Post Stroke Exercise Training

Intensity, Dosage, and Timing of Therapy

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KEYWORDS

• Stroke • Rehabilitation • Exercise • Intensity • Dose • Timing • Therapy • Recovery

KEY POINTS

- Greater intensity/dosage of therapy results in improved motor outcome.
- There are practical challenges to deliver therapy at optimal intensities, including adequate resources, limited rehabilitation stays, feasibility especially with elderly patients, and uncertainty over ideal dosing.
- There are new opportunities arising through innovative approaches, including new technologies, group-based therapies, and telerehabilitation.
- As time post stroke increases, the dose of therapy required to improve motor outcomes increases.
- Intensive therapy very early on, particularly within the first 24 hours, is best avoided.

INTRODUCTION

Stroke is a leading cause of disability among the adult population.[1] Hemiparesis is an iconic feature of stroke that manifests itself in difficulties with gait, coordination, balance, and increased tone. Exercise in task-specific activities under the supervision of physiotherapists and occupational therapists is critical to maximizing motor recovery and improving functional outcomes.

Stroke rehabilitation, more than any other area of neurorehabilitation, has well-developed clinical practice guidelines aimed at standardizing best practices for patient care.[2] This initially focused on a specialized interdisciplinary rehabilitation approach (stroke rehabilitation units) and evolved to include important elements of care on those units, particularly therapy intensity, timing of rehabilitation, and a greater

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focus on task-specific therapy. Intensity, dosing, and timing of rehabilitation are arguably becoming one of the biggest contributors to improved rehabilitation outcomes for individuals post stroke.

INTENSITY OF THERAPY POST STROKE

Definition

The definition of *intensity* varies across studies as it relates to rehabilitation. For example, "time spent in therapy" is commonly used to describe the amount of therapy received in observational studies.[3–5] It is also defined as "augmented therapy time," which describes the extra time an experimental group spends in therapy compared with conventional care.[6,7] Other definitions include the number of repetitions, or measures of how hard a person is working. The latter can be described in a variety of ways, including heart rate or perceived level of exertion. Therefore, the definition of intensity terms is often context dependent and may not reflect the same process.

VARIABILITY IN TREATMENT PROTOCOLS

Determining the effects of intensity of therapy on functional outcomes is challenging due to variability in treatment protocols. This is complicated by differences in the type of treatments provided, timing and duration of their delivery, and the outcomes assessed. Additionally, documentation of time spent in therapy and patient engagement in rehabilitation activities differs considerably across studies, units, institutions, and countries, making it difficult to compare studies or generalize results. Variations in outcomes have also been attributed to time spent in bed, sitting out of bed, or in standing/walking activities.[8]

IMPORTANCE OF INTENSITY OF THERAPY POST STROKE

Increased therapy intensity, however defined, has been shown to improve the recovery of motor deficits following stroke.[6,7] A meta-analysis of 34 randomized controlled trial (RCTs) found that increasing time spent in therapy (57 hours in the treatment groups vs 24 hours in the control groups) strongly predicted overall functional improvement.[9] Kalra was one of the first to show that more intensive therapy, delivered on a stroke rehabilitation unit, significantly improved outcomes (Barthel Index) and reduced hospital length of stay.[10] In this study, the same amount of therapy delivered over a shorter period of time on inpatient rehabilitation resulted in significantly different outcomes (improved Barthel Index and shorter lengths of stay).[10] Given the limitations of health care systems on hospital length of stay, therapy intensity may simply reflect how much therapy is received while in hospital. In a meta-analysis, Kwakkel and colleagues[6] found that increased intensity of physical therapy, at least 16 hours of additional therapy in the first 6 months, was associated with significant improvements in activities of daily living and walking speed.

THERAPEUTIC OPTIONS

Repetitive Task-Specific Training

Repetitive task-specific training involves performing repetitions of active motor sequences within a single training session, with the goal of improving specific functions.[11] It combines elements of intensity and task specificity, and is used for both upper and lower extremity training.[11] In a systematic review, repetitive task training of sit-to-stand exercises was found to be beneficial for mobility when compared with conventional therapy.[11] Repetitive task-specific training of the upper extremity

was found to be similarly beneficial in a systematic review.[12] With respect to upper limb function, increasing repetitions during rehabilitation are effective in improving functional recovery.[13–15]

High Intensity Exercise

Stroke survivors with hemiparesis require twice the energy for ambulation[16] and have half the cardiorespiratory capacity[17] compared with healthy individuals. This contributes to inactivity and deconditioning.[18,19] In turn, deconditioning limits the ability of stroke survivors to take advantage of rehabilitation therapies and achieve their full motor recovery.[20]

