Early Rehabilitation after Acute Stroke: The Golden Recovery Period

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Abstract

Stroke is a leading cause of disability worldwide. Neuroplasticity, a condition wherein the brain's dynamic response to injury is heightened and rehabilitation might be effective, is observed shortly after acute stroke. However, although several trials have demonstrated that initiating treatment within 24 hours after stroke is potentially harmful, some have shown that early rehabilitation of patients is beneficial. Administration of constraint-induced movement therapy within two weeks after stroke appears to be beneficial for the upper extremities. In addition, intensive early post-stroke therapy may be beneficial for patients with severe aphasia. Novel approaches to early treatment of post-stroke dysphagia appear promising; however, the high rate of spontaneous improvement makes it difficult to gauge their benefits. Overall, although increasing evidence indicates that initiating rehabilitative strategies within two weeks after stroke is beneficial for some deficits, the optimal time for initiating post-stroke rehabilitation remains undetermined.

Keywords: stroke, early rehabilitation, neuroplasticity, early mobilization

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INTRODUCTION

According to global statistics in 2020, stroke is the second leading cause of death and the third leading cause of long-term disability worldwide. Among patients with stroke, 10% die in the acute phase, whereas 45% suffer from moderate to severe disability, requiring long-term care[1,2,3,4]. Thus, the burden of stroke should not be underestimated. Stroke leads to variable neurological deficits due to damage to different brain regions, including the long-term loss of motor sensation, slurred speech, balance problems, dysphagia, emotional problems/distress, cognitive disorders, and neglect. Thus, patients with stroke need long-term rehabilitation and joint care from experts across several fields.

The best time to start rehabilitation in the acute phase after stroke is a complex and unresolved issue. Based on the current clinical evidence in the available literature, "early rehabilitation" is defined as initiation of rehabilitation within 14 days after stroke. According to the 2019 treatment guidelines of the American Heart Association and American Stroke Association, patients

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with stroke should receive early rehabilitation and stroke care (COR I, LOE A) from an organized and multidisciplinary team of professionals during their hospital stay, but should avoid high-intensity, very early rehabilitation within 24 hours after stroke (COR III, LOE BR)[5].

1. Neuroplasticity and changes in neurological function during the acute phase of stroke

Evidence from animal studies shows that a series of neuroplastic changes occur in the brain after acute ischemic injury. These changes trigger a series of genetic, molecular, cellular, and electrophysiological events to promote nerve recovery. These events jointly promote cortical reorganization, structural changes and regeneration, and genetic-level effects.

The first neuroplastic change that occurs after stroke is the reorganization of the cortex. An animal study demonstrated that when the uninvolved (right) limb of an animal model of right brain stroke is stimulated three days after stroke, more activation signals are observed on the left cerebral cortex than on the contralateral side, if it is affected. When the limb on the affected (left) side is stimulated, the right brain activation signal on the stroke side is low, whereas the left brain signal is high. The contralateral brain area temporarily replaces the function of the affected brain area. Another study showed that when the same stimulation is performed 14 days after stroke, the activation signal of the right cerebral cortex increases on the affected (left) side, the activation signal of the left cerebral cortex of the contralateral brain area decreases, and the bilateral balance is gradually restored. These signal changes indicate the process of cortical reorganization[6]. In that study, functional magnetic resonance imaging (MRI) of patients with stroke showed that when the stroke and healthy side are stimulated, patients show more signal activations on both sides than healthy individuals to compensate for the impairment in the damaged brain area[7].

Studies of animal models in the acute phase of stroke have shown that growth factors that are triggered by ischemic events appear within three days and peak between 7 and 14 days[8]. Angiogenesis occurs within 10 days, and collateral circulation is established to supply the ischemic brain area. New nerve synapses also rapidly appear around the lesion and in the subventricular zone[9]. The brain-derived neurotrophic factor (BDNF) is an example at the molecular and genetic level. Previous studies have shown that BDNF plays an important role in neurogenesis, inhibits apoptosis, stimulates neural differentiation, and increases synaptic plasticity. Overall, this role significantly increases sensory and motor functions and reduces infarct volume[8]. Another important protein is methyl-CpG-binding protein 2 (MeCP2), which is a transcriptional regulator responsible for nerve growth, differentiation, and maturation. Experiments in rats with MeCP2 knockout genes have shown that rats with MeCP2 gene deletion have larger infarct volume than rats without the knockout gene[10].

