Access this article online

Quick Response Code:

Website: http://www.braincirculation.org

DOI: 10.4103/bc.bc_33_23

Optimal rehabilitation strategies for early postacute stroke recovery: An ongoing inquiry

Yanna Tong[1,2], Yuchuan Ding[3], Zhenzhen Han[1,2], Honglian Duan[1,2], Xiaokun Geng[1,2]

Abstract:

Early rehabilitation is crucial in reducing stroke-related disability, but the optimal training model remains unclear. We conducted a trial comparing different initiation timings and intensities of mobilization strategies after stroke. Results showed that early intensive mobilization had favorable outcomes at 3 months post-stroke, while very early intensive mobilization had poorer chances of favorable outcomes. Our investigation into brain injury mechanisms induced by very early exercise within 24 hours of stroke onset aligned with guidelines advising against high-dose very early mobilization. Additionally, we are studying the effects of various exercise intensities and frequencies on early stroke rehabilitation. Integrated rehabilitation models, such as combining remote ischemic conditioning (RIC) with exercise (RICE), hold promise. Our study found RICE to be safe and feasible for early rehabilitation of acute ischemic stroke patients, and further research is underway to determine its efficacy in a larger sample size. Despite extensive research, identifying the most effective early recovery strategies remains a complex challenge, necessitating ongoing work in the field of early rehabilitation after stroke.

Keywords:

Early rehabilitation, acute stroke, timing and intensity, remote ischemic conditioning and exercise

Introduction

In recent decades, substantial advancements have been achieved in managing acute ischemic stroke (AIS) patients, leading to a significant reduction in mortality rates.[1-4] However, as mortality rates decline, the disability burden among stroke survivors increases.[5] Rehabilitation is a crucial component in managing cerebrovascular diseases, which effectively reduces disability rates in stroke patients. Neuroplasticity, which has the most significant potential to enhance motor recovery, occurs primarily during the early stages after a stroke.[6] Consequently, interventions that encourage neuroplasticity soon after a stroke could unleash maximum potential to boost motor recovery in poststroke individuals.[7] Early rehabilitation after a stroke is advocated by the current stroke rehabilitation guidelines,[8] but an ideal rehabilitation training strategy has yet to be determined.[8,9] This lack of consensus has become a critical obstacle in practical clinical rehabilitation.

Optimal Timing and Intensity for Poststroke Rehabilitation

The ideal time to initiate mobilization after an AIS remains to be determined and has been a focal point of research. To deal with this issue, we performed a randomized controlled trial (RCT) from 2015 to 2017, comparing very early mobilization to early mobilization and intensive mobilization to routine mobilization.[10] Very early

[1]Department of Neurology, Beijing Luhe Hospital, Capital Medical University, [2]Department of Neurology, Luhe Institute of Neuroscience, Capital Medical University, Beijing, China, [3]Department of Neurosurgery, Wayne State University School of Medicine, Detroit, MI, USA

Address for correspondence:
Dr. Xiaokun Geng, Department of Neurology, Beijing Luhe Hospital, Capital Medical University, No. 82 Xinhua South Road, Tongzhou, Beijing 101149, China.
E-mail: xgeng@ccmu.edu.cn

Submission: 24-04-2023
Revised: 26-08-2023
Accepted: 29-08-2023
Published: 30-11-2023

How to cite this article: Tong Y, Ding Y, Han Z, Duan H, Geng X. Optimal rehabilitation strategies for early postacute stroke recovery: An ongoing inquiry. Brain Circ 2023;9:201-4.

