedish manual (123). Physical and mental component summaries (PCS, MCS) were calculated according to the SF-36 manual for summary scales (124).

Data were reported as frequencies and percentages for nominal variables and as medians and interquartile ranges (IQR) for continuous variables. Between-group comparisons were conducted using the Chi-square or Mann-Whitney U-tests, as appropriate. Within-group comparisons were performed using Wilcoxon matched-pairs signed-ranks test. A two-tailed p-value ≤0.05 was considered significant.

Study II specifics

Descriptive statistics for baseline characteristics, including FMA HSP sum, motor function (BLMA) and active/passive ROM, were summarized for both the study cohort and the drop-out cohort at follow-up. Outcome data were analyzed for the study cohort as well as stratified and analyzed separately for women and men, and time from stroke to CIMT dichotomized at 6 months.

Study IV specifics

Descriptive statistics for baseline characteristics, including FMA subscale for lower extremity motor function, BBS and 10mWT self-selected speed, were summarized for both study cohort and non-responders to SF-36.

Correlations were performed using Spearman´s rank correlation. The sample size of the present study allowed detection of correlations exceeding 0.52 with sufficient power (80%).

Results

Study cohorts

The participants in all four studies included in this thesis are young with median ages between 53-56 years; they are predominantly in the chronic stage post stroke and approx. one third are women (Table 3).

Table 3. *Baseline characteristics for study cohorts Studies I, II, III and IV.*

Characteristics	Study I	Study II	Study III	Study IV
Participants (n)	221	95	147	30
Gender F/M (n, %)	84/137 38/62	39/56 41/59	47/100 32/68	10/20 33/67
Age (years, median (IQR))	54 (46-61)	56 (49-63)	53 (45-59)	53 (45-59)
Time stroke to CIMT (months, median (IQR))	9 (5-14)	9 (5-18)	11 (7-16)	12 (8-17)
Affected side right/left (n, %)	111/110 50/50	49/46 52/48	84/62 57/43	17/12 59/41

The studies are based on data from four different size cohorts of 221 (I), 95 (II), 147 (III) and 30 (IV) individuals respectively, between 18 and 75 years of age. The four cohorts are partly and to differing degrees intersecting for Studies I and II and for Studies III and IV. Additionally, there is an overlap of 20.8% between CIMT and LE-CIMT cohorts meaning that 64 participants received both upper and lower extremity CIMT (Figure 1).

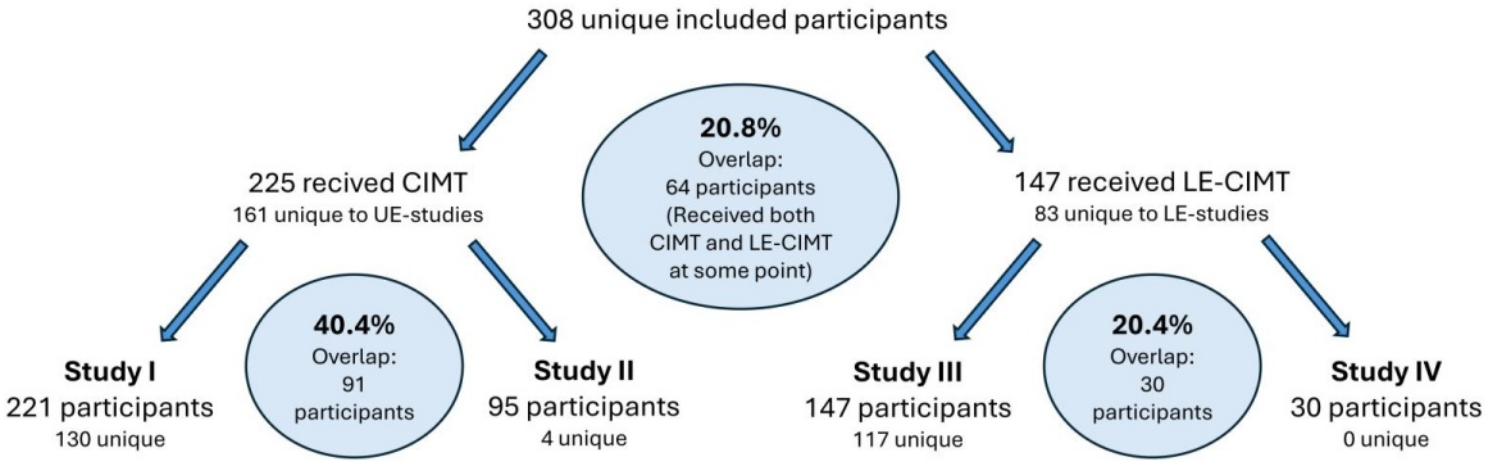

Figure 1. *Patients included in the four studies with cohort overlaps specified in numbers and percentages.*

Studies I and II

Upper extremity-CIMT reduced HSP and improved HRQoL

Out of 221 subjects included in Study I, 46% (101subjects) had pre-CIMT shoulder pain at passive shoulder motion (HSP group) and 120 had no pre-CIMT shoulder pain (no HSP group). Study II entailed 95 participants in all, 91 of whom were part of both study cohorts.

FMA shoulder pain scores improved from pre- to post-CIMT as well as to follow-up with a strong ES and maximum shoulder pain intensity decreased from pre- to post-CIMT and to follow-up (Figure 2A and B).