High intensity interval training (HIIT) involves intermittent bursts of effort separated by periods of recovery.[19,21] HIIT has been shown to be more effective in improving aerobic capacity[22–24] more quickly and efficiently through greater neuromuscular recruitment.[21] Wiener and colleagues[19] conducted a systematic review and found that HIIT using a treadmill or stationary bike resulted in significant improvements in walking speed and endurance as well as balance. Adverse effects were minor and not common. HIIT sessions were short lasting 20 to 30 minutes, 2 to 5 times a week, for 2 to 8 weeks and still resulted in improved functional outcomes.[19]

Other trials evaluating HIIT on treadmills for motor recovery post stroke revealed significant lower limb improvements in walking speed and motor evoked potentials.[25,26] Body weight supported treadmill training at faster walking speeds resulted in greater paretic limb support and peak muscle activation relative to exercise at lower walking speeds.[27] Additionally, high-intensity resistance training using training machines was shown to be more effective at improving paretic leg strength compared with lower intensity rehabilitation.[28] In this case multiple series of 8 repetitions at maximal loading was performed 3 times a week for 12 weeks with the loading progressively increased every 2 weeks. Forced exercise was also more effective improving functional movement compared with voluntary exercise.[29]

PRACTICAL CHALLENGES WITH THERAPY INTENSITY

Providing intensive rehabilitation has many practical challenges that often center around resources, or lack thereof. In many countries, there are limits to hospital length of stay; therefore, therapy intensity may simply reflect how long a person is in hospital. Another dilemma is the feasibility of high-repetition, task-specific training. Research suggests that hundreds of repetitions in task-specific practice may be required to optimize function post stroke.[13] Currently, the number of repetitions provided during post-stroke rehabilitation is a small fraction of what is optimal.[30] As an example, Lang and colleagues[30] in an observational trial found only half of upper extremity rehabilitation sessions practiced task-specific, functional upper extremity movements and in those, the average number of repetitions per session was 32. Lastly, there is a significant amount of downtime for patients undergoing rehabilitation. De Wit and colleagues[4] observed that patients spent 72% of their time in nontherapeutic activities on average. Further, an Australian study by Simpson and colleagues[31] found that patients spent more time upright and walking during the first week at home compared with their last week of rehabilitation. This suggests that stroke patients may be discouraged from achieving their full activity potential while on an organized stroke rehabilitation unit. Reasons for this may be safety concerns, lack of opportunity to be up and about, etc.

Another challenge is that the benefit of increasing therapy intensity is inconsistent across studies. In the VECTORS trial of upper extremity recovery, they found that

increasing therapy intensity did not result in better outcomes.[32] Fang and colleagues[33] suggested that a physiotherapy program of greater intensity may simply enable patients to achieve independence in activities of daily living faster through compensation of the nonparetic limb rather than actual neurologic recovery. Intensity of treatment also depends on the willingness of the patient to participate in therapy, and it can hinder progress when it becomes too intense.[34] This is especially true for patients who are frail, elderly, or have significant comorbidities.

All together, these issues limit the generalizability of findings, making it difficult to draw conclusions on the overall effectiveness of higher intensity programs. Although it is recognized that greater therapy intensity improves rehabilitation outcomes, there is some uncertainty as to what the ideal dose should be. Gimigliano commenting[35] on a Cochrane review by Clark and colleagues[36] concluded, *"It seems that functioning may improve when the increase in time spent in rehabilitation exceeds a threshold; however, there is currently insufficient evidence to recommend a minimum beneficial daily dose of rehabilitation."*[35]

Guidelines

The ideal amount of therapy has never been well defined and guidelines from different countries differ regarding therapy time recommendations (**Table 1**).[3] The Canadian Best Practice Guidelines[2] recommend 3 hours of direct task-specific therapy 5 days per week, though previous work has shown few patients receive this amount.[37] This recommendation in Canada was based largely on experiences in the United States. There, this *"3 hour rule"* was legislated and shown to be feasible for many stroke patients with significantly improved outcomes[38,39] when compared with less than 3 hours a day, and when compared with Canadian results.[40] In the Ontario Stroke Rehab Audit the median amount of inpatient therapy in 2019/2020 of direct physiotherapy/occupational therapy (PT/OT) and speech language pathology (SLP) was 69 minutes per day or 60% below target.[37] This situation is not unique to Ontario and Canada, with various countries around the world reporting similar issues.[41]

