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

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Short title: Early versus late CIMT

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Abstract

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

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

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

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

Introduction

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

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

A number of randomized controlled trials have investigated the effect of CIMT applied in the early phase after stroke ($\leq$ 45 days) (Page, Levine, & Leonard, 2005; Boake et al., 2007; Dromerick et al., 2009; Singh & Pradhan, 2013; Yoon et al., 2014; Thrane et al., 2015; Kwakkel et al., 2016). A recent systematic review showed a trend toward a positive effect for early-applied CIMT (Etoom et al., 2016). However, none of these studies followed the participants for > 6 months (Etoom et al., 2016). One of the included studies, the Norwegian Constraint-Induced Therapy Multisite Trial (NORCIMT), was conducted to assess the effect of CIMT applied at 7-28 days after stroke (Thrane et al., 2015). Compared with patients receiving standard rehabilitation, the patients who received CIMT early showed a significantly improved motor capacity at the end of the intervention; however, this difference was no longer significant at the 6-month follow-up (Thrane et al., 2015). Kwakkel *et al.* (2016) also confirmed this improvement in motor capacity at the end of the intervention and

lack of long-term effect in early-applied CIMT. The results from both trials indicate that CIMT applied in the early phase may result in faster recovery; however, the standard rehabilitation group also reached a high level of motor capacity at 6 months post stroke. Moreover, the Extremity Constraint-Induced Therapy Evaluation (EXCITE) trial, the largest randomized controlled trial (with 222 participants) on CIMT in the subacute and chronic phases after stroke, showed clinically relevant improvements in arm motor capacity that persisted for at least 1 year (Wolf et al., 2006). Thus, it would also be of interest to investigate whether further improvements will occur if CIMT was administered to patients who received standard rehabilitation initially.

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

Methods

Study design and participants

This study was a single-blinded, multicenter, randomized controlled crossover trial. The participants were recruited from five Norwegian hospitals: University Hospital of North Norway, Trondheim University Hospital, Oslo University Hospital, Vestfold Hospital, and Telemark Hospital. The inclusion criteria were as follows: diagnosis of stroke, persistent unilateral arm or hand paresis within 5–26 days after stroke, and Modified Rankin Scale (MRS) score between 0 and 2 prior to stroke. Furthermore, a Mini-Mental State Examination

(MMSE) score of > 20, ability to extend two fingers or the wrist, and ability to follow a two-step command were also required. The exclusion criteria included MRS > 4 after stroke, large hemispatial neglect, life expectancy of < 1 year due to other illness, injury in the affected upper limb prior to stroke, and other conditions affecting motor function. All participants signed a written informed consent.

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

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

Study interventions

Constraint-induced movement therapy

The participants in the intervention groups received CIMT in the rehabilitation departments of their corresponding treatment sites. Both the early and delayed intervention groups had an equal dose of CIMT, i.e., 10 consecutive workdays with a 3-h daily treatment. The intended daily duration of the different parts of the treatment was as follows: 2 h shaping tasks, 0.5 h standard task practice, and 0.5 h adherence-enhancing behavioral strategies. Shaping tasks consisted of a high number of structured exercises of short duration where task difficulty was successively increased according to the patients' performance. Standard task practice consisted of continuously performed activities. Behavioral strategies (Morris, Taub, & Mark, 2006) consisted of a treatment contract, daily use of the motor activity log, home skill assignment, and home diary. To increase the use of the more affected arm, the participants

wore a mitt on the less affected arm for up to 90% of their waking hours. The therapist responsible for the intervention attended a 4-day training program on the study procedures. Further details of the treatment protocol have been described elsewhere (Stock et al., 2015).

Standard care

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

Outcome measures

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

The WMFT consists of 17 items to assess arm motor capacity: 15 tasks measuring speed and quality of movement and 2 tasks measuring strength. The median time for the 15 tasks was used in the analysis. Video recordings of all movement tasks were used to calculate performance time and quality of movement, following a 6-point functional ability scale

(ranging from 0 = does not attempt to 5 = normal movement). The WMFT has high validity and reliability in stroke patients (Morris et al., 2001).