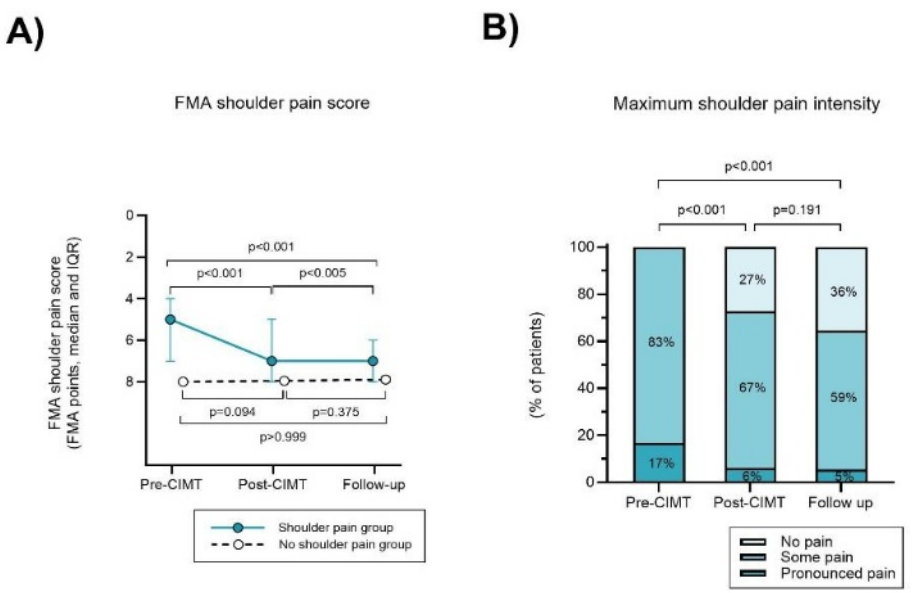

Figure 2. Reduced shoulder pain after CIMT in the group with pre-CIMT hemiplegic shoulder pain. (A) The total of FMA shoulder pain scores in four directions of motion (flexion, abduction, external- and internal rotation) are presented on a reversed scale as a higher score indicates less pain. (B) In the hemiplegic shoulder pain group, maximum shoulder pain intensity for each time of assessment was scored as the highest degree of shoulder pain in any of the four directions of motion tested. *Previously published in Study I.*

In the HSP group, active and passive ROM increased significantly. Substantial improvements were seen in motor function for the total

cohort with a strong ES. Interestingly, when stratified into quartiles on BLMA scores, no differences were registered regarding degree of improvement regarding motor function in the HSP group (Figure 3). Importantly, no increase in HSP was seen in either subgroup post CIMT or at follow-up. There was no significant difference regarding prevalence of HSP depending on time from stroke to CIMT.

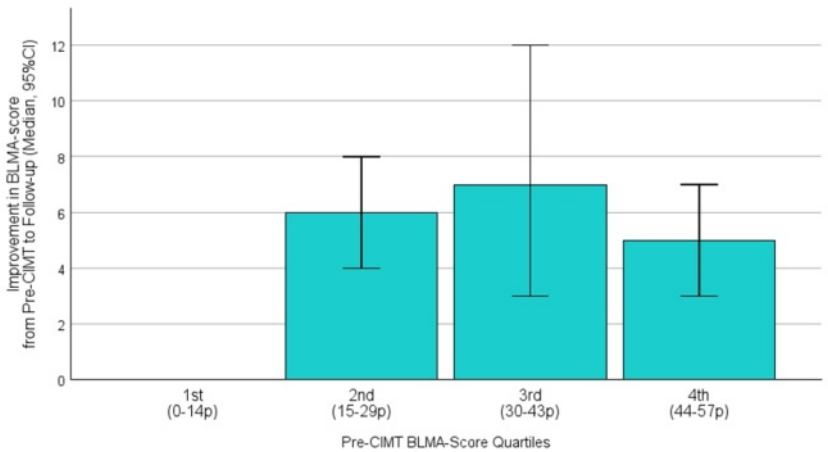

Figure 3. *Median improvements in BLMA-score from pre-CIMT to follow-up for HSP-group. Individuals stratified by BLMA-scale quartile at pre-CIMT. Nobody had a BLMA-score lower than 15. The Kruskal-Wallis test showed that regardless of pre-intervention motor function, no significant differences between improvement were observed.*

Drop-out analysis for participants lacking data for SF-36 at follow-up in Study II revealed that the drop-out group was younger and had poorer pre-CIMT motor function score compared to the study cohort. From pre-CIMT to follow-up for the total cohort, the PCS median was improved while the MCS score did not improve significantly. A gender difference was observed for the component summary scores, where female participants improved significantly more on PCS and male participants improved significantly more on the MCS while no gender difference was seen for motor improvements as registered in Study I.

Significant improvements were demonstrated for HRQoL in five out of eight separate SF-36 domains namely Physical Functioning, Physical Role, Bodily Pain, Vitality and Social Functioning (Figure 4).

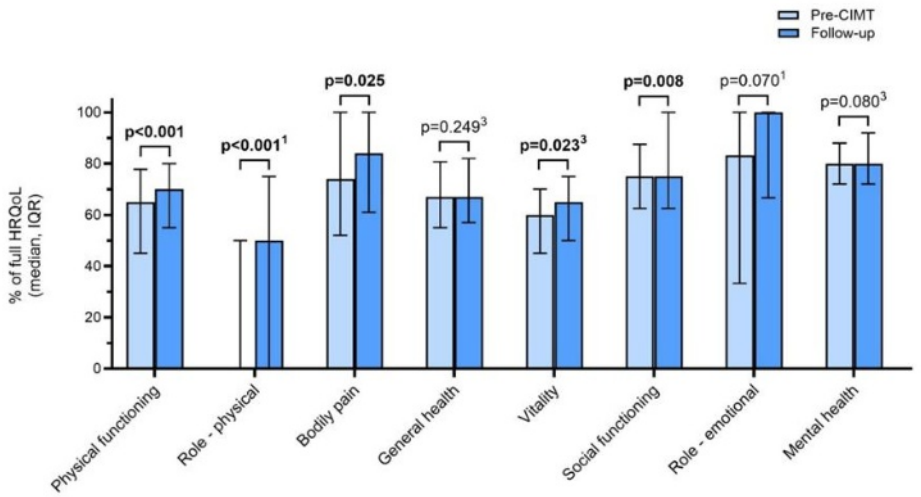

Figure 4. *SF-36 domains at pre-CIMT and follow-up. Results presented as median and interquartile range. P-values for comparisons between time-points, performed using Wilcoxon signed ranks test. The bold p value indicates statistical significance. Number of missing data in super script. Previously published in Study II.*