Table 1
Different guidelines for inpatient rehabilitation[3]

Guideline	Recommendation
AHA/ASA 2005	"…as much therapy as needed to adapt, recover and/or establish … optimal level of functional independence."
European Stroke Organization	"Increase the duration and intensity of rehabilitation"
Intercollegiate Stroke Working Party 2008	A minimum of 45 min daily of each therapy required in the early stages of stroke
SIGN 118	Increased intensity of therapy to improve gait should be pursued Increased intensity of therapy for improving upper limb function is not recommended
National Stroke Foundation, Australia 2010	Minimum of 1 h of occupational and physiotherapy 5 d per week
Canadian Best Practice Recommendations 2010	Minimum of 1 h per day, 5 d a week of each of the relevant core therapies (PT, OT, SLP)

From Foley et al. 2012.

Increasing Intensity of Therapy Through Innovative Practices

Because of the apparent benefit, there is a desire to increase therapy time within the fiscal restraints facing most health care systems. Donnellan-Fernandez et al[42] recommended several ways to increase the intensity of therapy including constraint-induced movement therapy, robotics, circuit therapy, gaming technologies, HIIT, goal-oriented instructions, and cardiovascular exercises. Some more innovative approaches include group-based therapy, including dance therapy or playing card games,[43] and greater use of weekend therapy, though evidence these are more effective remains uncertain.[44] Newer technologies, including nonimmersive virtual reality and technology assisted devices that deliver repetitive therapy, have been shown to improve outcomes.[45,46] Telerehabilitation, with use increasing throughout the COVID-19 pandemic, may be one means to deliver increased therapy more efficiently.[47]

CLINICAL PEARLS FOR INTENSITY

- Intensity of therapy is defined in different ways, making comparisons between studies challenging.
- Increased therapy intensity has been shown to improve motor recovery when compared with less intensive therapy. This benefit is greatest when it involves repetitive task-specific training.
- HIIT offers one method of increasing intensity without increasing additional therapist time.
- There are practical challenges to implementing more intensive therapy programs which include insufficient therapy staff or inefficient practices, inability or unwillingness of patient to participate, getting in enough repetitions to further enhance recovery, insurance-related limitations on therapy frequency allowed and the demotivating nature of institutional/hospital stays.
- There are a number of innovative approaches to improving therapy intensity including greater use of technologies, telerehabilitation, additional weekend and/or group therapies, and more intensive therapy approaches such as HIIT or circuit therapy.

TIMING OF THERAPY

Timing of therapy refers to time post stroke onset. Timing of therapy impacts patient outcomes and is often studied in relation to intensity. Although many studies have examined this topic, there is no clear consensus as to the optimal time to initiate rehabilitation after stroke.

PRE-CLINICAL STUDIES

Animal studies have shown the brain demonstrates maximal response to therapies when initiated early after a stroke, and if not, delays may worsen clinical outcomes.[48–51] The precise timing of what constitutes early to achieve the window of heightened neuroplasticity has not been fully determined,[42] but delays of more than a few days appear to be detrimental.

CLINICAL ASSOCIATION BETWEEN EARLY ADMISSION TO REHABILITATION UNITS AND IMPROVED FUNCTIONAL OUTCOMES

Clinically, comparative studies have shown a strong association between early admission to rehabilitation and improved functional outcomes, as well as decreased length

of stay.[52–60] For example, the Post-Stroke Rehabilitation Outcome Project (PSROP) was a prospective multisite observational study of 1291 patients from 6 inpatient facilities in the United States. They found that a longer period between stroke onset to admission to stroke rehabilitation was associated with an increased length of stay and lower Functional Independence Measure (FIM) scores at discharge,[61] particularly for individuals with moderate and severe strokes. It is possible, however, that some patients were admitted later due to a greater number of comorbidities, less medical stability, and more severe strokes, which confounds the findings. That said, other observational studies that have accounted for severity and comorbidities have found there is an association between earlier admission to rehabilitation and better recovery.[57] Delaying neurorehabilitation by a single day is associated with significant decreases in functional independence (0.3 FIM points/d) and significantly increased rates of institutionalization following discharge.[62]

MORE INTENSIVE THERAPY IN THE ACUTE PHASE

Given the importance of early transfer to rehabilitation post stroke, there has been increasing interest in the concept of very early mobilization (VEM). VEM is defined as an intervention designed to reduce the time from stroke onset to first mobilization and increasing the amount of out-of-bed physical activity shortly after stroke.[8,63] VEM occurs within 24 to 48 hours following stroke onset, generally while in acute care.

