

Combination of stem cell and repetitive transcranial magnetic stimulation in acute ischaemic stroke as a promising treatment: A case report

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Case Report

ABSTRACT

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Stroke is a major contributor to long-term disability and its incidence continues to rise annually. This case report aimed to explore the promising benefits of combining stem cell therapy with repetitive transcranial magnetic stimulation (rTMS) in managing acute ischaemic stroke patients. A 62-year-old male presented with left-sided hemiparesis and hemineglect, as well as a cognitive disturbance in the attention domain. His medical history included uncontrolled hypertension over decades and diabetes mellitus for five years. A non-contrast head computed tomography (CT) scan revealed infarction in the right middle cerebral artery (MCA), with an initial National Institutes of Health Stroke Scale (NIHSS) of 13 upon admission to the Emergency Room. The infection and tumour markers were conducted to confirm no contraindication in this patient receiving stem cell therapy. Following the acute phase, the patient underwent a comprehensive treatment regimen involving both stem cell therapy and serial rTMS. Clinical assessments included NIHSS, Barthel Index, and Fugl-Meyer Assessment to evaluate neurological deficits. Additionally, the Montreal Cognitive Assessment-Indonesian version (MoCA-INA) assessment, electroencephalography examination and motor threshold were conducted. The results of this case report revealed noteworthy improvements in NIHSS, motoric strength, and cognitive function post-treatment. In this case report, improvement in clinical outcomes was obtained in the form of motor strength and higher cortical function. Stem cell therapy combined with rTMS has good potential in treating various neuroregenerative and rehabilitative aspects in ischaemic stroke patients.

INTRODUCTION

Stroke is a major contributor to long-term disability worldwide, and it stands as the second biggest killer after ischaemic heart disease. Among the various aetiologies of stroke, ischaemic stroke emerges as the most frequent type.¹⁻³ The incidence of strokes has been on the rise each year. Based on our stroke registry and medical record, from January 2021 to August 2023, the Stroke Unit Department at Moewardi General Hospital recorded 2,953 stroke cases. Among these cases, 1,914 (64.8%) were male, while 1,039 (35.19%) were female. Upon examination using

non-contrast computed tomography (CT) scans, it was determined that 1,962 (66.4%) patients had ischaemic strokes, 837 (28.3%) patients had haemorrhagic strokes, and the remaining 154 (5.21%) patients suffered from subarachnoid haemorrhage.

Long-term severe disability caused by stroke significantly reduces mobility in over 50% of individuals aged over 65 years. In addition, stroke incidence in young adults has increased by 23% in one decade. Stevano et al., in their study, observed patients with early onset acute stroke (<50 years old) between October 2021 to

February 2022, showing over 153 total cases. Early onset stroke was found in 30 cases (19.61%). This young-onset stroke is responsible for significant psychosocial and economic burdens due to post-stroke disability in the productive population.^{4,5}

Unfortunately, therapeutic approaches aimed at promoting neurogenesis and recovery remain limited. Current stroke treatments are constrained by a narrow time window and have not yet achieved significant regenerative effects. The consensus in the medical community has not recognised any neurorestorative treatment thus far. However, stem cell therapy emerges as a promising and potential avenue for restorative treatment, offering a broader time window for intervention. This therapy is designed to enhance neurogenesis, facilitate the renewal of damaged neurons, or protect survived neurons to accelerate the recovery process.⁶⁻⁸

Another neurorestorative approach that demonstrates efficacy in enhancing functional neuroregeneration and post-stroke neuroplasticity is repetitive transcranial magnetic stimulation (rTMS).⁹ Exposure to rTMS stimulates the proliferation of neural stem cells (NSC) in adults and promotes the regeneration of new neuronal cells.¹⁰ Combination of rTMS and stem cell therapy could accelerate functional recovery in ischaemic stroke by enhancing neurogenesis, level of brain-derived neurotrophic factor (BDNF), and neural differentiation.¹¹ This case report aimed to highlight the clinical impact of combining stem cell therapy with rTMS administration in improving clinical outcomes for ischaemic stroke patients.

