

The Role of Mesenchymal Stem Cells for Hemorrhagic Stroke Management

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ABSTRACT

Stroke is ranked as the second-leading cause of death worldwide. As a result, the long-term sequelae of motor and cognitive abnormalities, such as hemiparesis, paralysis, psychomotor, chronic pain, and behavioral symptoms, can delay the patient's full recovery and function in society. In this context, stem cell-based treatment for stroke has been proven effective due to the potential to provide neurorestorative benefits. This study presented a case of a 50-year-old patient admitted to Cipto Mangunkusumo National General Hospital, Jakarta, in 2022 with intracerebral hemorrhage in the left thalamus, surrounding perifocal edema, and left lateral intraventricular hemorrhage. The patient was given mesenchymal stem cells (MSCs) treatment three times through Digital Subtraction Angiography (DSA). The patient achieved good outcomes in terms of body mobility, balance, and voluntary movement of the upper and lower right limbs.

Keywords: Mesenchymal Stem Cells, Hemorrhagic Stroke, Digital Subtraction Angiography.

INTRODUCTION

The Global Burden of Diseases, Injuries, and Risk Factors Study 2021 showed that stroke was the third-leading cause of death worldwide after ischaemic heart disease and COVID-19. It was also ranked as the fourth common cause of disability-adjusted life years (DALYs).¹ The overall incidence of stroke is shifting toward younger age groups, particularly in countries with low or middle incomes.² Among several countries, Indonesia has the most DALYs lost (3,382.2/100,000), with age and sex-standardized mortality (193.3/100,000). The prevalence

of stroke was higher in cities and urban areas (0.022%) than in rural areas (0.0017%).^{3,4} Stroke is defined as a neurological impairment resulting from an immediate focal injury to the central nervous system (CNS) caused by a vascular source, such as subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), or cerebral infarction. Moreover, hemorrhagic stroke is more common in Asians (15–40%) than in developed countries (15–20%).⁵ In Indonesia, hemorrhagic stroke contributes to 32.9% of incidents, with a 48-hour mortality rate of 20.3%, higher than the 8.3% ischaemic stroke.⁶

The long-term persistence of motor and cognitive abnormalities after hemorrhagic stroke, such as hemiparesis, paralysis, psychomotor, chronic pain, and behavioral symptoms, can delay a patient's full recovery and functioning in society.⁷ However, available treatments offer little in the way of enhancing neurogenesis and recovery. This shows the need for new stroke treatments, such as stem cell-based, which have the potential to provide neurorestorative benefits.⁸

Stem cell-based treatment theoretically can inhibit the devastating effects caused by inflammatory response and oxidative stress, which play an important role in the pathophysiology of hemorrhagic stroke, while at the same time promoting angiogenesis and neurogenesis.⁹⁻¹²

CASE ILLUSTRATION

A 50-year-old woman was referred to Cipto Mangunkusumo General Hospital with a chief complaint of losing consciousness three hours before entering the hospital. The complaint started with a severe headache and projectile vomiting seven times. Then, the patient felt sudden tingling on the right side of the body, followed by muscle weakness. There were also five episodes of vomiting and slurred speech, including a history of hypertension.

On physical examination, the patient was found to be unresponsive, with a GCS E2V2M4. There was evidence of stage I hypertension (blood pressure: 140/90 mmHg), and other vital signs were within normal limits. Meanwhile, thoracic and abdominal examinations were normal. The neurological examinations showed that cranial nerve VII was paralyzed on the right side, motor effects were lateralized to the right, physiological reflexes were 3/2, 3/2, a positive right-sided Babinski's pathological reflex, and problems in figuring out the sensory and autonomic functions. From laboratory examination, there were slightly elevated transaminase and D-dimer levels (800 ng/mL).

Based on the laboratory examination results, the patient was subjected to a non-contrasted brain computed tomography (CT). The results showed an intraparenchymal hemorrhage in the left thalamus, left posterior horn internal capsule, left lentiform nucleus, and left side mesencephalon, accompanied by left intraventricular and ventricular IV hemorrhages (**Figure 1A**).

