

Pain, Fatigue, and Intensity of Practice in People With Stroke Who Are Receiving Constraint-Induced Movement Therapy

Background and Purpose. There is little available information about changes in pain and fatigue status among people receiving constraint-induced movement therapy (CI therapy). This study examined such changes. **Subjects.** All participants were a subset of individuals with stroke enrolled in the Extremity Constraint-Induced Therapy Evaluation (EXCITE) trial and received 2 weeks of CI therapy either 3 to 9 months after stroke (subacute therapy group, n=18) or 1 year later (chronic therapy group, n=14). **Methods.** Pain, fatigue, and intensity of therapy were evaluated. The Wolf Motor Function Test (WMFT) and the pain scale of the Fugl-Meyer Assessment for the upper extremity were administered before and after training. Single-item measures for pain and fatigue were administered twice daily during therapy. **Results.** All participants reported low mean pain ($\bar{X}=2.0$, $SD=0.93$) and fatigue ($\bar{X}=2.7$, $SD=1.23$) scores. Generally, differences between the subacute and the chronic therapy groups for pain, fatigue, intensity, and WMFT change scores were nonsignificant. **Discussion and Conclusion.** For selected patients with stroke, the intensive practice associated with CI therapy may be administered without exacerbation of pain or fatigue, even early during the recovery process. [Underwood J, Clark PC, Blanton S, et al. Pain, fatigue, and intensity of practice in people with stroke who are receiving constraint-induced movement therapy. *Phys Ther.* 2006;86:1241–1250.]

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Strong evidence is emerging that patients with stroke benefit from exercise programs in which functional tasks are directly and intensively trained.¹⁻⁴ Intensive task practice, that is, multiple repetitions to achieve a challenging motoric goal, is identified as one of the most crucial components for recovery after stroke.^{3,5,6} Constraint-induced movement therapy (CI therapy) is an example of an approach that involves repetitive task practice, that was developed directly from basic science research, and that provides an avenue for significant functional improvements in the hemiparetic limb.^{7,8} This intervention has been shown to facilitate cortical reorganization possibly by increasing the excitability of neurons innervating functionally relevant muscles and by increasing excitable neuronal tissue in the infarcted hemisphere.⁸⁻¹¹ The fundamental premise underlying the benefit of CI therapy requires that the patient undertake task practice with both behavioral shaping and repetition within the context of an intensive therapy regimen while the less affected upper extremity is restrained for 90% of the patient's waking hours.^{7,12} Patients participate in this intensive therapy with the affected limb for 6 hours 5 days per week over a 2- or 3-week period after stroke,¹²⁻¹⁵ although distributed practice of CI therapy has been provided over longer time intervals, often up to 10 weeks.^{16,17} Deter-

mining whether the therapy exacerbates adverse symptoms, such as pain and fatigue, is an important consideration with this type of intensive therapy regimen.

In that context, shoulder pain after stroke is a common problem¹⁸ with devastating sequelae.¹⁹ Development of a painful hemiplegic shoulder complicates and prolongs rehabilitation, increases the length of hospitalization, and can result in poor arm function 12 weeks after stroke.²⁰ In addition, the presence of shoulder pain related to weakness of the upper limb and restriction in active range of motion ultimately may contribute to poor functional recovery of the upper limb during rehabilitation.²⁰ Despite multiple studies evaluating CI therapy, little has been written about the occurrence of shoulder pain. Ploughman and Corbett²¹ documented the incidence of shoulder pain in patients at less than 16 weeks after stroke and undergoing up to 6 hours per day of forced-use therapy (restraint of the stronger upper extremity only, no intensive therapy). The amount of restraint wearing did not correlate with worsening of shoulder pain, and shoulder pain did not correlate with recovery. However, there was a clinical trend toward less recovery in the small female subgroup that experienced more pain. Conversely, in a CI therapy case study involving a patient in the chronic recovery period after

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The institutional review boards at all sites, including Emory University, approved the study protocol.

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stroke, Bonifer and Anderson²² noted that the patient actually reported a decrease in shoulder pain as the therapy progressed.