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

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

Statistical analysis

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

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

Results

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

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

- Insert figure 1

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

- Insert table 1

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

- Insert figure 2

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

- Insert figure 3

Both the early and delayed CIMT groups showed significant improvements in the primary outcome measure logWMFT (p < .004) and in the secondary outcome measures from T1–T5 (Figures 2 and 3). Visual inspection of the recovery curve of the logWMFT revealed that the early intervention group recovered faster and apparently reached a plateau at T3 without further improvements at T5, while the delayed intervention group seemed to improve during the intervention until T5. However, the within-group differences were similar in the two groups, and significant differences between T2 and T5 in both the early (p=.05) and delayed

(p=.001) intervention groups, but not between T3 and T5 (p=.993 and p=.172, respectively) were observed. NHPT showed recovery curves similar to those of logWMFT. The SIS (Figure 4) showed no significant difference between the 6-month and 12-month follow-up and between the two groups.

- Insert figure 4

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

Adverse events

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

Discussion

This single-blinded, multicenter, randomized controlled trial compared the effect of CIMT applied early after stroke with that of CIMT applied in the chronic phase. Compared with baseline data, both groups showed significant improvements in the outcome measures at the 12-month follow-up, recovered considerably, and had only mild impairment after 6 months. No significant differences in any of the outcome measures between the two treatment groups were found before and after the delayed intervention group received CIMT at 6 months and at the 12-month follow-up. However, the early intervention group had a faster recovery and showed significantly better logWMFT and NHPT results than the delayed intervention group immediately after the early group finished treatment as reported by Thrane *et al.* (2015).

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

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

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

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

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

Implications for Physiotherapy Practice

This study showed that both early and delayed CIMT significantly improved outcomes; however, no differences between the groups were found at the 12-month follow-up. This result indicates that commencing therapy early is as good as delayed intervention in the long term. Nevertheless, the early CIMT intervention group showed faster recovery with less dependency in activities of daily living than the delayed intervention group, which can be a clinically important finding for patients in the acute phase. Further large-scale studies are needed to determine the dose and optimal time point for commencing CIMT. Excluding higher-functioning participants may be advantageous to minimize the influence of spontaneous recovery.   (Last sentence deleted)