By the findings of the laboratory, radiological, and clinical assessments, the patient was diagnosed with grade 2 hypertension and hemorrhagic stroke, intracerebral hemorrhage of the thalamus, and intraventricular hemorrhage (ICH thalamus + IVH). The initial management

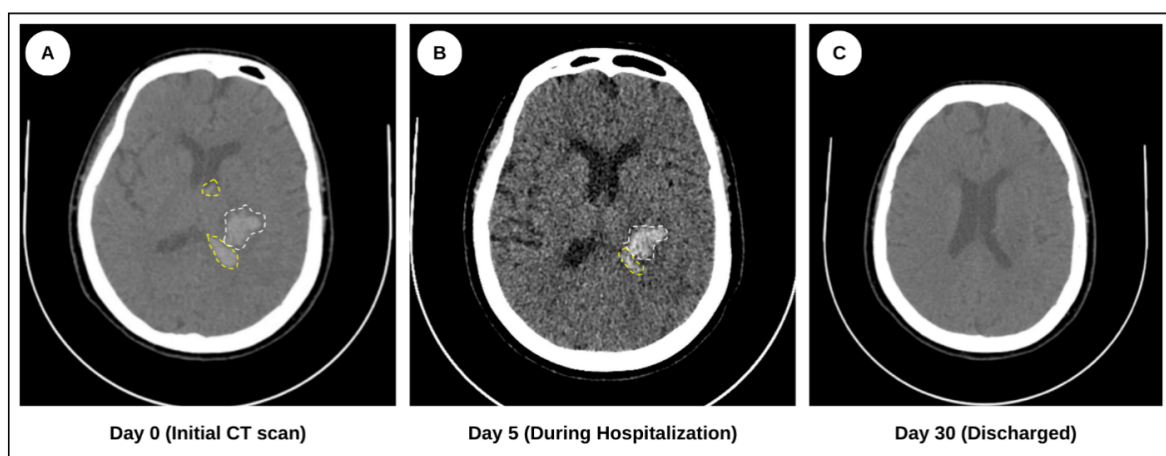


Figure 1. Serial CT scans showing the Evolution of Intracerebral Hemorrhage (ICH) and Intraventricular Hemorrhage (IVH) With Clinical Progression During Hospitalization. (A) **initial CT scan pre-admission.** Intracerebral hemorrhage in the left thalamus (white line) with surrounding perifocal edema and left intraventricular hemorrhage (yellow line). (B) **day 5 CT scan (during hospitalization).** Slightly reduced intracerebral hemorrhage in the left thalamus (white line) and reduction of left intraventricular hemorrhage (yellow line). (C) **day 30 CT scan (discharged).** No hemorrhage is seen on the CT scan.

included controlling blood and intracranial pressure using mannitol 4x125 ml, amlodipine 1x10 mg, and nicardipine 10 mg/hour titration, with a target TDS of 150 mmHg. The patient also received additional medications such as citicoline 2x500 mg, paracetamol 3x1000 mg, mecobalamin 2x500 mg, tranexamic acid 3x1, adequate sedation, and analgesics in the intensive care unit.

The patient received a series of non-contrast brain CT scans five days later for assessment. Compared to the initial day of treatment, the CT scan results showed a slight decrease in intraparenchymal hemorrhage in the left thalamus, left posterior horn of the internal capsule, left lentiform nucleus, and left lateral mesencephalon. The left lateral IVH has reduced, and no further bleeding was observed in the anterior horn of the left lateral ventricle or ventricle IV (**Figure 1B**). One month later, a brain CT scan without contrast showed no additional IVH compared to the prior brain CT scan (Figure 1C). After one month of treatment, the patient was discharged, and the outpatient clinic administered routine follow-up.