Along with pain, fatigue after stroke is a serious and frequent symptom. This fatigue interferes with the rehabilitation process, may decrease the potential for the patient to regain function, and often is mentioned by patients as one of the most difficult symptoms to which to adjust after stroke.²³ Fatigue also was an independent predictor for dying within 3 years after a stroke and, among these patients, a strong correlation between pain and fatigue after 2 years was observed.²³ Fatigue may interfere with rehabilitation and measurement of a patient's ability to use the paretic arm for functional activities but is rarely documented.²³ In one CI therapy case study, investigators noted that the patient was so fatigued after a day of training that "her activities at home were limited to eating dinner, watching television, and going to bed earlier than she normally would."²⁴(p851) However, a clear understanding of how fatigue affects rehabilitation activities or how therapy may augment fatigue remains elusive.

Given that CI therapy involves intensive demands of focused use of the upper extremity over an extended time period, determining the effects of pain and fatigue on a patient's ability to participate in such a challenging practice schedule is important. Surprisingly, the effect of this intervention on fatigue or pain has never been evaluated systematically. Consequently, there is a need to explore the relationship between these important post-stroke symptoms and the application of CI therapy. Accordingly, this report represents the first effort to evaluate this relationship as part of the Extremity Constraint-Induced Therapy Evaluation (EXCITE) trial¹² by examining this relationship in participants at one EXCITE site (Emory University). Understanding the relationship among these variables is fundamental for physical therapists in determining whether adherence to and effectiveness of, CI therapy are affected if patients experience pain or fatigue. This study addressed the following key research questions for people receiving CI therapy in the subacute and chronic recovery periods. What are the relationships among pain, fatigue, intensity of practice, and motor function? Do pain and fatigue change over time during CI therapy? Are there differences in pain, fatigue, and motor function on the basis of whether CI therapy takes place in the subacute or in the chronic recovery period?

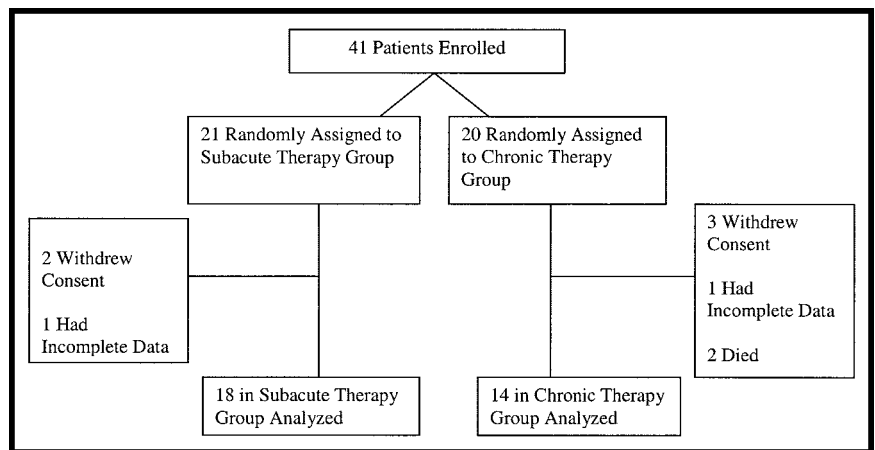


Figure 1. Participant enrollment flow diagram.

Method

Participants

Data for this EXCITE trial substudy were obtained from 41 people seen at Emory University. These participants met the eligibility criteria, which included minimal elbow, hand, and wrist active range of motion in extension. These criteria and the data collection procedures for the larger multicenter clinical trial have been described in detail elsewhere.¹² All participants had a stroke 3 to 9 months earlier and were randomly assigned to either a subacute therapy group (CI therapy 3–9 months after stroke) or a chronic therapy group (CI therapy 1 year after enrollment). The information in Figure 1 shows that for 32 participants, complete data were available for analysis; 18 participants were randomly assigned to the subacute therapy group, and 14 participants were randomly assigned to the chronic therapy group. The participants were 22 men (mean age=63.8 years, SD=12.2) and 10 women (mean age=56.8 years, SD=15.4). There were 16 participants with right-side hemiparesis and 16 participants with left-side hemiparesis. The majority were right-hand dominant. Of the 3 participants with left-side dominance, only 1 had left-side hemiparesis.

Design

The clinical trial involved a randomized 2-group design and included a dynamic, random assignment process to ensure that the groups were balanced with respect to functional capability, sex, hemiplegic side, and hand dominance. The institutional review boards at all sites, including Emory University, approved the protocol for the primary study, and written consent was obtained from all participants.

For the analysis of this subset of participants, measures related to pain, fatigue, and intensity of practice were

collected during the 2-week CI therapy intervention period. Before CI therapy and after the completion of the 2 weeks of therapy, joint pain and upper-extremity function were assessed by evaluators who were unaware of when the participants received the intervention.