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Tables

Table 1. Baseline characteristics of participants

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

CIMT, constrained-induced movement therapy; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale
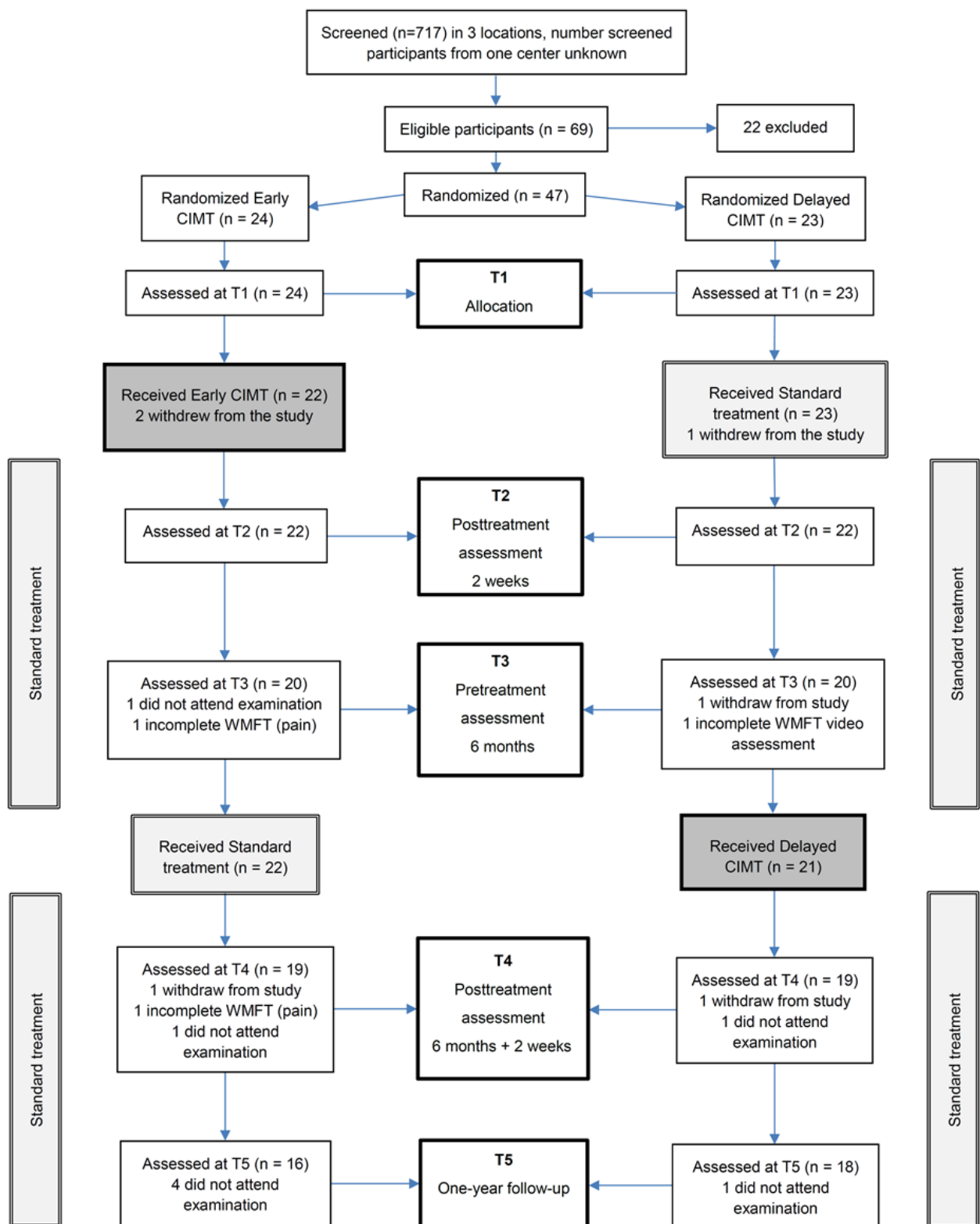
Figure 1. Study flow chart, including the recruitment, allocation, and withdrawal of participants
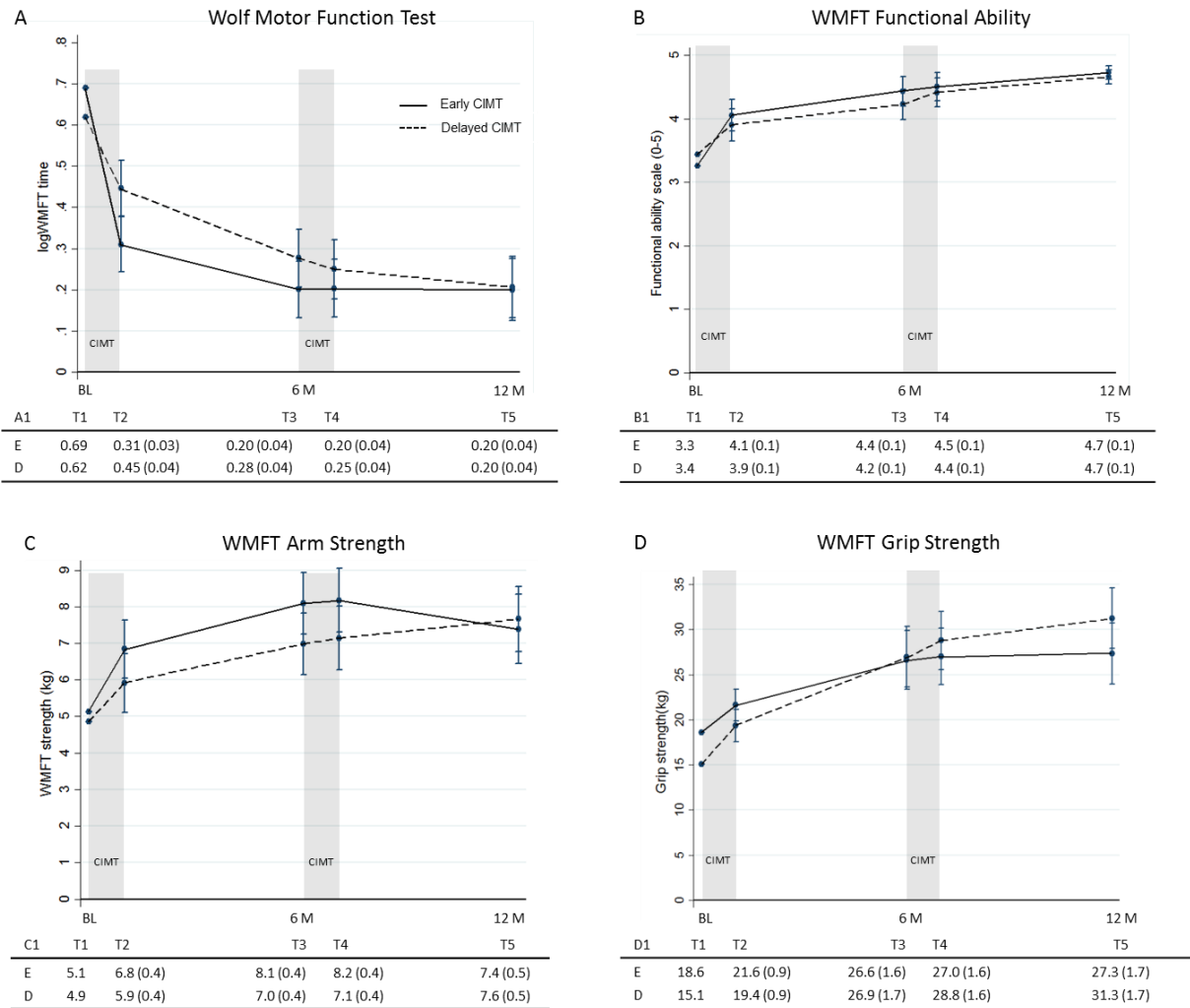
Figure 2. Comparison between early- and late-applied CIMT

