Rehabilitation is Initiated Early After Stroke, but Most Motor Rehabilitation Trials Are Not A Systematic Review

Cathy Stinear, PhD; Suzanne Ackerley, PhD; Winston Byblow, PhD

Stroke is the third most common cause of death and the most common cause of acquired adult disability in developed countries.1 Motor impairment is common after stroke, and a critical factor influencing the patient’s ability to live independently.2,3 The neurobiological mechanisms of plasticity and spontaneous recovery during the initial days and weeks after stroke have been reasonably well characterized using animal models.4,5 These mechanisms include cell genesis, functional plasticity, and structural adaptations, such as axonal sprouting and synaptogenesis. The nature and time course of these mechanisms map onto the trajectory of motor recovery observed in human patients, most of whom reach their recovery plateau within 3 months of stroke.5,7 Rehabilitation is primarily delivered in this time period, to capitalize on the unique physiological conditions that prevail, and shape the spontaneous recovery process for the patient’s benefit. Recovery of function is likely to be enhanced by novel treatments that interact with and facilitate the underlying mechanisms of spontaneous recovery.

A variety of neurorehabilitation techniques aimed at improving motor recovery after stroke have been developed and trialed over the past 3 decades. These include repetitive task training, biofeedback, constraint-induced movement therapy, robotics, virtual reality, motor imagery, noninvasive brain stimulation, and pharmacological agents.8,9 However, despite almost 1000 randomized controlled trials (RCTs) in stroke rehabilitation,10 there is very little translation of this evidence base into clinical practice.11,12 Research efforts to develop the evidence base are challenged by difficulties in recruiting patients, resulting in small sample sizes; the heterogeneity of impairments after stroke and the complexity of their interactions with factors affecting recovery; and limited collaboration between scientists, clinicians, patient groups, and industry.11 Even when the research evidence base supports the development of clinical guidelines, significant barriers to implementation remain.10,13

Reviews of stroke rehabilitation commonly identify the need to perform research in real-world clinical settings8,11; however, they do not routinely report the timing of RCTs with respect to stroke onset. Similarly, Cochrane reviews typically draw conclusions about the efficacy of an intervention based on RCTs performed at any time after stroke.14–19 These conclusions are then used to develop guidelines that recommend initiating rehabilitation as soon as safely possible after stroke.20–24 A misalignment between the timing of RCTs and the real-world delivery of stroke rehabilitation may be an important aspect of the evidence base that limits its translation to clinical practice.

The first 30 days after stroke represent a critical time period for treatment initiation.25 Delays in RCT initiation may reduce the efficacy of the new treatment being tested, in the same way that delays in initiating rehabilitation lead to worse outcomes.26–28 The evidence base for new treatments initiated within the first month after stroke has not been evaluated. Rehabilitation of motor function is a common goal after stroke, and RCTs in this area are likely to be fairly representative of the stroke rehabilitation evidence base. The aim of this review was to determine the percentage of motor rehabilitation RCTs initiated within 30 days of stroke, and characterize these studies.

Method
This is a systematic review of RCTs investigating rehabilitation therapies and adjuvants with a main outcome measure of voluntary motor function after stroke. Trials were excluded if they were not published in English, had a pediatric sample, or primarily aimed to treat secondary motor complications, such as spasticity or shoulder subluxation. Studies were identified by searching PubMed and the Evidence-Based Review of Stroke Rehabilitation.29–31 These studies were categorized as early, late, or chronic, based on the time after stroke by which all participants were recruited. Early studies enrolled all patients within 30 days after stroke; late studies enrolled all patients within 180 days after stroke; and chronic studies enrolled patients who were >180 days after stroke.