When is the most appropriate time to start rehabilitation after a stroke event? Initiation of intervention within 24 hours to 48 hours after a stroke can increase BDNF levels and nerve and synaptic regeneration, but can cause damage through ischemia. The cerebrovascular barrier is tight and it reduces the levels of inflammatory cytokines, ischemic volume, and cell apoptosis to improve behavioral performance. In an animal model study, rehabilitation was initiated 5, 14, or 30 days after induction of brain ischemia and the group that started rehabilitation at five days scored higher than the other groups in skilled forelimb reaching ability, ladder-run, and narrow-beam-walking tasks[11]. Constraint-induced movement therapy (CIMT) was used in another animal model test of cerebral artery stroke in 2019, with the early intervention group starting treatment one day after stroke, and the late intervention group starting treatment 14 days after stroke. The results showed that the early intervention group had better behavior evaluation scores on the 8th day after stroke than the late intervention group. However, both groups showed significant progress on the 21st day[12]. In another animal study from 2021, rats with induced stroke underwent peripheral nerve stimulation three days after the stroke event. In the stimulus group, the rats that underwent electrical stimulation had better behavioral evaluation-object test scores than those that did not[13]. Conversely, some studies indicate that premature rehabilitation and exercise after stroke may be detrimental. Specifically, that starting rehabilitation exercise 6-24 hours after a stroke can increase the levels of inflammatory cytokines, increase the size of ischemic

lesions, and decrease neuronal differentiation. Synaptic proliferation (neurogenesis and dendritic sprouting) in turn affects the recovery of functions. Therefore, initiation of a rehabilitation plan within the vulnerable period of the first 24 hours after a stroke should be avoided.

2. Large-scale clinical research and application of rehabilitation treatment

Stroke causes multiple types of neurological deficits. Rehabilitation plans include rehabilitation of the upper and/or lower limbs; improvement of aphasia, dysphagia, and neglect; and non-invasive therapies, such as electrotherapy, computer-assisted, and repetitive transcranial magnetic stimulation (rTMS). Some emerging non-invasive therapies are very safe; however, more research and trials are required to determine the effective treatment guidelines for clinical applications of these therapies.

There is ample evidence regarding the early rehabilitation of patients with stroke. In 2015, a large international trial, named 'A Very Early Rehabilitation Trial after stroke' (AVERT), was conducted and included 2104 patients with ischemic or hemorrhagic stroke. The patients were divided into a "usual care" group, which started rehabilitation after 24 hours, and a "very early rehabilitation" group, which started rehabilitation within 24 hours. At three months, the "very early rehabilitation group" had fewer people with 0-3 points than the "usual care" group (46% vs. 50%; odds ratio: 0.73). Patients with minor stroke (National Institutes of Health Stroke Scale/Score [NIHSS]: 1-7) accounted for 55% of the AVERT study population. Thus, the rate of falls and bleeding in the very early rehabilitation group was not statistically different from that of the usual care group[14]. In 2018, Cochrane Review integrated and analyzed nine randomized controlled trials to explore the necessity and the advantages and disadvantages of "very early rehabilitation." Patients who started rehabilitation 24-48 hours after stroke were classified into the "very early rehabilitation group" and compared with a "normal group." The results showed that starting rehabilitation within 24 hours may reduce the number of days of hospitalization, but will increase the risk of adverse events. Specifically, starting forced sitting and standing too early will reduce blood circulation to the brain, affect self-regulation, and aggravate the scope of ischemia. In patients with hemorrhagic stroke or large infarction, the risk of bleeding increases. However, due to the high heterogeneity of the study design and patient admission conditions, further experiments are needed to verify and explore the findings of that study[15]. Several other studies were conducted to determine the most appropriate early rehabilitation treatment strategy. In 2019, a large randomized controlled trial for stroke rehabilitation was conducted and the patients included were divided into three groups based on the time rehabilitation was initiated (within 24 hours or between 24 hours to 48 hours) and the duration of rehabilitation (one day, less than 1.5 hours, or more than 3 hours). The results showed that the high-intensity rehabilitation group performed better 48 hours after stroke. However, there was no benefit to initiating treatment within 24 hours. Another randomized controlled trial showed that early rehabilitation within 24-48 hours yields better results and lower limb function recovery after 1-3 months than rehabilitation after 24 hours[16]. A study from 2020 showed that patients with an average NIHSS of 14.3 points who started rehabilitation 6 days after stroke showed improved functional recovery[17]. In a 2021 research study, patients in the early rehabilitation group who started exercising 24-48 hours after the onset of stroke, had a more favorable outcome at 3 months than those in the standard rehabilitation group who started exercising 48-96 hours after stroke. These findings indicate that early physical rehabilitation training within 24-48 hours may be beneficial and improve a patient's lower extremity function within the first week[18].