CI Therapy

Participants received CI therapy for 6 hours per day for 10 days over a 2-week period. Two procedures were used during training: shaping (adaptive task practice) and standard repetitive task practice.¹² During adaptive task practice, the primary goal of a chosen functional task was approached through emphasis on distinct parts of the task that may be limited by the participant's impairments (eg, repeating the action of bringing a fork toward the mouth when a participant was limited in elbow flexion as part of the task practice for eating). The task was made progressively difficult through manipulation of temporal or spatial elements to create a demanding and challenging motor learning environment for skill acquisition. Each adaptive task practice activity was carried out in a set of 10 trials, and explicit feedback was provided with regard to the participant's performance in each trial. Standard repetitive task practice was less structured and consisted of functionally based activities performed continuously for 15 to 20 minutes. These activities tended to be more complex and often contained component sub-tasks that were practiced during adaptive task practice (eg, eating lunch or writing). More global feedback regarding performance was provided at the end of the 15- to 20-minute period. For the larger national clinical trial, a large bank of tasks was created for each type of training procedure. Tasks were chosen on the basis of each participant's preferences, goals, and movement limitations. Frequent rest breaks were provided throughout the 6-hour training day. The amounts of time spent on each task in addition to the rest breaks were recorded to ensure accurate data collection regarding time actually spent by participants performing the CI therapy training.

Measures

Upper-extremity motor function. Upper-extremity function was measured before and after the intervention with the Wolf Motor Function Test (WMFT). The WMFT is an impairment-based assessment used to measure the functional level of the upper extremity. The WMFT consists of 15 timed performance items (maximum time=120 seconds) and 2 strength items. Performance items progress from simple joint movements to complex movements. The average of the timed tasks was used for this study to obtain a total score. In the data analysis, a log transformation of the mean scores was used to adjust for skewness of the data (because of the variance between participants with high performance and those

with low performance). The WMFT has been shown to have good clinimetric properties in people with stroke^{25,26} and to correlate well with the Fugl-Meyer Assessment (FMA).^{25,27}

Upper-extremity joint pain. Upper-extremity joint pain was measured with the joint pain subscale of the FMA for the upper extremity. The FMA is a well-established instrument used to evaluate recovery from hemiplegic stroke, and it yields data with excellent intrarater reliability,²⁸ interrater reliability,^{29,30} and construct validity.^{31,32} The pain experienced by a participant during passive range of motion (PROM) of the more affected side for the shoulder (flexion, abduction to 90°, external rotation, and internal rotation), elbow (flexion and extension), wrist (flexion and extension), fingers (flexion and extension), and forearm (pronation and supination) was rated by the evaluator. A total of 12 items were rated on a scale of 0 to 2 on the basis of the participant's response during PROM of a joint as no pain (2), some pain (1), or marked pain (0) through the range of motion. Thus, the total pain score ranged from 0 to 24, with 0 indicating marked pain throughout the arm and 24 indicating no pain experienced with PROM.

Intensity of therapy. For each of the 10 training days, the intensity of therapy was measured in minutes of total time that participants actually spent engaged in the task practice of CI therapy. This time was recorded by the therapist and excluded rest breaks.

Fatigue and pain during training. Fatigue during CI therapy was measured by use of a single-item scale with a rating of 1 to 10, with 1 indicating no fatigue and 10 indicating absolute exhaustion. This single-item scale was selected because of the established validity of a single-item measure and because of its clinical relevance and ease of use.³³ Pain during CI therapy was measured by use of a similar single-item rating scale, with a rating of 1 indicating no pain and a rating of 10 indicating unbearable pain. In contrast to the FMA joint pain measure, in which higher scores indicated less severe pain, in the daily pain measure, higher scores indicated more severe pain. This scale was selected because of its common use in clinical practice, ease of administration, and demonstrated validity and reliability in a sample of subjects with chronic illness.³⁴ For each scale, participants were asked to "indicate on this scale the amount of pain/fatigue you experienced today during treatment." Scales were completed by participants at the end of the morning activities and again at the end of the afternoon activities during each day of CI therapy.

Table 1.