Study III and IV

Lower extremity-CIMT improved balance and HRQoL

A total of 147 subjects were included in Study III and 30 subjects in Study IV, where Study IV intersected fully with Study III. Analyses of Study III results revealed significant improvements for balance and SLS on weaker leg as well as regarding dual-task ability.

Significant improvement was also registered for leg muscle strength for both legs but more so for the affected leg. Results demonstrated a decrease in leg strength asymmetry of approximately 20% after LE-CIMT, with effects persisting at the 3-month follow-up (Figure 5A and B)

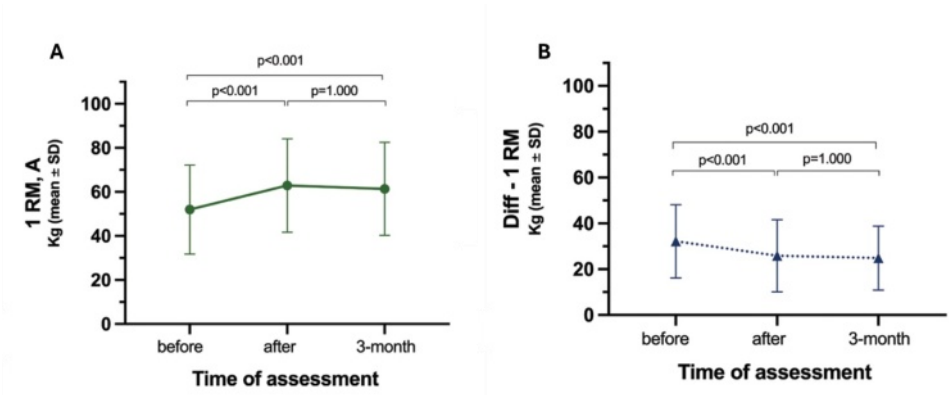

Figure 5*. Improvements in leg strength for the affected leg (A) and the difference in leg strength between the nonaffected and affected legs (B). Previously published in Study III.*

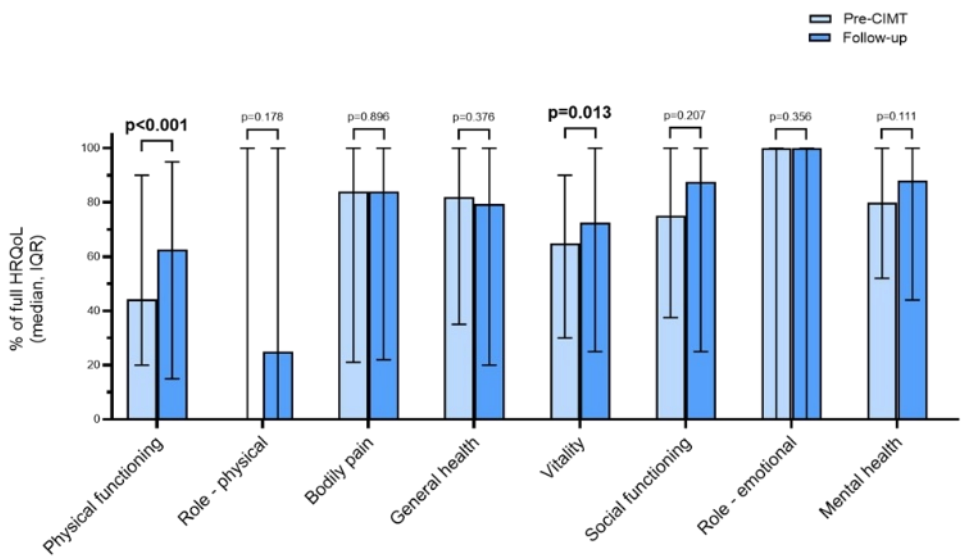

Figure 6. *SF-36 domains at pre-CIMT and 3 months follow-up. Within-group comparisons were performed using Wilcoxon signed ranks test. CIMT – Constraint-Induced Movement Therapy, HRQoL – Health Related Quality of Life, IQR – Interquartile range.*

In study IV, with a wide range of time between stroke onset and CIMT, participants were mostly in the chronic phase post stroke. Improvements in HRQoL from pre-CIMT to follow-up were seen in the Physical Functioning domain, where 80% of participants improved with a strong ES and the Vitality domain improved in 58.6% of participants. No significant differences were seen for the summary scores PCS or MCS (Figure 6).

No correlations between descriptive characteristics, including age, gender and affected side, and change in any of the eight SF-36 domains were noted. A significant negative correlation was observed for time from stroke onset to LE-CIMT and change in the Physical Function, Physical Role and Bodily Pain domains, indicating that earlier intervention is associated with greater improvements in these domains.

Discussion

Key findings

The studies included in the present thesis demonstrate Constraint-Induced Movement Therapy (CIMT) and Lowe Extremity-CIMT (LE-CIMT), performed in a clinical setting, to be effective treatment interventions in middle-aged stroke patients in the subacute and chronic stages post stroke.