Regarding the frequency of rehabilitation, a large randomized controlled trial of 1759 patients conducted in Japan in 2021 assessed the effect of early intensive rehabilitation. The patients were divided in a high-frequency group, which received treatment twice a day, and a normal group, which received treatment once a day. The results showed that the high-frequency group had a better prognosis and lower medical costs than the normal group[19]. In another study conducted by a Chinese team to determine the most appropriate timing and frequency for rehabilitation after stroke, the stroke population with NIHSS <16 points, which underwent high-intensity rehabilitation 2 to 3 times a day, showed the best performance 24-48 hours after stroke[20]. There are

still some large-scale studies of rehabilitation after stroke in progress[21,22].

Lower extremity function and gait rehabilitation in patients with stroke have also been evaluated. In 2016, Morreale et al. conducted a study of patients with acute stroke and lower extremity weakness who underwent proprioceptive neuromuscular facilitation and cognitive therapeutic exercise within two days (early rehabilitation group) and four days (standard rehabilitation group) after the onset of stroke. Comparison of the Palliative Prognostic (PaP) and modified Rankin scale (mRS) scores of the two groups at 3 months showed no statistical difference between them. However, the early rehabilitation group had better PaP scores after 12 months[23]. In the 2019 study by Yen et al., the patients with stroke were divided into two groups; one group was treated with standard care, whereas the other underwent more transcutaneous nerve stimulation within 24 hours. The results showed that the group that underwent more transcutaneous nerve stimulation performed better in postural stability and walking tests than the standard care group[24].

Upper limb rehabilitation after stroke has been investigated in studies conducted in 2015, 2016, and 2017[25,26,27]. These studies were clinical trials for specific task training and modified restricted-induced movement therapy (mCIMT) administered within one week, eight days, and two weeks after stroke. The results showed more activation signals on functional MRI scans and a better prognosis after the end of the test and 12 weeks later, but was not maintained beyond 3 months and 26 weeks, respectively.

Existing research indicates that early rehabilitation within 14 days may not have significant clinical benefits for the improvement of aphasia. However, significant progress has been reported in the analysis of sub-ethnic groups who received a complete high-intensity training course for aphasia[28,29]. In early rehabilitation trials for neglect after stroke, treatment was initiated within 15, 14, and 2 days after stroke. The results indicated that initiation of half-field patch treatment within 15 days has no obvious benefits. Additionally, treatment of the patient group using half-field coverage therapy and repetitive optokinetic stimulation of eye movements within 14 days showed no significant benefit compared to the control group (those who did not receive half-field coverage therapy and repetitive optokinetic stimulation of eye movements). However, patients who started mirror therapy within two days achieved significant functional recovery after 1, 3, and 6 months of follow-up compared to the placebo group[30,31,32].

In a study on the rehabilitation of swallowing function, patients who underwent neuromuscular electrical stimulation of the subhyoid area within 10 days after stroke showed better functional recovery, and those who underwent rTMS on the ipsilateral or contralateral side showed better swallowing recovery than the placebo group. Studies in which traditional swallowing training was initiated within 3, 14, and 30 days demonstrated that the earlier rehabilitation is started, the better the recovery and the lower the risk of aspiration pneumonia. However, researchers also found that patients with small swallowing disorders after stroke have a high natural recovery rate. If they do not recover within a short period, patients in the late rehabilitation group also experience more severe damage and poor follow-up recovery in the future, which may be a deviation factor[32,33,34].