Differences in Wolf Motor Function Test Times (in Seconds) Before and After Constraint-Induced Movement Therapy (CI Therapy) in Subacute and Chronic Therapy Groups^a

Therapy Group	$\bar{X} \pm SD$ for Time		<i>t</i>	<i>df</i>	<i>P</i>
	Before CI Therapy	After CI Therapy			
Subacute	25.45±26.39	17.56±21.95	3.83	17	.001
Chronic	33.65±24.59	24.24±22.25	3.61	13	.003

^a Both the log mean Wolf Motor Function Test (WMFT) data and the raw data were significant. The log mean WMFT data were used in the analysis, but for the ease of comprehension, the raw data are reported here.

Data Analysis

Data were analyzed by SPSS software.* Data for 2 participants were not included in the analysis because more than 3 consecutive data points were missing. Single data points missing for daily pain were replaced by averaging the other known morning or afternoon pain data points for that same week.³⁵ Only 4.5% of the total data points (640) each for pain and fatigue were missing. Descriptive statistics, paired and independent *t* tests, and repeated-measures analysis of variance (ANOVA) were used to determine the relationships among pain, fatigue, and function for participants receiving CI therapy. Although parametric tests are robust to violations of assumptions for the test, violations of these assumptions are a concern in small sample sizes. One approach is to conduct both parametric and nonparametric tests and compare results, and that was done. The results of parametric and nonparametric tests were similar; therefore, parametric test results are reported. When there was a difference in significance with these approaches, that difference is noted. For all statistical analyses, the significance was set at $P < .05$. The Pearson correlation was used to examine relationships among pain, fatigue, and upper-extremity function. For both groups, the participants' average (over 10 days) morning and afternoon fatigue ($r = .81$, $P < .01$) and morning and afternoon pain ($r = .72$, $P < .01$) scores were significantly related. Thus, overall total fatigue and pain scores for each day were used in some analyses.

Results

WMFT

Motor function improved in both groups, as indicated by significant changes in scores before CI therapy and after CI therapy (Tab. 1). However, there were no significant differences between groups in upper-extremity function and joint pain before CI therapy or after CI therapy, except that the chronic therapy group reported less joint pain before receiving CI therapy (Tab. 2).

Overall, there were low, nonsignificant correlations (Tab. 3) between joint pain (as measured by the FMA) and the WMFT (log mean) before CI therapy or at the completion of CI therapy and daily pain reports during therapy for both groups. A separate analysis that examined change scores for the WMFT and average daily pain reports did not reveal a relationship in the subacute therapy group ($r = -.04$, $P = .87$), but there was a relationship between change scores for motor function and daily pain reports in the chronic therapy group ($r = -.53$, $P = .05$) (nonparametric tests: $r_s = -.26$, $P > .05$). Among participants in the chronic therapy group, as motor function improved (less time), pain increased slightly.

There were low, nonsignificant correlations (Tab. 3) between fatigue and the WMFT before CI therapy or after CI therapy in both the subacute therapy group and the chronic therapy group. However, again, an additional analysis of WMFT change scores yielded gains in upper-extremity function that were associated with more fatigue in the chronic therapy group ($r = -.75$, $P < .01$) but not in the subacute therapy group ($r = -.17$, $P > .05$).

Intensity

Overall, both groups averaged approximately 4.5 hours of therapy per day (Tab. 2). There was no significant difference between the subacute and the chronic therapy groups with regard to intensity of therapy (Tab. 2), indicating that both groups were able to tolerate the same level of therapy. However, individual characteristics of participants were related to intensity of therapy. Faster performance on the WMFT in the subacute therapy group (Tab. 3), indicating better upper-extremity function before training, was associated with significantly more time spent in therapy, relative to the time spent by participants with slower performance on the WMFT. After therapy, intensity (amount of time spent in therapy) and upper-extremity function (WMFT times) remained moderately correlated. In contrast, in the chronic therapy group (Tab. 3), there was no relationship between average intensity and the WMFT before CI therapy or after CI therapy.

Additional analyses showed that, for both groups, there was no relationship between time spent in therapy and upper-extremity joint pain (FMA) before CI therapy (subacute therapy group: $r = .16$, $P > .05$; chronic therapy group: $r = .05$, $P > .05$). Pain during therapy was not associated with intensity of CI practice (subacute therapy group: $r = .04$, $P > .05$; chronic therapy group: $r = .11$, $P > .05$). There were moderate correlations, indicating that less time spent in therapy was associated with more fatigue (subacute therapy group: $r = -.27$, $P > .05$; chronic therapy group: $r = -.53$, $P = .05$).