A prominent finding in Study I is the pain-relieving effect on Hemiplegic Shoulder Pain (HSP) from this highly intensive treatment modality with pain relief sustained at 3-month follow-up. One fourth of HSP participants were pain-free post-intervention, with pain reduction being even more prominent at follow-up as more than one third were pain-free at follow-up. The findings that CIMT alleviated HSP for stroke patients with some as well as pronounced shoulder pain, are novel. Randomized Controlled Trials (RCT) studies addressing post-stroke motor impairments have tended to exclude patients with HSP from concerns of worsening pain.

Both HSP and no HSP groups showed significant and lasting gains in active shoulder Range Of Motion (ROM) and motor function. Participants in the HSP group with the lowest baseline motor function scores on the B. Lindmark Motor Assessment (BLMA) (15-29 points of 57) showed improvements comparable to those of individuals with higher baseline levels, thereby challenging indications that HSP negatively impacts the stroke patient´s ability to respond as well to rehabilitation interventions. Despite considerable improvements for the HSP group, they however reached merely the level of motor function that the subgroup without HSP had pre-CIMT. This raises the question whether the HSP group might have benefited from additional CIMT treatment.

Improvements in motor function, ROM and simultaneously reduced pain after CIMT is noteworthy. Treatments utilized to reduce HSP such as oral analgesics, electrical stimulation, local injections with different substances, injections with botulinum-toxin A or the use of a sling, some of which have demonstrated different degrees of effectiveness on HSP,

have not led to simultaneously improved and lasting motor function and ROM (82, 125, 126).

Health Related Quality of Life (HRQoL) in Study II improved significantly from pre-CIMT to 3-month follow-up regarding the Physical Component Score (PCS), reaching Minimal Clinically Important Difference (MCID), while the Mental Component Score (MCS) did not improve significantly. Notable gender differences were observed, with males improving on most of the mental domains and women improving strongly regarding physical domains and mostly so in the domain Physical Functioning. No differences were seen between men and women regarding improvements in motor function, shoulder ROM or regarding reduction of HSP. The results implicate that functional improvements affect men and women differently or possibly men evaluate the experience of participating in the group setting differently.

Study III, including 147 post-stroke individuals, revealed significant improvements in balance, lower limb muscle strength, leg strength symmetry and dual-task ability after LE-CIMT and persisting at 3-month follow-up. Effect sizes were small to moderate and effects on balance were not influenced by sex, affected side or time since stroke onset. Younger participants demonstrated generally better balance than older participants within this middle-aged cohort.

In Study IV, with 30 middle-aged, subacute and chronic post-stroke individuals receiving LE-CIMT, self-perceived HRQoL improved significantly in the SF-36 domains Physical Functioning and Vitality from pre-intervention to 3-month follow-up, indicating LE-CIMT to be a feasible treatment modality applicable in a clinical setting. Shorter time from stroke onset to CIMT intervention was associated with greater gains in Physical Functioning. No significant changes were seen from pre-CIMT to follow-up in the component scores PCS or MCS.

Studies I & III

Improvements in function and activity

Physiotherapy interventions mostly address improvement on the ICF level of impairment. The aim of improvement on the body function and structure level is for the improvements achieved to transfer to activity and participation levels. Improvement on function level is crucial for improvements in activity level to not merely be based on compensatory

strategies. Research results and experiences of CIMT and other high-intensity, task-specific, repetitive treatments provide a means of enhancing brain plasticity and achieving recovery.

This thesis demonstrated that high-intensity CIMT produced a marked reduction in HSP, improvements in passive and active shoulder ROM and improved motor function, in subacute and chronic post-stroke patients where spontaneous recovery is unlikely in merely two weeks. Despite the obvious limitations of a single-center, uncontrolled study, the rapid and substantial improvements in the included studies suggest recommendations in clinical guidelines to include high-intensity interventions, joint-mobility exercises and strength training in stroke rehabilitation.

Additionally, this thesis demonstrated that LE-CIMT effectively improved balance, leg strength, and dual-task ability in stroke survivors, confirming and extending findings from previous RCTs and reviews. Despite a ceiling effect on the Berg Balance Scale, the observed improvement suggests clinically meaningful change and supports the feasibility of LE-CIMT in an outpatient clinical setting. The medium effect size for leg strength aligns with prior controlled studies, underscoring LE-CIMT's potential to enhance both affected and non-affected limb strength and reduce leg strength asymmetry which are known key factors for gait and functional mobility. Moreover, the observed gains in dual-task ability, which are novel results after LE-CIMT, may indicate reduced risk of falls. The improvements persisting at 3-month follow-up highlight the lasting benefits of high-intensity, task-oriented training.

Studies II & IV

Improvements in health-related quality of life

The SF-36 domains assess the levels of participation and activity with somewhat more emphasis on activity items that address lower than upper extremity function. Improved health-related quality of life, closely related to quality of life, could be considered the ultimate goal for rehabilitation.

HRQoL has been reported to be more severely impacted in middle-aged individuals post stroke (127) indicating that relatively small motor impairments can affect HRQoL extensively in younger stroke victims. It

may be assumed that a smaller impairment from a subjective perspective can be of major importance to an individual with a high level of activity prior to stroke (Harno 2014).

High-intensity CIMT, both upper- and lower-limb protocols, demonstrated to be effective in improving HRQoL in cohorts of younger stroke victims in the subacute and chronic phases. In Study II, significant gains were revealed in the Physical Component Summary of the SF-36, as well as in the separate domains Physical Functioning, Physical Role, Bodily Pain, Vitality, and Social Functioning, with gender-specific effects in mental health outcomes. In Study IV improvements were seen in the Physical Functioning and Vitality domains. The improvement in Vitality in Studies II and IV may indicate reduced fatigue as the SF-36 Vitality domain is frequently used in research and clinical settings to assess fatigue. These improvements in Vitality could potentially also be supported by social interaction with other participants and substantial access to the therapist.