CASE DESCRIPTION

A 62-year-old man with a sudden onset of left limb weakness, slurred speech, and left facial drooping. His symptoms persisted for twelve hours before admission to the hospital. The patient had a history of hypertension for over a decade and diabetes mellitus for more than five years, but he had not been consistently managing these conditions. His vital signs were stable, with blood pressure at 150/90 mmHg, heart rate at 80 beats per minute, respiratory rate at 20 breaths per minute, and body temperature at 36.5 °C. His neurological examination revealed left-sided hemiparesis and hemineglect, upper motor neuron paresis of left facial and hypoglossal nerves, as well as a cognitive disturbance in the

attention domain. We conducted a comprehensive examination and screening to ensure the patient's eligibility (Figure 1). The initial National Institutes of Health Stroke Scale (NIHSS) was 13, indicating a moderate stroke. Laboratory tests revealed abnormal findings, including an HbA1C level of 10.9%, two-hour postprandial blood glucose of 149 mg/dl, uric acid level of 9.1 mg/dl, and high-density lipoprotein (HDL) level of 36 mg/dl, and a D-dimer level of 794.05 ng/ml. A non-contrast head CT scan confirmed an infarction in the right of the middle cerebral artery (MCA), consistent with the diagnosis of an embolic infarction stroke. Carotid Doppler ultrasonography supported the presence of atherosclerosis in both common carotid arteries. An echocardiography examination revealed left ventricular concentric remodelling with a healthy ejection fraction and normal valve function. As part of his treatment regimen, the patient was prescribed oral medications, including aspirin 80 mg once daily, atorvastatin 40 mg once daily, allopurinol 300 mg once daily, and fast-acting insulin at a dose of 4-4-4 IU. Additionally, the patient received daily physical therapy with range of motion (ROM) exercise and early mobilisation. Speech therapy was done for dysarthria symptoms. The infection and tumour markers were examined to confirm no contraindication to receiving stem cell therapy. No infection was present and tumour markers' results were normal, with prostate-specific antigen (PSA) of 3.20 ng/ml, carcinoembryonic antigen (CEA) of 1.77 ng/ml, and carbohydrate antigen 19-9 (CA 19-9) of 8 U/ml. Informed consent was obtained from family members to perform the stem cell therapy and rTMS, and the benefits and side effects were explained to make informed decisions.

Following the resolution of the acute phase of stroke, patients received intrathecal administration of twenty million stem cells two weeks after the stroke onset. Additionally, the patient underwent supplementary therapy involving serial rTMS for five consecutive days, commencing three days after receiving stem cell therapy. A comprehensive evaluation, as shown in Table 1, was performed both before and after the treatment, including NIHSS, Fugl-Meyer Assessment, Montreal Cognitive Assessment-Indonesian version (MoCA-INA) scores, electroencephalography, Barthel index, and motor threshold.