The mean values and standard errors of Wolf Motor Function Test (logWMFT) (A), WMFT Functional Ability (B), WMFT Arm Strength (C), and WMFT Grip Strength (D) scores from enrollment to the 12-month follow-up. The early intervention group received CIMT treatment between 8–28 days after stroke for 2 weeks; the delayed intervention group, at 6 months after stroke. Note that the treatment intervals are upscaled to improve readability. Numbers below the figure are the mean and standard error (A1-D1) for the early CIMT (E) and delayed CIMT (D) groups from T1 to T5. No significant differences between the groups were found except for logWMFT at T2, as earlier reported (Thrane et al., 2015)
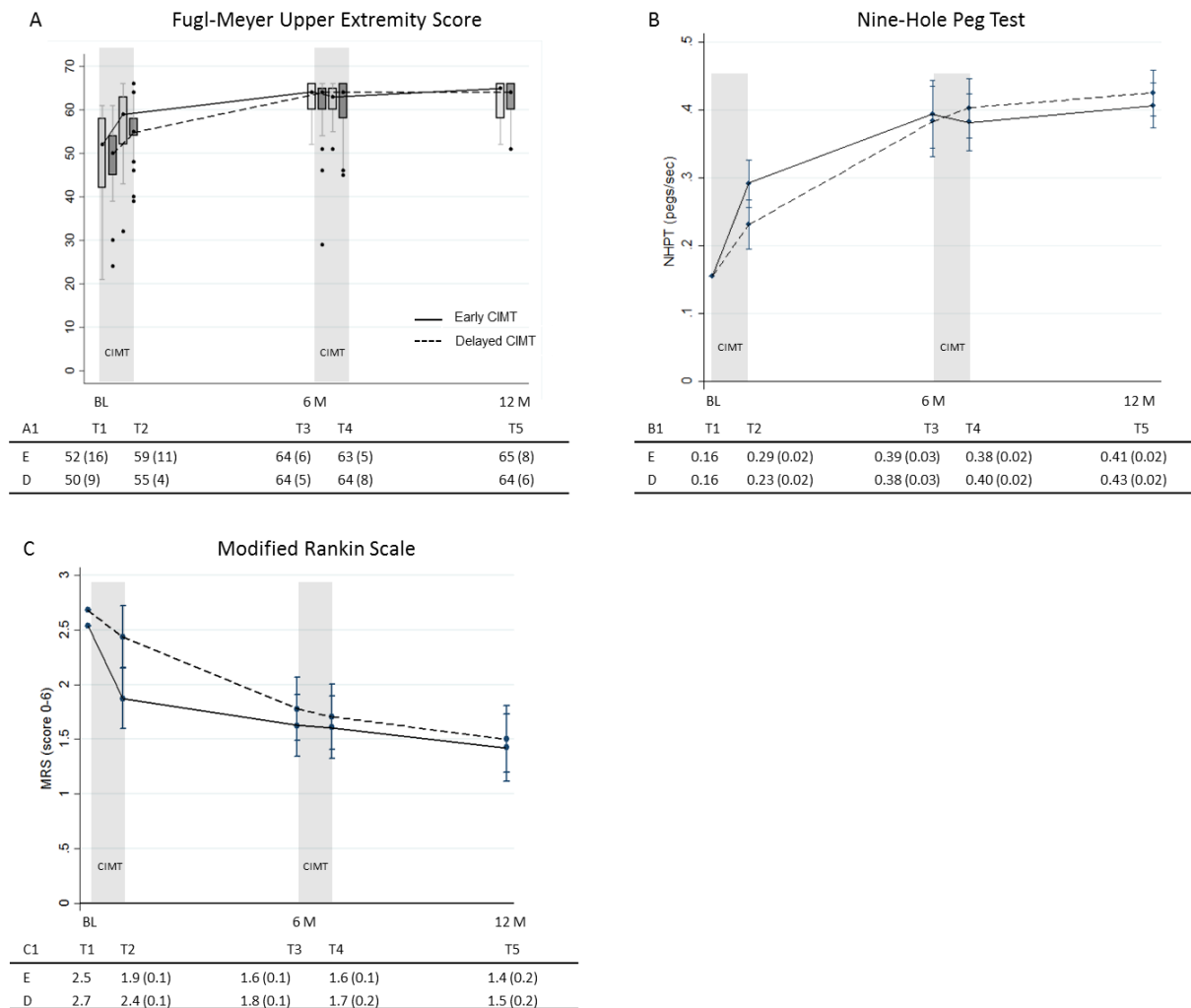
A — Fugl-Meyer Upper Extremity Score