Early mobilization was studied in the Very Early Rehabilitation or Intensive Telemetry After Stroke (VERITAS) trial, an observer blinded RCT, where early mobilization was compared with standard care.[64] Mobilization activity, defined as the mean time spent upright per working day, was 61 minutes in the early mobilization group compared with 42 minutes in the standard care group. By day 5, 74% of patients in the early mobilization group were independently walking, compared with 44% of patients undergoing standard care. Patients in the very early mobilization group also experienced fewer medical complications and there was a trend toward less disability (defined as modified Rankin Scale [mRS] score of 0–2) at 3 months.

Other studies found similar results. Liu and colleagues[65] found that earlier rehabilitation (within 48 hours) was associated with greater independence at 6 months compared with later rehabilitation (after 7 days). Bai and colleagues[52,53] conducted 2 RCTs, one published in 2012 with 364 subjects and another in 2014 with 165 subjects, which evaluated a rehabilitation program provided within 24 hours of stroke onset and compared it to standard care. The very early rehabilitation programs were associated with greater improvements in impairment (Fugl-Meyer scores), independence (modified Barthel Index),[52] and spasticity (modified Ashworth Score).[53] Chippala and Sharma[66] performed an RCT of 86 subjects and showed patients who received mobilization within 24 hours had greater levels of independence based on the Barthel Index at discharge and at 3 months compared with patients receiving standard care. Morreale and colleagues[67] enrolled 340 stroke subjects into early (<24 hours post stroke) and late (>4 days) therapy involving Proprioceptive Neuromuscular Facilitation and Cognitive Therapeutic Exercise. They found with early intervention there were significant improvements in activities of daily living (Barthel Index), ambulation, and strength (Motricity Index), but not in general disability (mRS).

One of the largest studies assessing very early rehabilitation post stroke was the A Very Early Rehabilitation Trial (AVERT). This was a large, 8-year, multicenter, 3-phase trial of 2104 patients.[68] In contrast to the studies described above, AVERT found that patients receiving standard care were less likely to die or have expansion of stroke volume compared with those receiving VEM.[68] This discrepancy may be attributable to

the use of different tools to assess clinical outcomes: AVERT used the mRS, whereas the other trials measured improvements using the Barthel Index. Luft and colleagues[69] argued these findings should not prolong inactivity of stroke patients early after the stroke. Paradoxically, subsequent analysis of AVERT results found that shorter and more frequent early mobilization improved chances of regaining independence, whereas higher doses of early long-term mobilization worsened outcomes.[70] This may be due to compromised reperfusion of the at-risk penumbral area with higher intensity exercise. These results suggest that intensity may be an important mediator of recovery during rehabilitation when applied very early after stroke.

Rethnam and colleagues[71] in a review of 6 studies found significantly more favorable outcomes for patients in the early mobilization compared with the usual care control group (Modified Rankin), with no difference in mortality or activities of daily living (Barthel Index). Langhorne and colleagues[11] conducted a Cochrane review and found that early mobilization was comparable to usual care, with no significant differences in mortality or functional outcomes.

Overall, it appears that most studies find early rehabilitation is important to maximize stroke recovery and function, while very early aggressive therapy in the first 24 hours after stroke may be detrimental to recovery, or at best neutral.

INTENSIVE THERAPY IN THE SUBACUTE PHASE

The above has focused on early transfer to rehabilitation and early therapy, generally within the first few days, post stroke. But what about later? Dromerick and colleagues[72] in the Critical Period After Stroke Study (CPASS) examined the optimal time for motor recovery. Twenty extra hours of self-selected task-specific motor therapy were provided to 3 different groups each at different time intervals post stroke: (1) acute ($\leq$30 days); (2) subacute (2–3 months); and (3) chronic ($\geq$6 months). Each group was compared to each other and a control group receiving standard motor rehabilitation. On the ARAT, the greatest difference when compared with the control group was in the subacute phase, there was a significant but smaller difference in the acute phase, and a non-significant improvement in the chronic phase post stroke. This may indicate that increased therapy had the greatest impact in the subacute phase to improve upper extremity function.