Stem cell treatment was conducted four months after discharge for the first time. Before this treatment, the clinical presentation of the patient showed hemiparesis dextra, spasticity in the fingers and toes of the right hand and foot, postural instability, as well as hemihypesthesia. The initial procedure was conducted with cerebral Digital Subtraction Angiography (DSA) through right femoral access. This included premedication with Paracetamol 1000 mg intravenously (IV), Dexamethasone 10 mg IV, and intravenous fluid administration of 0.9% NaCl at 500 cc every 12 hours. The DSA results indicated aplasia of the left anterior cerebral artery (ACA) and vascularization of the left ACA territory supplied by the right ACA. Stem cell implantation was conducted using a dosage of 2.5 million umbilical cord-mesenchymal stem cells (UC-MSCs) combined with 5 cc of secretome. The initial post-treatment evaluation showed a slight reduction in spasticity, but with persistent numbness and tingling on the right side of the body. The patient also remained unable to walk straight. Therefore, additional stem cell

treatment was scheduled 10 months following the previous procedure. Stem cell injection was conducted through DSA with right femoral access, with a dosage of 2.5 million UC-MSCs and 5 cc of the secretome. The clinical evaluation showed improvement in the patient's motor and sensory functions, particularly in the right leg (4444/5555, 3444/5555), physiological reflexes rated at 3/2, 3/2, bilateral absence of Babinski pathological reflexes, and optimal autonomic function.

The third stem cell treatment was conducted with double the dosage of stem cells, totaling 5 million UC-MSCs with 10 cc of secretome. This treatment was performed through DSA with right femoral access. Following the fourth stem cell implantation, the patient experienced enhanced mobility, balance, and voluntary movements in the right upper and lower extremities. However, there was a continuous experience of tingling, which further reduced. As shown in **Figure 2**, additional evaluation was carried out through DSA.

In line with stem cells, the patient received consistent physiotherapy, occupational treatment, acupuncture, and pharmacological intervention. The results consistently showed clinical improvement to the present time, alongside progressive enhancement after DSA and stem cell treatment.

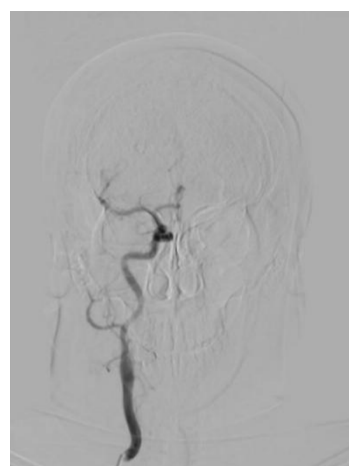


Figure 2. DSA evaluation after stem cell treatment. No abnormality was found in the right CCA cannulation and right vertebra. The left CCA cannulation showed left ACA aplasia, while the right ACA supplies the left ACA territory, indicating normal variation of cerebrovascular pattern. ACA anterior cerebral artery, CCA common carotid artery, DSA Digital Subtraction Angiography

DISCUSSION

This study presented a patient with an IVH in the ventricle and an ICH in the thalamus who improved after three MSC injections using DSA procedures. Laboratory results show that the patient's condition was attributed to hemorrhage and ischemic processes. In the initial phase, the D-dimer level was elevated, indicating activation of the fibrinolytic system. Elevated D-dimer was typically related to intravascular coagulation resulting from thrombotic or ischemic conditions. Furthermore, the patient showed gradual clinical improvement following the initial DSA and MSCs injection. This suggested the possibility of a thrombotic or ischemic component contributing to the clinical condition, in addition to hemorrhagic lesions.

Generally, the objective of acute ICH medical treatment is to stop the condition from getting worse. This is achieved by managing blood pressure, reversing anticoagulants when necessary, and preventing seizures, high ICP, hyperglycemia, fever, and secondary brain injury.¹³ The patient with acute ICH often presents with high BP. Therefore, individuals with ICH and high BP should not have their systolic blood pressure (SBP) abruptly lowered to less than 130 mmHg, as this could cause adverse effects.¹⁴

Management of anticoagulant-related hemorrhage should be administered when clinically significant anticoagulant levels are suspected based on the type and timing of anticoagulant dosing, rather than waiting for the results of blood tests.¹³ For the management of ICH related to direct-acting anticoagulant agents, reversal depends on the agent.¹⁴

The optimal agents for warfarin reversal are prothrombin complex concentrates (PCCs) plus vitamin K. This combination effectively reverses the international normalized ratio, prevents HE, and improves outcomes compared to fresh frozen plasma with vitamin K or given alone.¹³ In comparison, the reversal of the anticoagulant effect in direct thrombin and factor Xa inhibitors can be performed rapidly with specific agents such as idarucizumab and andexanet alfa. For a patient on heparin, protamine reverses the anticoagulant effect.¹⁴