Collectively, findings in the included studies highlight CIMT as a clinically valuable, task-oriented intervention that simultaneously addresses pain, mobility, motor function, and physical and mental aspects of recovery.

Methodological considerations

Study design

This is an uncontrolled, longitudinal study with data collected in an out-patient clinical setting. There are certain strengths with this study design such as providing temporal relationships and fascilitating within-subject comparisons. The study design enables assessing multiple outcomes and monitoring effects at follow-up. Simultaneously, our study encountered drawbacks such as substantial loss of data at follow-up and confounding variables. Followingly, our results regarding HSP, lower extremity motor outcomes and effects on HRQoL need to be confirmed in RCT studies. As for upper extremity motor results, the evidence situation is strong, and we merely confirmed CIMT to be clinically applicable by showing results on par with those of earlier research.

The retrospective data from the first 14 years were originally not intended to be part of a study cohort but were added to the prospective

part of the study which includes the latter 5 years of collecting data (2014-2018). Mixing retrospective and prospective data is not optimal. However, the assessment procedure was at large consistent and the same physiotherapist performing tests in both the retro- and prospective part decreases the risk of inconsistency and bias in data collection.

The original CIMT concept involves treatment of one participant by one therapist. It seemed unlikely that this concept would be attractive to public health authorities mostly for economic reasons and therefore different size groups were tested within a master project prior to the studies included in this thesis. It was thought that support from and sharing experiences with other group participants could add value to the treatment experience. In study II, men improved significantly in mental component scores after having participated in CIMT and having improved significantly regarding motor function and reduced shoulder pain. Possibly the results on mental domains and mental component score are explained by positive experiences from social interaction with the other group participants. Despite intense training regimens during the two-week intervention, participants often voiced the appreciation of other group participants.

Cohort, age, gender and time since stroke onset

Cohort

The referral process was largely handled in cooperation with the referring clinics who were extensively informed on the inclusion/exclusion criteria and if there was any uncertainty regarding the suitability for a specific individual the CIMT clinic would be consulted before a formal referral was made. Since the CIMT clinic was not actively involved in the process of deciding who was to be referred, the selection procedure at the referring clinic was based on personal experience and knowledge about the intervention among the involved professionals in the hospital clinic and the process was not standardized. There was extensive cooperation between referring clinics and the CIMT-clinic including site-visits by members of the rehabilitation team, a series of lectures on CIMT and feedback on the individuals having participated in CIMT. Although the referred patients were well chosen for participation in CIMT, it cannot be ruled out that a PT with extensive experience from working with CIMT could have made differing evaluations of potential candidates for CIMT. To optimize the process of referrals, it would seem preferable that CIMT is an integrated part of

rehabilitation clinics. Patients referred from specialized wards in hospital clinics were often intended to return to work, and since the demand for CIMT was larger than the availability, this most likely affected the decision on who to refer to CIMT.

Age

Participants in our studies are young in a stroke context with a median age of 53–56 in the four different cohorts. The inclusion criterium for age was >18 years but there was no upper age limit at the clinic. However, due to the organization of stroke care in Sweden, individuals over the age of 65 are mostly offered rehabilitation within geriatric care and the few individuals over the age of 65 included in this thesis came rather on their own behalf. Among stroke patients in Sweden some 4% are under the age of 50 while in our cohorts approximately 35% were <50 years. The corresponding numbers for ages <65 are 20% and approximately 95%. Not offering CIMT to people 65 years or older is not based on research evidence but merely on economics and tradition. A Cochrane review and others indicate that participants in studies on CIMT tend to be younger than the mean ages for stroke (128).

Gender

Average age in Sweden for first ever stroke is 73 years for men and 77 years for women. Of individuals under the age of 65, experiencing their first ever stroke, approximately 65% are men. The ration men/women referred and included in the thesis reflects this gender discrepancy.

Time since stroke onset

Participants in our study are mostly in the chronic stage, with one third being in the subacute phase at stroke onset. The first few years the referring clinics would mostly refer to CIMT as the final step in the rehabilitation process and the median time from stroke to CIMT was at the time considerably longer than in the studies of this thesis. With increased knowledge and awareness of treatment outcomes following CIMT, patients were referred earlier in the rehabilitation process, mostly before “back-to-work” efforts. Thus, the median time from stroke onset to CIMT in our cohorts may not mirror routines of later days.

Intervention

Hemiplegic shoulder pain

Premorbid shoulder pain was not systematically registered, which would have been desirable. A study investigating prevalence of HSP found that 27% of those who developed HSP had premorbid shoulder pain (SP) while only 4% of those who did not report premorbid SP developed HSP – which underlines the importance of asking the stroke patient about premorbid pain.

The global median self-reported prevalence of shoulder pain in the general adult population is estimated to 16% (129) and it can thus be considered likely that our Study I cohort included participants with premorbid shoulder pain. The probability that even participants with premorbid pain experienced reduced pain from CIMT is in line with research and clinical practice in other medicinal disciplines. In orthopedics immobilization of the shoulder joint is avoided from knowledge that immobilization may cause pain (130) and repetitive mobilizing exercises are utilized to treat shoulder pain (131). Exercises have been utilized in treatment of neuropathic pain (132) and a recently published single-subject experimental design study showed a pain-relieving effect in HSP from exercise therapy (133).

No attempts were made within this thesis to assess etiology of HSP. Referrals to CIMT most often did not specify a diagnosis but merely information about the pain. Pain at passive movement was assessed for flexion, abduction, external and internal rotation and some conclusions on etiology may be drawn from painful movements, i.e. painful internal rotation is not typical in HSP and internal rotation was the passive movement causing least pain at assessments supporting the diagnosis HSP.