A1	T1	T2	T3	T4	T5
E	52 (16)	59 (11)	64 (6)	63 (5)	65 (8)
D	50 (9)	55 (4)	64 (5)	64 (8)	64 (6)

B — Nine-Hole Peg Test

B1	T1	T2	T3	T4	T5
E	0.16	0.29 (0.02)	0.39 (0.03)	0.38 (0.02)	0.41 (0.02)
D	0.16	0.23 (0.02)	0.38 (0.03)	0.40 (0.02)	0.43 (0.02)

C — Modified Rankin Scale

C1	T1	T2	T3	T4	T5
E	2.5	1.9 (0.1)	1.6 (0.1)	1.6 (0.1)	1.4 (0.2)
D	2.7	2.4 (0.1)	1.8 (0.1)	1.7 (0.2)	1.5 (0.2)

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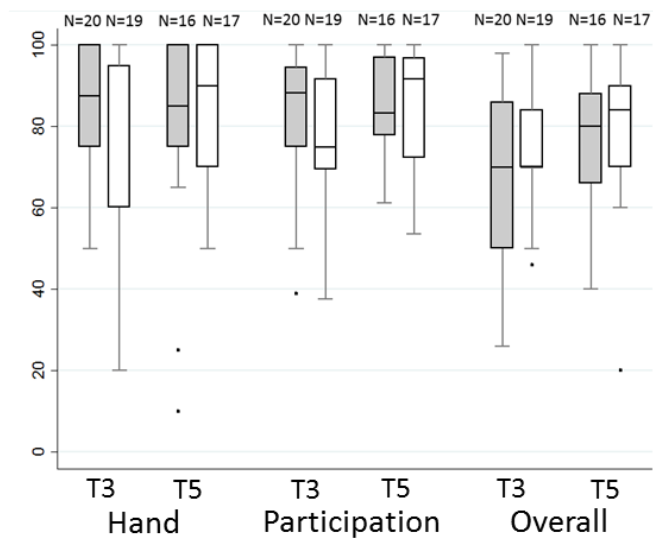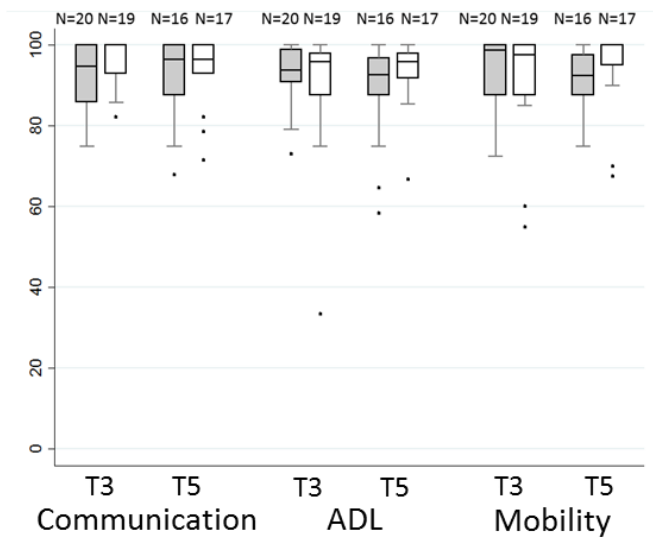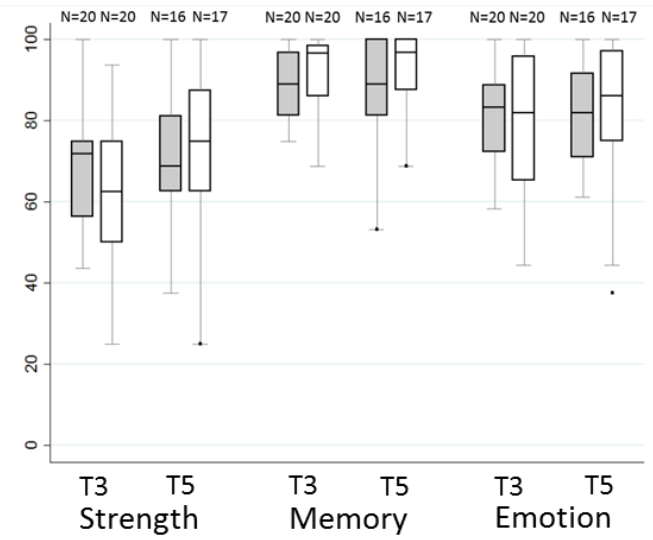
Stroke Impact scale

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