* SPSS Inc, 233 S Wacker Dr, Chicago, IL 60606.

Table 2.

Comparison of Subacute and Chronic Therapy Groups With Regard to Pain, Fatigue, and Function^a

Variable	$\bar{X} \pm SD$ Score		<i>t</i> ^b	<i>P</i>
	Subacute Therapy Group (n=18)	Chronic Therapy Group (n=14)		
Average morning pain	2.02±0.83	1.72±1.11	0.88	.388
Average afternoon pain	2.18±1.07	1.87±1.00	0.82	.417
Average morning fatigue	2.81±1.26	1.87±1.08	2.23	.034
Average afternoon fatigue	3.31±1.29	2.8±1.35	1.08	.290
Pretest joint pain (Fugl-Meyer Assessment)	20.06±3.15	22.57±2.50	2.44	.021
Posttest joint pain (Fugl-Meyer Assessment)	20.39±2.93	22.29±3.05	1.78	.085
Pretest log WMFT (s)	2.68±1.14	3.14±1.04	1.18	.246
Posttest log WMFT (s)	2.25±1.13	2.75±1.03	1.30	.203
WMFT change score	0.43±0.48	0.39±0.40	0.27	.790
Intensity of practice (average total minutes each day over 10 days)	250.96±23.33	260.66±26.46	1.10	.280

^a Joint pain and Wolf Motor Function Test (WMFT) scores were rated by the evaluator. Pain and fatigue during therapy were self-reported by participants. Intensity of practice was documented by the trainer.

^b *df*=30 for all *t* tests.

Table 3.

Relationships Between Log Wolf Motor Function Test [WMFT] and Pain, Fatigue, and Intensity of Practice in Subacute and Chronic Therapy Groups^a

Variable	Correlation for:			
	Subacute Therapy Group (n=18)		Chronic Therapy Group (n=14)	
	Pretest WMFT	Posttest WMFT	Pretest WMFT	Posttest WMFT
Pretest joint pain	-.21		-.24	
Posttest joint pain		-.24		.05
Fatigue during constraint-induced therapy	.32	.26	.08	-.22
Pain during constraint-induced therapy	-.05	-.06	.09	-.12
Intensity of practice (min)	-.51 ^b	.46 ^c	.06	.01

^a Joint pain and WMFT scores were rated by the evaluator. Pain and fatigue during therapy were self-reported by participants. Intensity of practice was documented by the trainer. Correlations for intensity of practice and subacute therapy group motor function differed, as determined by nonparametric tests: intensity of practice and pretest WMFT ($r_s = -.40$, $P = .11$) and intensity of practice and posttest WMFT ($r_s = -.44$, $P = .07$).

^b $P < .05$.

^c $P = .05$.

Fatigue

Overall average daily morning and afternoon fatigue scores were below 4.5 on a scale of 1 to 10 throughout the daily CI therapy for both groups (Fig. 2A). Repeated-measures ANOVA revealed that there was no change over the 10 days in morning fatigue (Greenhouse-Geisser test: $F = .10$, $P = .41$) or afternoon fatigue (Greenhouse-

Geisser test: $F = 1.70$, $P = .12$) or between groups (morning fatigue, Greenhouse-Geisser test: $F = .77$, $P = .59$; afternoon fatigue, Greenhouse-Geisser test: $F = .77$, $P = .60$). Generally, the highest fatigue scores were found in the subacute therapy group participants at the end of the daily training. The chronic therapy group participants had lower average fatigue scores at the end of the morning training (Tab. 2).

As expected, in both the subacute and the chronic therapy groups, the average levels of fatigue reported at the end of the daily therapy were significantly higher than the average fatigue levels reported at the end of the morning therapy session (subacute therapy group: $t = 4.2$, $df = 17$, $P < .01$; chronic therapy group: $t = 3.4$, $df = 13$, $P < .05$) (Tab. 2). There was no relationship between the average daily pain and fatigue scores during therapy in the subacute therapy group ($r = -.13$, $P > .05$), but in the chronic therapy group, there was a trend for more pain during therapy being associated with more fatigue ($r = .50$, $P = .07$).