Several other studies have also focused on increasing therapy in the subacute phase. Kwakkel and colleagues performed a meta-analysis and found that during the first 6 months post stroke, a 16 hour increase in therapy time over standard care was associated with a favorable outcome.[6] Van Peppen and colleagues[73] noted an additional therapy time of 17 hours over 10 weeks is necessary to see significant positive effects; this was affirmed by Verbeek and colleagues[74]

The Determining Optimal Post-Stroke Exercise (DOSE) RCT was designed to study the effect of higher exercise doses on walking for rehabilitation patients 1 to 4 weeks post stroke.[75] The study consisted of 3 groups: a control group receiving standard physiotherapy for 1 hour per day, 5 days a week for 4 weeks, DOSE 1 receiving 1 hour of more intensive physiotherapy during the same period, and DOSE 2 who received 2 hours of more intensive PT per day 5 days a week for 4 weeks. Both DOSE groups showed greater walking endurance at 4 weeks and at 1 year follow-up compared with controls.

INTENSIVE THERAPY IN THE CHRONIC PHASE

Although the greatest gains in post stroke recovery occur within the first 6 months, benefits still exist for rehabilitation in the chronic phase, though literature is more

conflicting. The ICARE (Interdisciplinary Comprehensive Arm Rehab Evaluation) trial, a multisite RCT, compared outpatients who received 30 hours of a structured, task-specific upper extremity exercise program over 10 weeks and found no significant difference in outcomes when compared with those receiving usual care.[76] Lang and colleagues[13] conducted a similar study and found a total of 32 hours of therapy in the chronic phase of stroke did not improve upper extremity function.

These results can be compared with 2 studies that provided much higher doses therapy.[77,78] McCabe et al[77] in a single-blind interventional study looking at upper extremity recovery found that chronic stroke patients provided 300 hours of activity-based technology assisted therapy (5 hours per day 5 days a week x 12 weeks) showed a substantial improvement of the Upper Extremity Fugl-Meyer Assessment score above the minimum clinically important difference. A retrospective review was conducted by Ward and colleagues[79] whereby 224 patients with a median of 18 months post stroke were treated with a high intensity rehabilitation program, 90 hours of therapy delivered for 6 hours a day, 5 days per week, for 3 weeks and compared it to 2 lower intensity therapy groups. The high intensity rehabilitation program resulted in significant improvement in a number of arm motor outcome measures, including the ARAT and the Upper Extremity Fugl Meyer Assessment.

Finally, a systematic review in this area conducted by Lohse and colleagues[9] examined the relationship between the amount of time spent in therapy and motor function. They found that in 34 RCTs of 1750 chronic stroke patients, those who receive more therapy as part of the intervention (on average, control was only 40% of that in the intervention group) were found to have greater improvement.

CLINICAL PEARLS FOR TIMING

- Earlier admission to a stroke rehabilitation unit/program has been associated with improved functional outcomes.
- Very early mobilization, especially if done in the first 24 hours, may be harmful and should be avoided.
- Early mobilization after the first 24 hours (with perhaps the exception of more severe stroke patients) is beneficial in improving recovery.
- Improved functional outcomes can be achieved with a more rigorous exercise program during usual planned therapy sessions at 1 to 4 weeks.
- Augmented therapy of about 20 hours in total is enough to improve motor outcomes in the subacute phase.
- Augmenting therapy in the chronic phase of stroke requires up to 90 hours of additional therapy to improve motor recovery outcomes.

SUMMARY

Although the exact intensity and timing of rehabilitation post stroke varies from study to study, in general, more intense, earlier rehabilitation results in improve motor outcomes. This is consistent with our understanding of the influence of repetitive task-specific exercises on neuroplasticity. There are pragmatic difficulties implementing more intense and earlier rehabilitation, but there are also innovative approaches including new technologies. As time goes by post stroke, the dosage of therapy required to result in improved outcomes increases. Very early rehabilitation exercises therefore offer the greatest opportunity, although rehabilitation should be carefully limited for the first 24 hours and longer for more severe strokes. Some recent data have shown that augmented rehabilitation in the subacute phase results in greater recovery in the upper extremity, when compared with recovery in the chronic phase,

with a suggestion it may be as good or perhaps better than the same augmented therapy delivered in the acute phase. Therapy in the form of task-specific exercises in the chronic phase requires higher doses to produce improved motor outcomes.

CLINICS CARE POINTS

- Clinical judgement is important in determining when therapy should be implemented early post stroke onset.
- Delays in therapy, including exercise and mobilization, are common, and run the risk of not acheiving maximal potential recovery.
- Intensity of therapy is often not optimized because of a lack of or failure to maximize therapy resources.
- The impact of therapy delivered early and of appropriate intensity should not be underestimated.
- Therapy resources applied in the acute/subacute phase will result in greater improvement in motor outcomes than similar resources applied in the chronic phase.
- Therapy provided in the chronic phase can improve motor recovery outcomes.

DISCLOSURE

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