mobilization commenced in 24 h after stroke attack, whereas early mobilization typically occurred 24–48 h postattack. Intensive mobilization protocols involved ≥3 h/day of mobilization, whereas routine protocols involved <1.5 h/day. Mobilization interventions consisted of out-of-bed activities with or without assistance, such as sitting, standing, and walking. A modified Rankin Scale (mRS) score of 0–2 at 3 months poststroke was determined as a satisfactory result. In addition, a total of 300 patients were assigned equally to three groups with random: Very Early Intensive Mobilization (VEIM), Early Routine Mobilization (ERM), and Early Intensive Mobilization (EIM). Our trial results revealed that patients in the EIM group experienced the most favorable 3-month outcomes, followed by those in the ERM group, with the VEIM group having the poorest likelihood of favorable outcomes. Concurrently, we investigated brain injury mechanisms induced by very early exercise using rat stroke models. We discovered that very early exercise could increase nicotinamide adenine dinucleotide phosphate oxidase (NOX) activity and the expression of subunit protein, worsen oxidative stress damage. Additionally, it stimulated the release of cytokine release [e.g., interleukin-1β (IL-1β) and interleukin-6 (IL-6)], triggering inflammatory responses. Furthermore, it upregulated pro-apoptotic proteins (e.g., Caspase-3), inducing cell apoptosis, while downregulating neurovascular remodeling proteins [e.g., synaptophysin (SYP)][11-14]; moreover, very early exercise inhibited hypoxia inducible factor-1α (HIF-1α) degradation and promoted incomplete gluconeogenesis, resulting in exacerbated lactic acidosis and oxidative stress injury.[15,16] It also amplified endoplasmic reticulum stress and activated the CCAAT-enhancer binding protein (C/EBP)-homologous protein (CHOP) and Caspase-12 mediated apoptosis pathway, further aggravating brain injury.[17]

Our clinical trial findings align with the largest and most evidence-based RCT on early rehabilitation of stroke to date, the A Very Early Rehabilitation Trial.[18] Consequently, the 2018 guidelines for early management of AIS patients from the American Heart Association/American Stroke Association[19] explicitly advised against high-dose, very early mobilization within 24 h of stroke onset, as it could decrease the chance of favorable outcomes at 3 months. While numerous trials have aimed to determine the optimal time to initiate mobilization after a stroke,[20-22] the ideal time window for early mobilization initiation remains uncertain. Currently, a randomized, 3-arm parallel group, multicenter clinical trial called "TIME"[23] is being conducted across 57 comprehensive hospitals in Chinese mainland. Participants with acute ischemic cerebral infarction are randomly settled into one of the following groups: (1) very early mobilization, with mobilization initiated within 24 h of an AIS; (2) early mobilization, with mobilization beginning at 24–72 h poststroke; or (3) late mobilization, with mobilization starting 72 h poststroke. Disability or death, evaluated by mRS at 3-month poststroke, is considered the primary outcome. We anticipate that the study's findings will provide valuable insights into the optimal time for initiating poststroke rehabilitation in the future.

Furthermore, the dosage of rehabilitation procedures is crucial for patient outcomes. High-dose mobilization within 24 h poststroke has been linked to a decreased chance of favorable outcomes at 3 months. However, the impact of lower-dose very early mobilization remains uncertain. Limited literature exists on this topic, and the optimal intensity for very early poststroke mobilization is yet to be determined. Our team is currently investigating the effects of different mobilization intensities and frequencies on early stroke rehabilitation. Our research findings may help enhance understanding of the optimal mobilization intensity following AIS.

Combining Rehabilitation Strategies

Rehabilitation plays a crucial role in reducing disability caused by stroke and should be initiated early.[8,19,24] Exercise, particularly mobilization, targets the recovery of active grip, sitting, standing, and walking activity, either with or without assistance, in the acute phase following a stroke.[18] While exercise is an established cornerstone of effective rehabilitation,[25] the choice of exercise, including gross or fine-motor training, comprehensive systemic rehabilitation, or focused single-limb rehabilitation, often depends on the specific needs, tolerance, and capabilities of the patient. Determining which type yields the most significant benefits remains an ongoing area of exploration. Exercise training is restricted in clinical application due to the potential exacerbation of cerebral injury during very early stages and patients' unstable conditions and disabilities.[26] This leaves an unoccupied period during early stroke recovery, hindering the full realization of early rehabilitation's theoretical benefits. Therefore, it is essential to explore feasible rehabilitation strategies which can be applied safely during the early periods of stroke recovery.