Non-invasive brain stimulation, including rTMS and transcranial direct current stimulation, has shown considerable efficacy in regulating brain activity and improving motor function after stroke. We found that four previous studies on early post-stroke intervention conducted using non-invasive brain stimulation showed excellent safety results; however, the efficacies reported in the studies vary. Investigation using functional MRI shows that effective activation of the cortex in the relevant brain area results in significant signal changes, but fails to reflect the obvious improvement in clinical function. However, the experimental population is still small, and the dose applied to humans is much lower than that of animals[35,36,37,38]. Thus, the experimental threshold, the most appropriate dose, and the frequency of early post-stroke rehabilitation are still under study.

The use of computer technology and machine assistance brings new opportunities for rehabilitation in the acute phase of stroke. Robotic tilt table stepper training combines computer technology, tilt table angle adjustment, and adjustable strength assistance for the rehabilitation of each joint. It is multi-faceted and tailor-made for patients with stroke and/or limb motor dysfunction, and is a suitable and safe rehabilitation method. In studies of total

237 patients with acute stroke, patients who underwent mechanical tilting bed stepper training within eight days after stroke achieved significant improvement in lower limb strength, quality of life, and NIHSS scores compared with the control group[39,40]. Early intervention (within 14 days) using a video game-like design that involves that use of plantar flexion and dorsiflexion to control objects on a computer to avoid obstacles can increase step distance[41]. Additionally, vibration feedback, which adjusts the correct action scores in the follow-up tracking of sports training, leads to improved performance[40]. However, certain technology-assisted post-stroke rehabilitation methods, such as the use of remote ischemic conditioning, in the acute phase of stroke are still under investigation[42]. Early bed activity and rehabilitation in the neuro-intensive care unit have also been observed to reduce pressure sores and pneumonia[43].

In addition to the promising results of previous studies, technology-assisted post-stroke rehabilitation methods have been applied successfully in the clinical setting. The Tri-Services General Hospital in Taiwan successfully applied virtual reality during the multiple rehabilitation of patients with acute stroke during hospitalization, and the patients showed good functional scores at the time of discharge[44,45].

SUMMARY AND CONCLUSION

Based on the results of several large and small previous studies, the first two weeks after a stroke is defined as the early post-acute stroke period. Animal studies and investigations using functional MRI demonstrated that neuroplasticity occurs in the early post-acute stroke period. Early initiation of rehabilitation may effectively increase functional recovery after stroke. However, premature initiation of activity (within 24 hours) causes an increase in acute cell inflammatory hormones and hemodynamic instability, which leads to an increased risk of bleeding. Further, injuries such as falls may occur during this vulnerable stage[5].

Regarding rehabilitation of deficits caused by stroke, rehabilitation of the upper limbs after stroke focuses on limited induced motion therapy, and initiation of such intervention within two weeks after stroke is significantly beneficial compared to starting treatment later. Mechanical tilting bed stepper training can be used to achieve significant progress in the rehabilitation of the lower limbs after stroke. Furthermore, early high-intensity training is helpful in the treatment of aphasia. However, as the rate of spontaneous slight recovery of dysphagia is very high and early rehabilitation is ineffective for patients with severe dysphagia, it is difficult to assess the true impact of early intervention for dysphagia. Regarding rehabilitation for neglect after stroke, early rehabilitation using mirror box training can yield satisfactory results. Non-invasive cranial nerve stimulation therapy is very safe for early intervention in acute stroke. However, more evidence is still needed to define its treatment criteria, such as the stimulation brain area, dose, and frequency. Furthermore, the induced cortical activation has not been effectively converted to clinical practice.

It is worth noting that the patients in the studies reviewed mostly had mild to moderate strokes. Furthermore, only patients with ischemic strokes were included in some studies, whereas cases of ischemic and hemorrhagic strokes were analyzed in other studies. The time points of intervention in the studies ranged from 1 day to 15 days. The intervention methods, time points for tracking main results, and the scoring scales showed great variability. These variations echo the variable nature of the symptoms, severity, clinical course, and prognosis of stroke.

Neurologists recommend that patients with stroke must stay in bed as much as possible within the first 24 hours. The appropriate rehabilitation plan should be initiated as soon as possible depending on the severity of the stroke, possible complications should be monitored, and a multidisciplinary professional team and bedside caregivers should be integrated to effectively execute the rehabilitation plan. These steps will facilitate the prevention of complications to achieve the mission of reducing disability and mortality and reducing medical, family, and economic burdens.

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