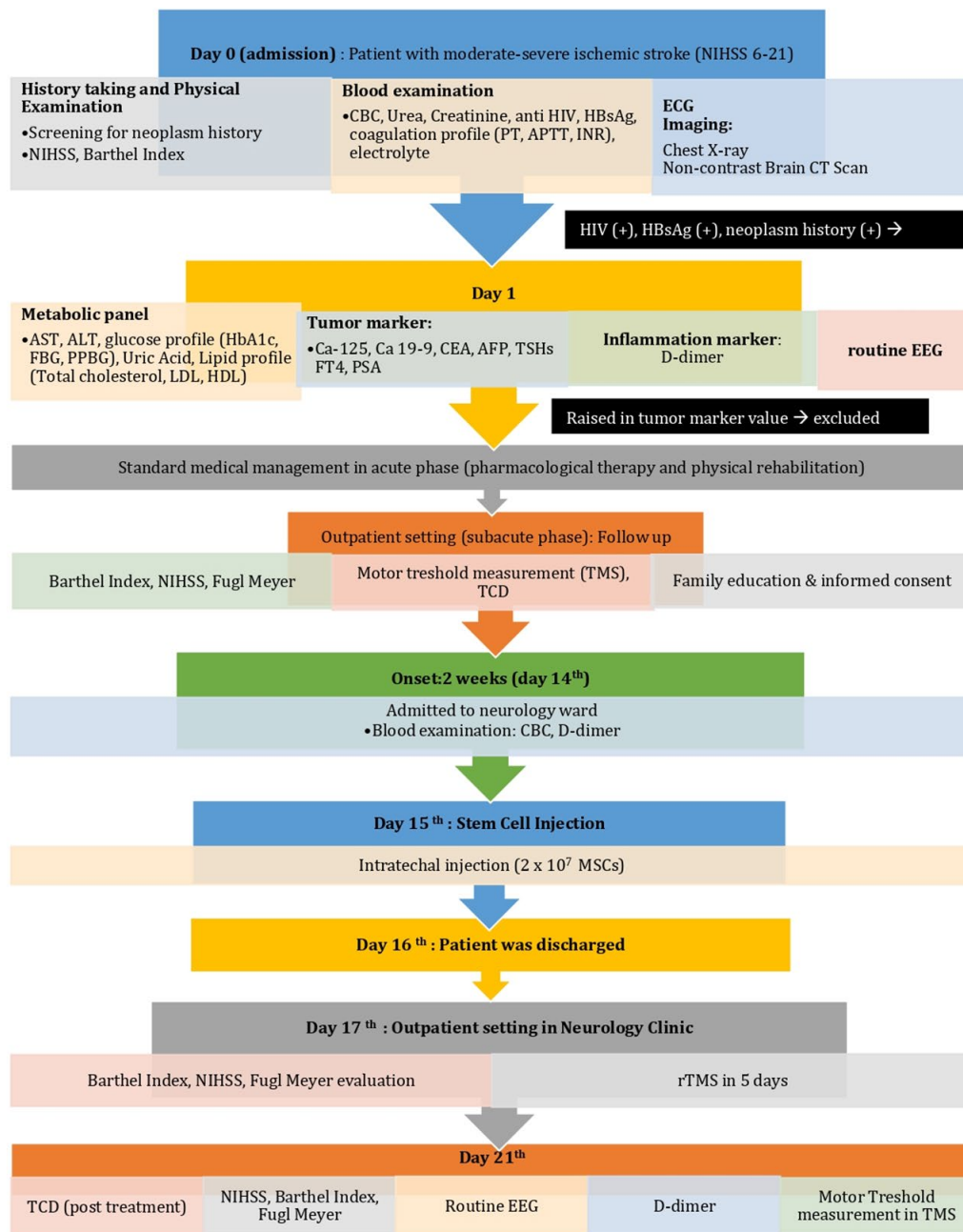


Figure 1. Algorithm of patient management.

ALT: alanine aminotransferase, AST: aspartate transaminase, AFP: alpha-fetoprotein, CBC: complete blood count, EEG: electroencephalography, FBG: fasting blood glucose, NIHSS: National Institutes of Health Stroke Scale, PPBG: postprandial blood glucose, TMS: transcranial magnetic stimulation, TCD: transcranial doppler, MSCs: mesenchymal stem cells

DISCUSSION

Following the neuroprotective management in the acute phase, the approach of stroke treatment changed towards neurorestorative therapy. Stroke caused a wide array of brain cell damage. Post-stroke therapy is directed towards enhancing processes such as neurogenesis, angiogenesis, axonal sprouting, and synaptogenesis within

the regions affected by the lesion as well as the surrounding tissue.^{12,13}

In this case report, we employed mesenchymal stem cells (MSCs) as the chosen stem cell type due to their favourable safety profile characterised by low levels of major histocompatibility complex (MHC) proteins. It is important to note that there is no established consensus regarding the specific

Table 1. Comparison of clinical parameters of patients before and after stem cell therapy