Remote ischemic conditioning (RIC) is a noninvasive and inexpensive novel neuroprotective therapy, which is simple and easy to operate.[24,27] RIC triggers endogenous protective mechanisms by inducing transient sublethal ischemia in the distal limbs through controlled blood flow restriction, protecting vital organs (e.g. brain, heart, and kidney) from severe lethal ischemic injury.[28-30] RIC has been proven to work through biochemical mechanisms similar to exercise, with a broader range of time window including hours after a stroke.[31,32] In addition, RIC

can be applied passively to patients and rely less on patient mobility, disability, as well as motivation[32] and, thus, feasible for patients regardless of their clinical presentation. RIC seems to be an appropriate strategy for very early, even hyperacute periods of stroke rehabilitation when patients may not be able to endure high-intensity exercise or other rehabilitation protocols.[33]

The complementary benefits and disadvantages of RIC and exercise indicate they could be integrated to be an optimized strategy for AIS patients. Consequently, we developed a novel strategy of early stroke rehabilitation to maximize the therapeutic potential of both therapies, named RICE (RIC + Exercise), in which RIC is started shortly afterward an ischemic stroke onset and exercise follows subsequently.[24,28,33] We performed a pilot clinical research to estimate the security and feasibility of the RICE strategy.[34] The trial compared the RICE strategy (RIC protocol combined with exercise) with a sham-RICE strategy (sham-RIC protocol combined with exercise). The RIC protocol interventions included five cycles of ischemia and reperfusion of both upper limbs, with cuff inflation to 200 mmHg for 5 min for ischemia, followed by cuff deflation for an additional 5 min for reperfusion. The procedure of the sham-RIC protocol was the same as that of the RIC group, except that the inflation pressure was 60 mmHg. All 40 enrolled participants were equally settled to either the sham-RICE or RICE group at random. The sham-RIC or RIC intervention was initiated within 24 h after stroke attack or symptom deterioration and repeated once daily for 14 consecutive days. An exercise protocol was initiated from the 4th day in both groups, twice a day, for 11 days in total. Our study results demonstrated that RICE could be safely implemented and was feasible for AIS subjects, which appears to be a promising strategy for early rehabilitation of AIS. A further multicenter RCT with a larger sample size to determine RICE's efficacy is in progress currently.

Conclusion

The period soon after ischemic stroke onset is critical for recovery, and early rehabilitation plays a vital role in reducing stroke-related disability. Although considerable effort has been made to determine the optimal timing and dosage of current interventions, no universally accepted model of poststroke rehabilitation exists. Early rehabilitation holds significant potential beyond just ischemic stroke subjects. It is increasingly being recognized as a critical intervention for those who have suffered from hemorrhagic stroke, traumatic brain injury,[35] as referenced in PMID: 36321858, and subarachnoid hemorrhage,[36] as detailed in PMID: 37082756. For all these varied neurological impairments, determining the most effective early rehabilitation strategy remains a complex challenge, underscoring the need for comprehensive studies across different neurological conditions. Thus, conducting clinical studies aimed at addressing this issue is of paramount importance for the field of neurorehabilitation. Expanding our understanding of the most effective rehabilitation strategies will ultimately lead to improved patient outcomes and contribute to the development of evidence-based guidelines for poststroke care. By continuing to refine and optimize rehabilitation practices, health-care professionals will be better equipped to help stroke survivors regain their functional abilities and achieve the highest possible quality of life.

Financial support and sponsorship

This work was partially supported by the National Natural Science Foundation of China, (82002382) the Science and Cultivation Fund of Capital Medical University (PYZ21170), the Tongzhou District Health Development Research Project (KJ2023CX026, KJ2023CX030).

Conflicts of interest

Dr. Yuchuan Ding is an Associate Editor, Dr. Xiaokun Geng is an Editorial Board member of Brain Circulation. The article was subject to the journal's standard procedures, with peer review handled independently of them and their research groups.