For the HSP group, strength exercises were performed even when initially causing pain. Any painful exercise was discontinued only if causing increased pain after several repetitions but then tried again with adequate alteration to prevent further pain. Performing exercises past the individual´s pain limit is not common in stroke care and is not supported by evidence or clinical consensus but was practiced on the base of clinical observations made two decades ago and reinforced through years of practice. From the pain-relieving results the conclusion can be drawn that performing exercises despite some pain in this group

of patients seems not to be contraindicated. A minor and transient increase in shoulder pain was registered for five participants post-CIMT which lessens concerns about the risk of CIMT affecting shoulder pain negatively, while some studies have raised concerns about HSP being triggered by exercises (22).

Prescribing a shoulder orthosis to reduce HSP is highly recommended (level 2) in the Swedish national guidelines (9). The evidence base for this intervention is limited but based mostly on clinical consensus. There is a looming risk that the initiative to discontinue the use of the orthosis is not taken by an individual with HSP and thus the risk of long-term immobilization is obvious. Several mechanisms may explain why immobilization could lead to pain with muscle atrophy and muscle strength imbalance causing pain from the mechanical load on the joint and surrounding tissue (134). Long-term immobilization causes connective tissue to thicken and become less elastic, which in turn activates pain receptors (adhesive capsulitis or frozen shoulder) (135). High intensity training, including daily strength training for a limited period of two weeks, increases circulation, initiates strengthening of shoulder muscles and increases neuromuscular activation and might be the explanation to why participating in CIMT partly reversed and abolished HSP. The findings highlight the close relationship between HSP, ROM, and motor function, emphasizing the importance of addressing these components simultaneously to promote meaningful, functional recovery that transfers to the real-world.

Strength training

Strength training is not specifically recommended in the Swedish national guidelines but is recommended as “aerobic fitness and muscle strength training” while some other western world guidelines specify and strongly recommend progressive resistance training (77, 136). The association between leg muscle strength and walking speed and balance has been demonstrated by some authors while somewhat questioned by others (76). A cross-sectional study stated that lower limb strength is impaired in all muscle groups in individuals with stroke (42). Results in study III show significant improvements in balance and leg strength and in an earlier study with the same cohort, walking capacity and speed were significantly improved (137), supporting the notion of a correlation between leg muscle strength and walking capacity.

Progressive resistance training as performed in LE-CIMT in this thesis was performed for approximately 1½ hours/day for 10 consecutive

weekdays which is considerably more than the recommended strength enhancing dose of training three times/week. Effort was made to vary targeted muscle groups to avoid overloading except exercises in a leg-press that were performed daily and with a daily increase of load. Strength exercises for trunk, calf, wrist, including toes were emphasized as well whenever possible. In CIMT, daily strength and joint motion exercises were performed with 45 minutes of focus on shoulder, arm/wrist and hand/fingers respectively. Strength improvements in the weaker leg were extensive post CIMT and with effects consistent at follow-up. There were no adverse effects from this regimen.

The CIMT and LE-CIMT interventions in this thesis included both resistance training and functional exercises requiring strength like carrying a tray with the weaker hand only or climbing stairs with extra load attached to the affected leg.

Intensity and dose

In Sweden duration and intensity of stroke rehabilitation vary but "standard care" interventions are mostly to be considered low intensity compared to the magnitude considered necessary to reduce neurological impairments and is in contrast to international evidence-based recommendations on intensity and dose (71, 138). The European Stroke Organization (ESO) recently summarized several western national clinical guidelines resulting in a strong recommendation for high intensity and task specific interventions, including strength training, functional task-specific training, robotics and CIMT (77). These recommendations are based on high intensity task-specific training inducing activity-driven neuroplasticity.

It seems reasonable to question if the high intensity and dose levels recommended in studies and several international guidelines can be achieved in home rehabilitation and it seems equally reasonable to suggest that supervised, personalized, intensive rehabilitation interventions in a clinical setting are needed as a complement to home rehabilitation.

Rehabilitation interventions are mainly provided in the acute and subacute stages post stroke while the availability of additional rehabilitative measures in later stages is less common and unevenly distributed across Sweden.

"When I suffered a stroke on the 24th of January 2000, it led to aphasia and paralysis of my right arm and leg. In a column in Dagens Nyheter, after a few months of traditional stroke care, I tried to realistically describe what awaited me. The 'road back' was long and arduous, but I was determined to walk it. But that turned out to be just words! As time went by, I saw less and less of the 'road back.

...A farewell gift, the value of which I was unaware of, was given to me by Stora Sköndal [the rehabilitation clinic] at discharge: a referral for ...a course of CI therapy for my paralyzed hand and arm. It became a profound experience for me. Not that I suddenly became well—far from it. But for the first time, I saw how it could be done. What is special about the course is the intensive training under the physiotherapist's constant supervision."

Birgit Munkhammar, CIMT participant
Published in Dagens Nyheter, 2002-11-04

Group training

All treatment interventions included in this thesis, were performed in groups of four participants supervised by one PT. This group-based format is more efficient in the utilization of resources and simultaneously adds value to participants by providing an opportunity for social interaction and sharing experiences with other participants. The value of group treatment is strongly supported by the finding in study II where men improved significantly in mental component scores after having participated in CIMT.

"…one gains the greatest joy from one another. I hadn't laughed as much or so heartily since I became ill — it was as if an extra dose of humor came along with it. We all had experiences of illness and sorrow, and now we had all the more fun together. The involuntary comedy in everything one tried to do with an arm and a hand that had been out of use for so long created a sense of fellowship.