Parameter	Before stem cell therapy	2 weeks after stem cell therapy	1 month after stem cell therapy	2 months after stem cell therapy
NIHSS	13	10	9	8
Motoric Strength	555/222	555/322	555/322	555/322
	555/222	555/333	555/333	555/333
Fugl Meyer Assessment	Right Upper extremity: 36 Wrist: 10 Hand: 14 Coordination/speed: 6 Sensation: 12 Passive joint movement: 24 Joint pain: 24 Lower extremity: 28	Right Upper extremity: 36 Wrist: 10 Hand: 14 Coordination/speed: 6 Sensation: 12 Passive joint movement: 24 Joint pain: 24 Lower extremity: 28	Right Upper extremity: 36 Wrist: 10 Hand: 14 Coordination/speed: 6 Sensation: 12 Passive joint movement: 24 Joint pain: 24 Lower extremity: 28	Right Upper extremity: 36 Wrist: 10 Hand: 14 Coordination/speed: 6 Sensation: 12 Passive joint movement: 24 Joint pain: 24 Lower extremity: 28
	Left: Upper extremity: 6 Wrist: 0 Hand: 0 Coordination/speed:4 Sensation: 12 Passive joint movement: 22 Joint pain: 24 Lower extremity: 4	Left: Upper extremity: 11 Wrist: 2 Hand: 3 Coordination/speed:4 Sensation: 12 Passive joint movement: 22 Joint pain: 24 Lower extremity: 9	Left: Upper extremity: 14 Wrist: 4 Hand: 5 Coordination/speed:5 Sensation: 12 Passive joint movement: 22 Joint pain: 24 Lower extremity: 13	Left: Upper extremity: 17 Wrist: 4 Hand: 7 Coordination/speed:5 Sensation: 12 Passive joint movement: 22 Joint pain: 24 Lower extremity: 15
MoCA INA	Total: 8 Visuospatial: 0 Naming: 1 Attention: 1 Language: 1 Abstraction: 1 Delayed Recall:2 Orientation: 2	Total: 9 Visuospatial: 0 Naming: 1 Attention: 1 Language: 1 Abstraction: 1 Delayed Recall:3 Orientation: 2	Total: 14 Visuospatial: 1 Naming: 2 Attention: 2 Language: 1 Abstraction: 1 Delayed Recall:3 Orientation: 4	Total: 16 Visuospatial: 1 Naming: 2 Attention: 3 Language: 1 Abstraction: 1 Delayed Recall:4 Orientation: 4
EEG	Severe electrophysiological abnormalities tend to be structural lesions in the right hemisphere	N/A	Severe electrophysiological abnormalities suggestive of a structural lesion in the right hemisphere	Severe electrophysiological abnormalities suggestive of a structural lesion in the right hemisphere
Motor Threshold	Right: 53 μ V Left: 738 μ V		Right: 210 μ V Left: 872 μ V	

EEG: electroencephalography; MoCA INA: Montreal Cognitive Assessment-Indonesian version; NIHSS: National Institutes of Health Stroke Scale

dosage for MSC administration in stroke patients. However, the authors opted for a dose of 20 million MSCs via intrathecal administration. According to guidelines from the American Stroke Association for Stem Cell Studies, the most optimal and safe routes of administration include intravenous, intraarterial, intrathecal, and intracerebral methods, as outlined in Garza et al.¹² In the acute phase of stroke, intravenous transplantation is preferred, while intracerebral and intrathecal routes are preferred in chronic phase. Based on previous studies, stem cell doses varied widely, ranging between 1×10^6 to 1×10^9 cells.¹⁴ In clinical trial NCT02580019, participants with ischaemic stroke received 2×10^7 human umbilical cord MSC.¹⁵

The administration of stem cells was conducted two weeks after the stroke onset. This decision was justified by the understanding that significant natural clinical improvement typically does not manifest until 3-6 months following the onset of stroke. Several animal studies have also indicated that the optimal timeframe for administering stem cells is within the first month after a stroke.¹²