Pain

Average daily morning and afternoon pain scores were below 3 on a scale of 1 to 10 throughout the daily CI therapy for participants early and later in the recovery trajectory (Fig. 2B). Repeated-measures ANOVA revealed that there was no change over the 10 days for all participants in morning pain (Greenhouse-Geisser test: $F = .51$, $P = .79$) or afternoon pain (Greenhouse-Geisser test: $F = .51$, $P = .78$). In addition, there was no difference in morning pain or afternoon pain over the 10 days between the subacute and the chronic therapy group participants (morning pain, Greenhouse-Geisser test: $F = .53$, $P = .79$; afternoon pain, Greenhouse-Geisser test: $F = .53$, $P = .77$).

The average scores tended to be higher for afternoon pain in the subacute therapy group and lowest for morning pain in the chronic therapy group. There was no difference between the subacute and the chronic therapy groups for average daily morning pain or afternoon pain (Tab. 2). Additional analyses failed to reveal a change in joint pain scores within groups before CI

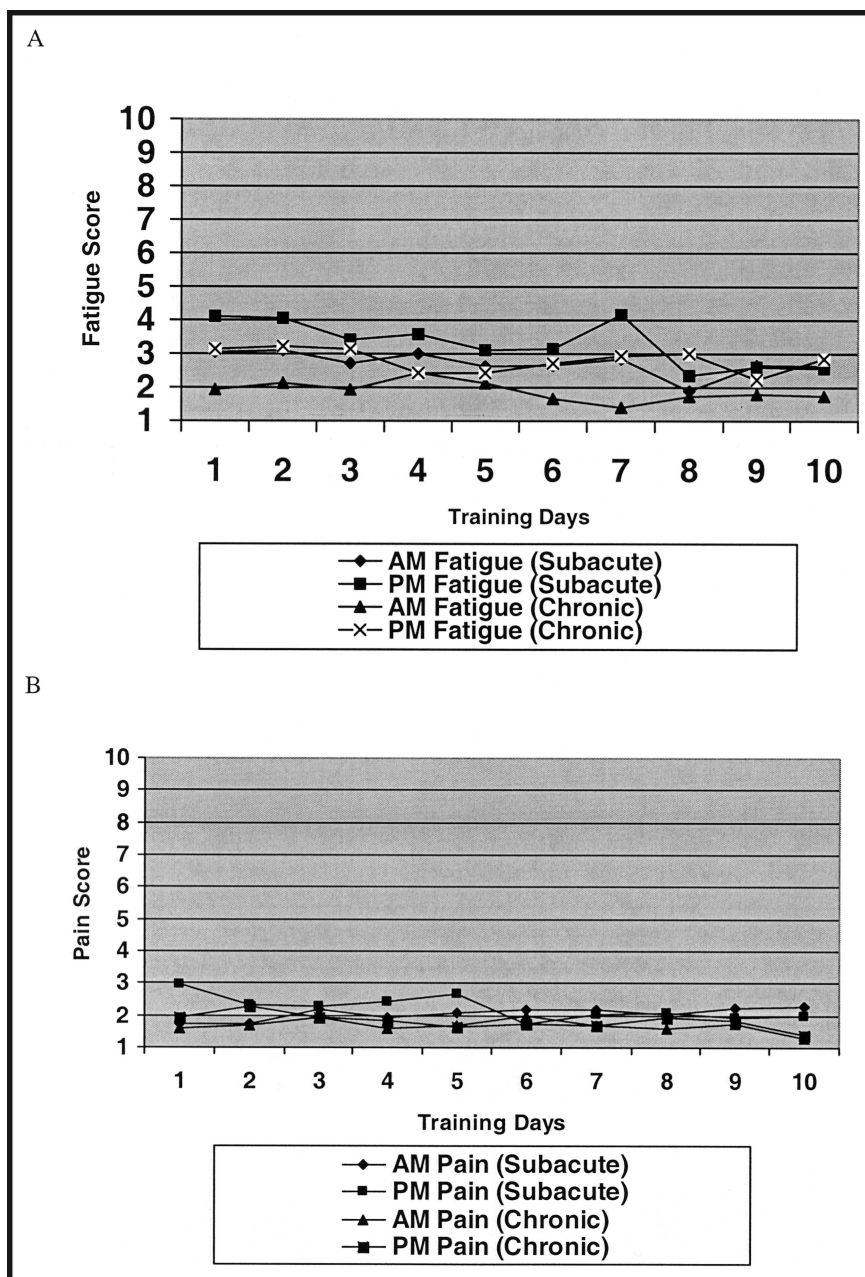


Figure 2. Average fatigue (A) and pain (B) scores for subacute and chronic therapy groups over 10 days of constraint-induced movement therapy. AM=morning, PM=afternoon.

therapy and after CI therapy for either the subacute ($t=.51, df=17, P>.05$) or the chronic ($t=.94, df=13, P>.05$) therapy group.