…What a triumph it was when someone managed something again for the first time! I still feel that same joy whenever I can once again ride a bike, knit, use the sewing machine, or blow-dry my hair — all that I had given up hope of ever doing again."

Birgit Munkhammar, CIMT participant,
Published in Dagens Nyheter, 2002-11-04

Goal setting

Prior to CIMT treatment, patients were asked to formulate at least 3 personally important goals which were discussed with the PT and could mostly be confirmed to be realistic. Participants typically wanted to be able to handle a knife and fork, tie shoestrings, button a shirt, write their signature or write two-handed on a keyboard, cross a street on a green light or walk up the stairs to the bedroom, but also more specifics like professional musicians striving to be able to play their instrument or parents wanting to be able to changing diapers or pick up kids toys from the floor. A locksmith needed to be able to assemble a door lock within a specified time frame to be able to be welcomed back to work and a dentist needed a perfect dominant hand to be able to handle the drill again. Goals were mostly on the spectra of autonomy and social role including going back to work and were astonishingly realistic.

Outcomes

Choice of assessments was made in the late 1990´s with the addition of SF-36 a few years later. To maintain continuity, the originally made choices were kept throughout both the retrospective part and as the prospective part of gathering data began. Retaining the same assessments is likely to increase reliability of the results as it ensures that the PT performing assessments are familiar with tests and procedures.

The BLMA is based on the FMA and was at the time considered preferable over the FMA in clinical practice for assessing both the weaker and the stronger side and for being a 4-point-scale as opposed to the FMA being a 3-point-scale. An additional point makes the assessment more sensible to change but at the same time may decrease reliability. The BLMA measures the ICF levels of function and activity as it focuses on movement capacity and task execution as opposed to the FMA assessing the ICF level of function. The BLMA has served well in clinical practice offering information on function and activity level that is valuable for planning the treatment intervention. The FMA however, would have been much preferred for being the internationally leading assessment scale in motor function and it would have facilitated comparisons of results with other studies.

The FMA pain subscale score was used to assess shoulder pain in study I whereas the complete pain subscale was used in clinical practice. This

choice was made as the study concerned merely shoulder pain as opposed to upper extremity pain. The pain subscale is a somewhat less valid subscale of the FMA and using only part of a subscale is likely to further reduce validity.

The BBS is the most utilized balance assessment scale in research and in clinical practice alike. In the study III cohort, participants were highly functioning with 40% scoring the maximum 56 points at pre-CIMT and another 10% scoring 55 points pre-CIMT, the results were affected by an obvious ceiling effect. For this cohort a different balance scale seems, in retrospect, to have been preferable to detect change and to avoid a ceiling effect. The BBS entails one-leg stance on the leg of choice. To somewhat compensate for the less fortunate choice of balance assessment, the bilateral SLS was added to the test arsenal.

A Swedish translation of the SF-36 was readily available at the time of a HRQoL assessment being introduced in the clinical practice of the CIMT-clinic in the early 21st century. The Swedish version of the stroke-specific assessment Stroke Impact Scale was available considerably later, and would have been an interesting and preferable alternative, specifically for its focus on hand function.

There is an increasing awareness within physiotherapy of the importance of assessments measuring not only on the ICF function level, but also on activity and participation levels and thus more recently developed assessments, including the Wolf Motor function Test (WMFT)(Morris 2001, Wolf) and the Motor Activity Log (MAL) (Winstein) measure on activity level. In stroke rehabilitation, there has been a tendency to assume that there is an automatic transfer of improvements on function level to improvements on activity level while the relationship between function and activity is not clearly investigated and understood. Studies on CIMT have demonstrated results to transfer to improvements in activity level.

Strengths and imitations

An obvious strength of Studies I, II and III is relatively large cohort sizes with 221, 95 and 147 participants respectively which enhances statistical power. Drop-out at follow-up is a potential cause of bias and drop-out rates in studies I, II and IV were substantial. However, drop-out analysis revealed no differences of significance between drop-out and follow-up groups, reducing bias concerns.

The lack of control groups is an obvious limitation in the included studies. Treatment and tests performed by the same PT renders consistency to the assessment procedure but is simultaneously a risk of bias. Attempting to reduce this risk, previous test results were not available to the PT at subsequent assessment occasion which was also standard clinical procedure throughout the 19 years included.

The cohorts of the included studies entailed primarily participants under the age of 65 and with predominantly high motor function which limits generalizability. Nevertheless, participants represented a wide variety of demographic characteristics, i.e. a variety of pre-treatment motor function, pronounced shoulder pain, some pain and no pain, aphasia and cognitive deficiencies, patients in subacute and chronic phases post-stroke, some of whom might have been excluded in RCT research settings and may again, when included, add to potential generalizability of findings.

The lack of structured documentation on compliance with the home-exercise program provided for the period between treatment and follow-up makes it impossible to draw causal conclusions regarding potential effects of the home-exercises.

Concerning Study I, spasticity and eventual treatment with botulinum toxin was not assessed as was neither pre-morbid shoulder pain or any ongoing pharmacological treatment which would have been of interest and could have added explanations to the pain-relieving effect as well as to the increase in active and passive range of motion. Reversely, possible pain-relieving effects of botulinum toxin with the substance administered approximately two weeks pre-CIMT would not have been likely to have a decisive effect at 3-month follow-up while the post-treatment pain-relieving effect was maintained at follow-up. Clinically, pain was assessed with the Visual Analogue Scale (VAS) as well – however since data was only available for a smaller subgroup and the decision was made not to include the VAS scale results in the analyses. Having VAS data for the total cohort would have added valuable information in assessing HSP.