References

1. Holmes DR Jr., Hopkins LN. Interventional cardiology and acute stroke care going forward: JACC review topic of the week. J Am Coll Cardiol 2019;73:1483-90.
2. Mavromoustakou K, Doundoulakis I, Soulaidopoulos S, Arsenos P, Laina A, Sideris S, *et al.* Impact of atrial fibrillation on the severity, progress, and disability of the ischemic stroke patients. Heart Mind 2022;6:26-31.
3. Hollist M, Morgan L, Cabatbat R, Au K, Kirmani MF, Kirmani BF. Acute stroke management: Overview and recent updates. Aging Dis 2021;12:1000-9.
4. Cheng Z, Geng X, Rajah GB, Gao J, Ma L, Li F, *et al.* NIHSS consciousness score combined with ASPECTS is a favorable predictor of functional outcome post endovascular recanalization in stroke patients. Aging Dis 2021;12:415-24.
5. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, *et al.* Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723-31.
6. Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, *et al.* Modulation of brain plasticity in stroke: A novel model for neurorehabilitation. Nat Rev Neurol 2014;10:597-608.
7. Lee H, Yun HJ, Ding Y. Timing is everything: Exercise therapy and remote ischemic conditioning for acute ischemic stroke patients. Brain Circ 2021;7:178-86.
8. Gittler M, Davis AM. Guidelines for adult stroke rehabilitation and recovery. JAMA 2018;319:820-1.
9. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, *et al.* Guidelines for adult stroke rehabilitation and recovery: A guideline for healthcare professionals from the American Heart