Mesenchymal stem cells are multipotent cells with the versatile capability to serve as neuroprotective agents, modulate neuroinflammatory responses, and facilitate neuroplasticity. These attributes are valuable contributors to functional recovery following strokes or degenerative diseases. Stem cell-based therapy holds the potential to enhance both the rate of improvement and the overall quality of life in stroke patients. Various theories propose that the administration of stem cells can stimulate neurogenesis, preserve axonal sprouting, and promote increased synaptogenesis, thereby facilitating the repair of affected neural pathways and tissues.¹⁶⁻²⁰

In this case report, rTMS was conducted over the course of five consecutive days, focusing on the stimulation of the M1 area. The rTMS protocol utilised featured a dose intensity of 64%, a frequency of 1 Hz, and the delivery of 1500 pulses to the left side. Conversely, on the right side, the employed dose intensity was 72%, the frequency was set to high at 10 Hz, and 1,500 pulses were administered. Various studies showed that rTMS had promising potencies in neurogenesis and functional improvement. In a study conducted by Caglayan et al.,²¹ it was reported that administration of rTMS to experimental mice at

a frequency of 20 Hz in ischaemic tissue results in a remodelling of perilesional tissue and the promotion of axonal sprout from the corticobulbar tract. High-frequency stimulation with rTMS could reduce the volume of infarction and mitigate inflammation.²¹

The NIHSS and Fugl-Meyer assessment were utilised for routine neurological evaluation in our clinical monitoring. The NIHSS is acknowledged for its simplicity, validation, ease of application, and reliability in assessing functional outcomes in stroke patients. It demonstrates a sensitivity of 73.7% and specificity of 74.1%, with a cut-off value of 15.5 for discerning the outcome of ischaemic stroke.²² The Fugl-Meyer assessment stands out as one of the most established and widely used outcome measures in stroke rehabilitative trials, proving its validity and reliability. The Fugl-Meyer assessment has garnered increased attention as a clinical trial outcome measure, partly due to its sensitivity to behavioural gains in the context of diverse interventions.²³ The MoCA-INA has been validated and is now a cognitive screening tool. The MoCA serves as a useful, concise screening tool for detecting mild dementia or mild cognitive impairment with a sensitivity of 83%. In the detection of post-stroke cognitive impairment, the MoCA exhibits notably high sensitivity (0.94) compared to the Mini-Mental State Examination (MMSE) (0.66).²⁴

This case shows positive clinical outcomes, particularly in terms of enhanced motor strength and higher cortical function. These findings align with previous studies indicating that stem cell-based therapy can serve as a protective measure against the degeneration of the corticospinal tract, leading to the improvement of clinical outcomes through the reorganisation and regeneration of this tract during the stroke recovery process.^{20,25,26} Furthermore, the activation of the motor cortex via rTMS has been shown to play a pivotal role in promoting the regeneration of the pyramidal tract. This concept finds support in previous research, which has demonstrated that even a single TMS pulse has the capacity to induce corticospinal activity and influence the synaptogenesis of motor neurons.^{13,27}

Numerous studies highlighted the capacity of stem cell therapy to enhance synaptic neuroplasticity and elevate cognitive performance. Stem cell therapy has the capability to differentiate

into components of the nervous cell system to stimulate neurogenesis. In a study conducted by Kim et al.,²⁸ mice that received stem cell treatment displayed elevated levels of paracrine thrombospondin-1 (TSP-1). This elevation in TSP-1 has been associated with preventing neuronal reduction in synaptic density caused by A β peptides, along with the inhibition of cell death linked to A β peptides and tau protein.²⁸

Stem cell therapy has beneficial effects on enhancing the release of the neurotransmitter acetylcholine, leading to the production of neurotrophins like BDNF and nerve growth factor (NGF).^{19,29} Moreover, BDNF is a pivotal protein influencing neuroplasticity that can also be stimulated by the application of rTMS at a moderate intensity level.¹²