The total Physiotherapy Evidence Database (PEDro)32 score was calculated, and studies with a score of at least 6 were further considered, in line with the common criteria for good quality PEDro scores used when evaluating levels of evidence (0–3=poor; 4–5=fair; 6–8=good; 9–10=excellent; see www.strokengine.ca and www. abiebr.com). To be considered good quality in the present review, trials had to meet 2 additional criteria: a dose-matched control intervention for comparison with the experimental intervention, and masked clinical assessments. Two independent reviewers applied these criteria to each early study, and disagreements were resolved by a third reviewer if required. Feasibility studies that involved a single application of the experimental treatment were excluded. Good quality early studies were further characterized by 2 independent reviewers, to identify sample size, the nature, and duration of...
the intervention, the timing of follow-up assessments, and whether the outcome was positive. Nonparametric statistics were used to explore whether RCTs with positive versus negative outcomes differed in sample size, treatment duration, and whether follow-up measures were made. Statistical significance was set at \( P<0.05 \) and SPSS (IBM, version 20) were used for all analyses.

Results

The review identified 532 RCTs of motor rehabilitation after stroke (Figure 1). Of these, there were 63 early studies (11.8%), 179 late studies (33.6%), and 284 chronic studies (53.4%). Thirty early studies met the criteria for good quality (5.6%), and their characteristics are summarized in Table 1 and depicted in Figure 2. Fifteen of these studies (2.8%) had a positive primary outcome, with a combined sample size of 634 patients (Figure 3). The other 15 studies had a negative primary outcome, with a combined sample size of 1813 patients. The distribution of sample sizes differed between positive and negative trials (Mann–Whitney \( U \) test, \( P=0.026 \), and this remained the case when an outlier\(^1\) was removed (Mann–Whitney \( U \) Test, \( P=0.046 \)). Trials with a negative outcome were more likely to recruit at least 40 patients (Pearson \( \chi^2 \) test, \( \chi^2=5.0, P=0.025 \)) and make follow-up measures (Pearson \( \chi^2 \) test, \( \chi^2=5.4, P=0.020 \)) than those with a positive outcome.

The most common type of intervention was pharmacological (n=12). The next most common types of intervention were variations of standard therapy (n=7) and noninvasive brain stimulation (n=6). The remaining 5 studies were trials of electrostimulation (n=2), constraint-induced movement therapy (n=2), and robotics (n=1). Of the 30 good quality early studies, 20 made follow-up assessments and 9 studies investigated mechanism by making imaging, neurophysiological, or kinematic measures, in addition to clinical assessments (Table 1). Seven studies assessed the effects of the intervention on the trajectory of patients’ recovery, by making clinical assessments during the treatment period (Figure 2). Only 5 studies reported the amount of therapy completed by patients in the treatment and comparison groups (Table 1).

Discussion

Approximately 6% of motor rehabilitation RCTs are good quality and initiated during the time when most rehabilitation occurs. Of these studies, less than a third investigated the mechanisms of action of the intervention, and those with a positive outcome recruited fewer patients and were less likely to make follow-up measures than those with a negative outcome. The evidence base for new motor rehabilitation techniques initiated early after stroke is therefore small, and includes only 15 positive, good quality RCTs, many of which are limited by small sample sizes and a lack of follow-up measures. Although there have been a number of new treatments and adjuvants developed for motor rehabilitation after stroke, this review indicates that we know very little about their interactions with the spontaneous recovery process or potential long-term benefits.

The early evidence base comprises mainly studies investigating existing treatments, as two thirds of the good quality early studies identified were RCTs of pharmacological agents and standard therapies. This is perhaps not surprising, as these modalities are known and administered by physicians and therapists working in the stroke rehabilitation environment. The early evidence base is relatively small for techniques such as electrostimulation, constraint-induced movement therapy, and robotics. Yet these treatments are recommended by clinical guidelines,\(^20–24\) which are intended to be implemented from the outset of rehabilitation. By drawing attention to this incongruity, and the limitations of the early evidence base, our intention is to energize efforts aimed at translating advances in neuroscience into stroke rehabilitation practice.