Association/American Stroke Association. Stroke 2016;47:e98-169.
10. Tong Y, Cheng Z, Rajah GB, Duan H, Cai L, Zhang N, *et al.* High intensity physical rehabilitation later than 24 h post stroke is beneficial in patients: A pilot randomized controlled trial (RCT) study in mild to moderate ischemic stroke. Front Neurol 2019;10:113.
11. Li F, Shi W, Zhao EY, Geng X, Li X, Peng C, *et al.* Enhanced apoptosis from early physical exercise rehabilitation following ischemic stroke. J Neurosci Res 2017;95:1017-24.
12. Shen J, Huber M, Zhao EY, Peng C, Li F, Li X, *et al*. Early rehabilitation aggravates brain damage after stroke via enhanced activation of nicotinamide adenine dinucleotide phosphate oxidase (NOX). Brain Res 2016;1648:266-76.
13. Li F, Pendy JT Jr., Ding JN, Peng C, Li X, Shen J, *et al.* Exercise rehabilitation immediately following ischemic stroke exacerbates inflammatory injury. Neurol Res 2017;39:530-7.
14. Li F, Geng X, Khan H, Pendy JT Jr., Peng C, Li X, *et al.* Exacerbation of brain injury by post-stroke exercise is contingent upon exercise initiation timing. Front Cell Neurosci 2017;11:311.
15. Li F, Geng X, Huber C, Stone C, Ding Y. In search of a dose: The functional and molecular effects of exercise on post-stroke rehabilitation in rats. Front Cell Neurosci 2020;14:186.
16. Li F, Geng X, Ilagan R, Bai S, Chen Y, Ding Y. Exercise postconditioning reduces ischemic injury via suppression of cerebral gluconeogenesis in rats. Brain Behav 2023;13:e2805.
17. Li F, Geng X, Lee H, Wills M, Ding Y. Neuroprotective effects of exercise postconditioning after stroke via SIRT1-mediated suppression of endoplasmic reticulum (ER) stress. Front Cell Neurosci 2021;15:598230.
18. AVERT Trial Collaboration group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): A randomised controlled trial. Lancet 2015;386:46-55.
19. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al.* 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46-110.
20. Wang F, Zhang S, Zhou F, Zhao M, Zhao H. Early physical rehabilitation therapy between 24 and 48 h following acute ischemic stroke onset: A randomized controlled trial. Disabil Rehabil 2022;44:3967-72.
21. Wang W, Wei M, Cheng Y, Zhao H, Du H, Hou W, *et al.* Safety and efficacy of early rehabilitation after stroke using mechanical thrombectomy: A pilot randomized controlled trial. Front Neurol 2022;13:698439.
22. Liu L, Lu Y, Bi Q, Fu W, Zhou X, Wang J. Effects of different intervention time points of early rehabilitation on patients with acute ischemic stroke: A single-center, randomized control study. Biomed Res Int 2021;2021:1940549.
23. Zheng Y, Yan C, Shi H, Niu Q, Liu Q, Lu S, *et al.* Time window for ischemic stroke first mobilization effectiveness: Protocol for an investigator-initiated prospective multicenter randomized 3-arm clinical trial. Phys Ther 2021;101:pzab038.
24. Han Z, Zhao W, Lee H, Wills M, Tong Y, Cheng Z, *et al.* Remote ischemic conditioning with exercise (RICE)-rehabilitative strategy in patients with acute ischemic stroke: Rationale, design, and protocol for a randomized controlled study. Front Neurol 2021;12:654669.
25. Dimitriadis K, Bletsa E, Lazarou E, Leontsinis I, Stampouloglou P, Dri E, *et al*. A narrative review on exercise and cardiovascular events: "Primum non nocere". Heart Mind 2022;6:127-38.
26. Saunders DH, Greig CA, Mead GE. Physical activity and exercise after stroke: Review of multiple meaningful benefits. Stroke 2014;45:3742-7.
27. Sangeetha RP, Venkatapura RJ, Kamath S, Christopher R, Bhat DI, Arvinda HR, *et al.* Effect of remote ischemic preconditioning on cerebral vasospasm, biomarkers of cerebral ischemia, and functional outcomes in aneurysmal subarachnoid hemorrhage (ERVAS): A randomized controlled pilot trial. Brain Circ 2021;7:104-10.
28. Wang Q, Wills M, Li F, Geng X, Ding Y. Remote ischemic conditioning with exercise (RICE) promotes functional rehabilitation following ischemic stroke. Neurol Res 2021;43:874-83.
29. Doeppner TR, Zechmeister B, Kaltwasser B, Jin F, Zheng X, Majid A, *et al.* Very delayed remote ischemic post-conditioning induces sustained neurological recovery by mechanisms involving enhanced angioneurogenesis and peripheral immunosuppression reversal. Front Cell Neurosci 2018;12:383.
30. Gao Y, Ren C, Li X, Yu W, Li S, Li H, *et al.* Ischemic conditioning ameliorated hypertension and vascular remodeling of spontaneously hypertensive rat via inflammatory regulation. Aging Dis 2021;12:116-31.
31. Zhao W, Li S, Ren C, Meng R, Ji X. Chronic remote ischemic conditioning may mimic regular exercise: Perspective from clinical studies. Aging Dis 2018;9:165-71.
32. Zhao W, Li S, Ren C, Meng R, Jin K, Ji X. Remote ischemic conditioning for stroke: Clinical data, challenges, and future directions. Ann Clin Transl Neurol 2019;6:186-96.
33. Wills M, Ding Y. Mini-review (Part II): A clinical consideration on exercise and ischemic conditioning in stroke rehabilitation. Brain Circ 2021;7:225-9.
34. Tong Y, Lee H, Kohls W, Han Z, Duan H, Cheng Z, *et al.* Remote ischemic conditioning (RIC) with exercise (RICE) is safe and feasible for acute ischemic stroke (AIS) patients. Front Neurol 2022;13:981498.
35. Findlay MC, Bauer SZ, Gautam D, Lucke-Wold B. Rehabilitation after neurotrauma: A commentary. J Surg Care 2022;1:19-26.
36. Nwafor DC, Kirby BD, Ralston JD, Colantonio MA, Ibekwe E, Lucke-Wold B. Neurocognitive sequelae and rehabilitation after subarachnoid hemorrhage: Optimizing outcomes. J Vasc Dis 2023;2:197-211.