Ethical considerations

The small-scale clinic and the same PT performing initial information, assessments, treatment and asking participants about their willingness to participate in the study presents an ethical dilemma where the

patients in the prospective part of the study could consider themselves in a situation of dependency towards the PT. Referred patients were often well aware that they were somewhat exclusively chosen to be referred to CIMT which was not accessible to everybody from the hospital clinic. Most participants in the retrospective part of the study were contacted by someone from a group of medical students who informed about the study. Upon agreeing to participate, they were sent written information and an informed consent form to sign and return by mail. The procedure for the retrospective part of the study presented less of an ethical dilemma, however individuals being contacted may still have felt pressured to agree to participate since the relationship with the PT was personal with the clinic being staffed with only one PT.

Generalization

Age groups ≤ 65 constitute approximately 20% or 5000 persons/year in Sweden. This young age group is often highly functioning with long life expectancy, including many working years ahead and is a relatively small, but not negligible group. Study participants in this thesis were mostly highly functioning, well-motivated, middle-aged and without pronounced cognitive deficits and were thus not representative for the general stroke population. These facts may indicate that CIMT and LE-CIMT improvements could be different in a population with more pronounced impairments including cognitive deficits and older age. These concerns need to be studied. We can followingly not generalize results from this thesis to most stroke patients who are >65 years but merely claim that results may be generalizable to the age group <65 years in the subacute and chronic stages post stroke.

Clinical implications and future perspectives

Upper extremity

CIMT and modified CIMT have a strong evidence base and are recommended in Swedish (9) as well as in several international clinical guidelines (77) for improving upper-extremity motor function.

The observed reduction in HSP and improvements in shoulder ROM and upper extremity motor function following CIMT indicates that highly intensive rehabilitation is both safe and effective in the subacute and chronic post-stroke phases. These findings support task-specific training, joint mobility and strengthening exercises and ROM exercises to promote functional recovery. CIMT also significantly improved the Physical Component Score of the SF-36 (HRQoL), reaching the MCID, while gender-specific effects were observed in the Mental Component Score (MCS), with men benefiting more, possibly due to social interactions during therapy. Significant gains in the separate SF-36 domains including Physical Functioning, Physical Role, Bodily Pain, Vitality, and Social Functioning indicates that CIMT positively impacts both physical and mental recovery. Clinically, these results support incorporating CIMT into routine stroke rehabilitation to simultaneously alleviate shoulder pain, improve ROM and motor function, and enhance aspects of HRQoL, with attention paid to gender-specific considerations to optimize individualized outcomes.

Future studies should investigate the mechanisms behind CIMT alleviating HSP including potential effects on nociceptive versus neuropathic pain pathways. Larger, controlled trials are needed to confirm the safety and efficacy of active, high-intensity shoulder joint motion and strength training in both subacute and chronic post-stroke populations. Research should also explore the optimal dose, intensity, and timing of CIMT to maximize motor and ROM gains while minimizing the risk of pain exacerbation.

Our results together with others´ may lead to recommendations in clinical guidelines being altered to emphasize strength and mobility in contrast to immobilizing shoulder orthosis and other more conservative approaches to HSP. The combined effect of pain relief and motor improvement is an advantage of CIMT including strength and motion

exercises which cannot be expected from traditional pain-relieving treatments alone.

Finally, integrating CIMT with adjunct interventions such as robotics, virtual reality or brain stimulation may further enhance recovery and develop personalized rehabilitation strategies for stroke patients.

Lower extremity

The evidence base for LE-CIMT is less solid than that of CIMT. This thesis indicated however that LE-CIMT is a feasible and effective intervention in an outpatient clinical stroke rehabilitation setting, with improvements in functional mobility, balance, leg muscle strength, and dual-task performance in the subacute and chronic post-stroke phases. The functional gains are likely to have contributed to perceived improvement on the Physical Functioning and Vitality domains as measured with the HRQoL assessment SF-36. Sustained improvements at follow-up suggest that LE-CIMT promotes continued use of the affected limb in daily activities, supporting the integration of LE-CIMT into routine clinical interventions to optimize both functional recovery and to improve HRQoL for stroke survivors.

In line with research on CIMT, future studies should explore the optimal intensity, duration, and timing of LE-CIMT to maximize improvements across different post-stroke stages. Large multicenter trials are needed to validate the effectiveness of LE-CIMT and examine long-term outcomes such as fall incidence, community ambulation and perceived Quality of Life. Additionally, integrating technology-assisted approaches, such as sensors or virtual reality, could provide feedback to support sustained functional recovery and compliance with treatment regimen. Finally, studies should assess cost-effectiveness and feasibility of implementing LE-CIMT in routine outpatient and community-based rehabilitation settings, possibly enabling accessibility for a broader population of stroke survivors.

Conclusions

In conclusion, the results from this thesis, including middle-aged cohorts in the subacute and chronic phases post stroke indicate that:

- CIMT may reduce hemiplegic shoulder pain, improve shoulder range of motion and upper extremity motor function from before to after CIMT with results remaining at 3-month follow-up.

- Individuals with HSP and low initial motor scores benefit as much as higher-functioning individuals from CIMT.

- Health-Related Quality of Life may improve in both physical and mental aspects of the SF-36 at 3-month follow-up after CIMT, while exhibiting gender differences.

- Balance, leg strength and dual-task ability may improve after LE-CIMT with effects remaining at 3-month follow-up.

- Health-Related Quality of Life may improve in the domains Physical Function and Vitality at 3-month follow-up after LE-CIMT.

- Earlier initiation of LE-CIMT intervention correlated with better HRQoL outcomes, highlighting the importance of early implementation.

- CIMT is a feasible and applicable treatment modality in an outpatient clinical setting with results comparable to those achieved in controlled studies.

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