Designing rehabilitation RCTs to enroll and randomize patients to begin the intervention within 30 days of stroke has at least 3 potential benefits. The first is that more studies need to be performed under the unique physiological conditions that support spontaneous recovery during the first few weeks after stroke. In this review, we found that the majority of motor rehabilitation RCTs are performed with patients who are at least 6 months poststroke. But the most effective treatments may be those that interact with and benefit the spontaneous recovery process. At present, this critical period

![Figure 1. Review method. A total of 532 randomized control trials (RCTs) of motor rehabilitation after stroke were identified and categorized according to the time poststroke by which all participants were recruited. There were 63 (11.8%) early studies that recruited all participants within 30 days of stroke. Of the early studies, 2 feasibility studies\(^3\) were excluded because they delivered the experimental intervention only once. An additional 18 studies\(^4–12\) were excluded because they did not have a PEDro score of at least 6. Eleven studies\(^13–23\) were excluded because there was no dose-matched control intervention, for comparison with the experimental intervention. Two studies were excluded because the clinical assessments were not masked, or this was not reported.\(^24–26\) This left 30 good quality early studies for further review, or 5.6% of the RCTs identified.](image-url)
of spontaneous biological change that could improve gains is all but ignored. The second potential benefit is that solving the problems related to initiating RCTs early after stroke simultaneously addresses many of the barriers to subsequent translation and implementation. To enroll all patients in a study within 30 days of stroke, a functional collaboration between clinicians and researchers needs to be established, along with timely access to patients, and the intervention needs to be feasible in the clinical setting, as well as acceptable to both staff and patients. Testing a new treatment in the time and place of its intended application paves the way for its translation to clinical practice. Other flow-on benefits include building research skills and capacity for clinicians, and the generally higher standard of care delivered by clinical teams engaged in research.

The third potential benefit is that increasing the relevance of the evidence base will strengthen clinical guidelines for rehabilitation after stroke. Guidelines recommend

### Table 1. Good Quality Early Studies. Each of These Studies Enrolled All Patients Within 30 Days After Stroke, and Had a PEDro Score of at Least 6, a Dose-Matched Control Intervention for Comparison, and Masked Clinical Assessments

<table>
<thead>
<tr>
<th>Study</th>
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<th>Duration (d)</th>
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LL indicates lower limb; N, sample size; nr, not reported; UL, upper limb; and Y, yes.
that rehabilitation should start as soon as safely possible, and they also recommend treatments that have not been adequately trialed at this early stage. For example, motor imagery is recommended by clinical guidelines,20–24 yet we were unable to locate any trials of motor imagery that enrolled all patients within 30 days of stroke. This is akin to recommending a new drug for postoperative pain management that has not been specifically tested with patients in the first 4 weeks after surgery. Guidelines typically summarize the level of evidence for each treatment, but not when it has been accumulated, although the Canadian guidelines do note whether trials were performed with patients ±6 months after stroke.22 The interaction of the treatment with the physiological mechanisms of interest—in this case, the spontaneous recovery process after stroke—needs to be evaluated before the treatment can be confidently recommended for widespread clinical use.

One of the barriers to performing trials early after stroke is that it is difficult to predict participants’ potential for recovery of motor function. Although treatment and control groups can be balanced in terms of motor impairment at baseline, initial impairment is not a particularly good predictor of the response to therapy, or new treatments, for individual patients.66 Therefore, groups that may seem balanced at baseline can still have underlying differences in their potential for

![Figure 2. Motor rehabilitation randomized control trials (RCTs) performed at the early stage of stroke recovery. The 30 studies depicted randomized patients within 30 days of stroke, and met our criteria for good quality. Time after stroke is on a pseudo-log scale on the horizontal axis to provide optimal resolution in the early period. The start of each bar represents the earliest patient recruitment time (mean or maximum was used when the earliest time was not reported). Bar length reflects duration of intervention, and height reflects the sample size. Studies with a positive primary outcome are indicated in green shading, and negative outcome is indicated in gray. Vertical lines indicate times when measures were made, and are green when a positive effect of the treatment intervention was found. Black vertical bars indicate no difference between treatment and control groups at these measurement times, and gray vertical bars indicate weekly assessment until walking independently or discharge. #, Duration of intervention differed for individuals. The type of intervention trialed is given on the right. CIMT indicates constraint-induced movement therapy; drugs, pharmacological agents; ES, electrostimulation; therapy, variations of standard physiotherapy; NIBS, noninvasive brain stimulation; and RO, robotics.](http://stroke.ahajournals.org/)