The MOCA-INA examination was conducted both before and after the administration of stem cell therapy and rTMS to patients. Notably, the most significant improvements were observed in attention and short-term memory domains. In terms of memory, patients exhibited enhancements, particularly in the immediate and recent memory components. These findings align with research conducted by Qin et al.,²⁹ as well as Liao et al.,³⁰ which demonstrated an increase in the release of pro-inflammatory cytokines interleukin-10 (IL-10) and IL-4, with a decrease in tumour necrosis factor-alpha (TNF- α) and IL-1 β in relation to hippocampal migration which contributes to the augmentation of spatial and cognitive abilities, as well as the amelioration of memory deficits.^{29,30} Furthermore, these results are consistent with existing studies in which stem cell therapy has been shown to enhance various abilities in patients with autism spectrum disorder or cerebral palsy, including comprehensive skills, attention, reading, writing, and memory capabilities.³¹

Numerous studies investigating the application of stem cell therapy in stroke patients have yielded promising outcomes. A study conducted by Lee et al.²⁰ showed that patients who received stem cell therapy displayed notable improvements in motor function, as assessed using the Fugl-Meyer assessment system, within a 90-day evaluation period. Furthermore, a study conducted by Muir et al.³² exploring direct administration of 20 million stem cells to ischemia site via stereotactic injection implantation revealed positive clinical motor improvement within a relatively brief timeframe,

specifically within 2-3 months following the administration of the stem cells.

In contrast, a study by Liu et al.³³ investigated the application of TMS in post-stroke patients. They found that when 10 Hz TMS therapy was administered in conjunction with exercise, the combination could lead to enhancements in daily activities and cognitive function, particularly in the attention domain. Additionally, prior research comparing the effects of TMS at low frequency (1 Hz) and high frequency (10 Hz) in post-stroke patients with visuospatial neglect revealed that the high-frequency treatment was more effective. This effectiveness became evident after a series of 10 sessions conducted over a span of 2 weeks.³⁴

Repetitive transcranial magnetic stimulation has the capacity to trigger the activation of NSC, which, in turn, plays an important role in preventing neuronal apoptosis and promoting the generation of new neural cells. The action of NSC initiates the process of endogenous neurogenesis, aligning with the goals of stroke rehabilitation to facilitate tissue recovery and restore functional capabilities. Moreover, cognitive impairment is closely linked to neuronal apoptosis, underscoring the potential of rTMS as a non-invasive technique with a promising potential to address this aspect of neural health.^{34,35}

Studies about the combination of stem cell therapy and rTMS remain relatively scarce. However, when stem cell administration is combined with rTMS in studies involving rat models of ischaemic stroke, there has been a notable enhancement in the recovery process. The combination of stem cell therapy and rTMS offers a heightened BDNF release. Administration of rTMS increased potency and differentiation of the stem cell. Repetitive transcranial magnetic stimulation also amplified the potential of exogenous stem cells to mature into neural cells and integrate within neural circuits in the affected region.¹¹

Based on the neurorestorative perspective, the stroke case still needs new potential therapies targeting cell plasticity and regeneration, such as stem cells and rTMS, other than existing standard therapies. Our case report showed that combining stem cell therapy and rTMS could substantially improve clinical outcomes. Nonetheless, it is crucial to emphasise that further clinical trials are imperative to ascertain the advantages of stem cell therapy and rTMS compared to the control

group, which follows the natural clinical course.^{12,36}

CONCLUSION

After administration of stem cell therapy and rTMS, we observed improved clinical outcomes, such as motor strength and higher cortical function. In this case report, the combination of stem cell therapy and rTMS showed good potential effects in neuroregenerative and rehabilitative aspects for patients with ischaemic stroke. Further clinical trials are imperative.

CONFLICT OF INTERESTS

The authors declare that this case report was conducted with no commercial or financial relationship that could be considered as a potential conflict of interest.

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AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: study conception and design: RD, YH; data collection: BLH, EAJH, RAAT; draft manuscript preparation: AFF, MODS. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

BDNF: brain-derived neurotrophic factor; MCA: middle cerebral artery; MoCA-INA: Montreal Cognitive Assessment-Indonesian version; MSC: mesenchymal stem cell; NSC: neural stem cell; NIHSS: National Institutes of Health Stroke Scale; rTMS: repetitive magnetic stimulation; TSP-1: thrombospondin-1

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