The relationships between daily pain and assessments of joint pain (scored by the evaluator) before and after the administration of CI therapy also were examined. Assessments of joint pain were related to self-reported average daily pain during therapy in the chronic therapy group (before therapy: $r=-.84, P<.001$; after therapy: $r=-.76, P=.001$) but not in the subacute therapy group

(before therapy: $r=.32, P>.05$; after therapy: $r=-.04, P>.05$).

Discussion

Although results from previous studies indicated that pain may affect a patient's ability to participate in therapy,^{18,21,36} the participants in this study had relatively low levels of pain throughout the CI therapy protocol. Furthermore, pain did not increase over the 2-week therapy period. These results are somewhat unexpected, on the basis of the high intensity and multiple practice hours of CI therapy. This limited complaint of pain is likely a function of several factors: the inclusion criteria (see minimal movement criteria described by Winstein et al¹²), which restricted participation to minimally to moderately impaired patients with stroke; the exclusion of patients who had sufficient complaints of pain that would interfere with daily activities; and the careful monitoring of symptoms during training activities. These encouraging results indicate that with cautious screening, pain should not be a concern for therapists who use CI therapy for their patients.

Fatigue resulting from many hours of intensive therapy is another reason that patients and therapists may be reluctant to use CI therapy.³⁷ In both subacute and chronic therapy group participants, fatigue level scores during CI therapy remained low over the course of therapy and were not related to upper-extremity functional capabilities, before or after training. This finding suggests that the level of fatigue should not increase over the course of this intensive therapy.

However, the magnitude of improvement in upper-extremity function experienced by the chronic therapy group participants was related to the participants' reports of pain and fatigue scores during therapy, suggesting that chronic therapy group participants may have experienced some pain and fatigue as upper-extremity function improved. Impressively, participants in the chronic therapy group showed as much improvement in upper-extremity function as did participants in the subacute therapy group, although they had not been forced to use their affected extremity for over 1 year.

Thus, low levels of pain and fatigue may not interfere with a patient's capability to maximize improvement in functional status if the therapy is started later, in the chronic phase of recovery. Both groups showed significant improvement in upper-extremity motor function after CI therapy training, a result that is consistent with those of other CI therapy studies involving patients in the acute,³⁸ subacute,^{24,39} and chronic^{7,13,40} phases of recovery after stroke.

Both subacute and chronic therapy group participants achieved the same intensity of therapy, about 4.5 hours of the scheduled 6 hours of contact each day. For the subacute therapy group, we found that participants with better upper-extremity function tolerated more time in therapy. However, there was no relationship between intensity of practice and joint pain or daily pain. A relationship between lower intensity of practice and higher fatigue during therapy was as expected, although not significant. Therefore, starting intensive therapy earlier in the recovery process was beneficial and did not have adverse effects.

One obvious limitation of this study involved the small number of participants in each group and the possibility of a type II error. Although the sample was small, strengths of the EXCITE clinical trial include the strict eligibility criteria to help control through homogeneity of the sample, random assignment to groups, and rigorous standardization of trainers and evaluators to control threats to internal validity. Larger samples will allow for testing of other patient attributes that may affect pain and fatigue. However, the results of this study suggest several additional avenues for exploration. Because of the specific criteria used for participants more than 3 months after stroke in this study, the levels of pain and fatigue that patients in a more acute phase and undergoing this therapy would experience are unknown. Although there were no differences in outcomes between the subacute and the chronic therapy groups for this small subset of participants, knowing at what point in the recovery trajectory CI therapy is most effective for patients with stroke would help to better direct optimal delivery of the intervention. Although participants in this study averaged about 4.5 hours of actual training, more research is needed to determine whether the optimal intensity needed to achieve maximal meaningful clinical benefit for nondistributed practice can be ascertained.

Conclusion

Although therapists always need to assess patients' pain and fatigue during therapy, patients meeting the EXCITE criteria, whether in the subacute or in the chronic phase of recovery after stroke, are likely to experience improvement in upper-extremity function

after participation in an intensive 2-week protocol of CI therapy without increases in symptoms of pain and fatigue. Clinicians and researchers should continue to evaluate whether intensive therapy may increase other undesirable outcomes for patients.

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