![Figure 3. Number of patients in good quality early studies, with positive or negative primary outcomes. CIMT indicates constraint-induced movement therapy; drugs, pharmacological agents ES, electrostimulation; NIBS, noninvasive brain stimulation; and therapy, variations of standard physiotherapy.](http://stroke.ahajournals.org/)
recovery, which can confound interpretation of the results of the trial. A new algorithm that sequentially combines clinical assessments within the first 72 hours after stroke, with neurophysiological and neuroimaging within the first 10 days after stroke if required, has been shown to have good specificity and sensitivity for predicting potential for recovery of upper limb function for individual patients. Such an algorithm could be useful for stratification and balancing of the treatment and control groups, and subsequently characterizing patients most likely to benefit from the experimental treatment. Further development of algorithms for predicting recovery potential of individual patients, including other motor functions, such as walking, seems feasible and are urgently needed.

Another barrier is the difficulty in detecting clinically meaningful treatment effects against a background of spontaneous recovery. Treatments designed to facilitate neural plasticity in response to traditional therapies, such as pharmacological agents and noninvasive brain stimulation, may accelerate recovery without altering final clinical outcomes. The benefits of treatments delivered at the early stage could go undetected if the primary outcome is ≥3 months after stroke, by which time the control group may have caught up. The sensitivity of RCTs performed at the early stage could be increased by including multiple clinical assessments during and after the treatment period. This would enable treatment effects on the rate of recovery to be detected even in the absence of an effect on final outcome.

The sensitivity of RCTs performed at the early stage could also be enhanced by ensuring (and reporting) that total therapy time is comparable between the treatment and control groups. Highly variable total therapy doses may make treatment effects more difficult to detect, and systematic between-group differences in therapy dose may confound the interpretation of treatment effects. Although most studies report the planned dose of therapy, this review found that only 3 of the good quality early studies also report the actual dose delivered, and 2 studies also reported the total amount of standard therapy completed by the treatment and control groups (Table 1). Although therapy dose can be difficult to measure, doing so is particularly important for trials performed early after stroke, when rehabilitation intensity is usually highest.

There are also good reasons for performing stroke rehabilitation research with patients at the chronic stage of recovery. Studies at this stage are important to explore the safety, feasibility, and mechanism of potential new treatments, some of which could then also be trialed early after stroke. Treatments that are found to be safe and feasible, but not beneficial, at the chronic stage may have clinically meaningful benefits if tested at the early stage, under the unique physiological conditions that prevail. Treatments with efficacy at the chronic stage of stroke, such as constraint-induced movement therapy, demonstrate that meaningful gains in function can still be achieved by selected patients even years after stroke, perhaps by addressing deconditioning, nonuse, and compensatory behavior. RCTs of treatments that are designed to be delivered at the chronic stage also need to consider what rehabilitation services are widely available at this time, such as outpatient or community rehabilitation services. If there is no clinical platform for translation, then the treatment needs to be self-directed to be implemented outside the academic research setting.

Despite the sobering results of this review, there is optimism for the future. More than half of the good quality early trials we identified were published after 2004. This indicates that the number and quality of RCTs initiated during stroke rehabilitation are increasing, which bodes well for the translation of new treatments to clinical practice. Treatments need to be tested at the time of their intended use, and designing RCTs to achieve this aim will advance stroke rehabilitation.

Summary

Only 6% of stroke motor rehabilitation RCTs have enrolled all patients during the first 30 days after stroke. Those with a positive outcome are often limited by small sample size and a lack of follow-up measures. Designing RCTs so that treatment is initiated within 30 days of stroke will improve stroke rehabilitation by evaluating the interaction between treatment and the spontaneous recovery process; overcoming many of the barriers for translation to clinical practice; and building a temporally relevant evidence base for clinical guidelines, to facilitate their implementation. Testing treatments at the time of their intended use will advance stroke rehabilitation.

Search Strategy and Selection Criteria

References for this review were identified from the Evidence-Based Review of Stroke Rehabilitation and by searches of PubMed from January 1, 1980, until December 1, 2012, with combinations of the terms stroke, cerebrovascular motor, hemiparesis, hemiplegia, rehabilitation, trial, upper limb, arm, hand, lower limb, walking, and balance. Articles were also identified through searches of the authors’ own files. Only studies of adult populations and published in English were reviewed.

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Disclosures

None.

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