Regarding promising treatment, stem cells have been proven effective due to a comparatively low incidence of major side effects.¹⁵ In this context, mesenchymal stem cells (MSCs) that are multipotent offer significant treatment potential. This is due to the availability of various tissue sources, including bone marrow, adipose tissue, and the umbilical cord.¹⁶ Furthermore, MSCs can differentiate into multiple cells, including adipocytes, osteoblasts, chondrocytes, neurons, myocytes, and β -pancreatic cells. It can also be transplanted by intravenous, intra-arterial, and intra-cerebral methods, which positively affected functional improvement.^{17,18}

Based on previous studies, MSCs have several roles in treating stroke patients. These include promoting angiogenesis, neurogenesis, synaptogenesis, immunomodulation, paracrine effect, neuroprotection, and reducing oxidative stress. The roles of MSCs in angiogenesis are conducted through several mechanisms by recruiting endothelial progenitor cells, attracting marrow-derived bone, and neural progenitor cells (NPCs) to the injured site. These cells also play a vital role in neurogenesis enhancement by promoting axonal growth through axonal growth-inhibiting protein reduction and the increase of axonal growth-associated proteins. Additionally, MSCs can enhance collagen IV and tight junction protein ZO-1, which will decrease blood-brain barrier disruption and neural loss. In addition to the significant potential, MSCs have immunomodulatory effects and play an important part in regulating immunological responses and disease progression.¹⁹

Stem cell treatment has been proven to have a significant effect on functional improvement in ischemic stroke by preserving the neural tissue during the acute phase and replacing lost tissue in the chronic phase. Growth factors secreted by MSCs activate the endogenous repair process, decrease glial scar, and induce the proliferation of cells in the subventricular area. This process promotes neurogenesis in the chronic phase of stroke.²⁸⁻³⁰

In the treatment of hemorrhagic stroke, MSCs function more as paracrine effects or the release of bioactive substances. These include soluble components such as proteins, lipids, and nucleic

acids, along with extracellular vesicles (EVs), namely secretome or mesenchymal stem cell-conditioned media (MSC-CM). The secretome has an anti-inflammatory, angiogenesis, synaptogenesis, and chemoattractant effect. Additionally, it can stimulate differentiation into neurogenic cells (**Figure 3**).^{20,21}

The immune suppression response is facilitated by the overexpression of several soluble bioactive molecules. These include ciliary neurotrophic factor, brain-derived neurotrophic factor (BDNF), oncostatin M, macrophage colony-stimulating factor, and interleukin-1 receptor antagonist. In addition, MSCs can reduce apoptosis by modulating signal pathways within the host cell.^{21,22,23}

Several factors affect the anti-apoptotic pathway. These include the upregulation of phosphorylated Akt, B-cell lymphoma-2 (bcl-2), as well as the downregulation of phosphorylated p38, JNK, and caspase 3 expression. Specifically, phosphorylated Akt and bcl-2 are responsible for reducing the cytochrome C from mitochondria.²⁴

The secondary effect of hemorrhagic stroke is perifocal edema. MSCs also affect anti-brain edema by decreasing the level of inducible nitric oxide synthase, 3-nitrotyrosine (hallmark of ONOO⁻), and matrix metalloproteinase-9. It also

increases the levels of tight junction markers such as zonula occludens-1 and claudin-5, which causes BBB permeability refinement. However, the effect of MSCs on AQP-4 water-channel expression can ameliorate the BBB permeability.²⁶

In the injured brain, using MSCs significantly increased the expression of VEGF and BDNF, which promoted angiogenesis and neurogenesis.²² In addition, MSCs showed the potential to differentiate into neurons and astrocytes around the bleeding site. These results showed that the functional improvement of MSCs in ICH was probably related to the ability to differentiate into appropriate cells.¹⁶ MSCs can also stimulate reactive oligodendrocytes, astrocytes, or axon-glia units to remodel injured axons and efficiently enhance white matter healing.

Although every route of administration has safety issues, intravenous delivery is a less invasive method than injection into the brain.¹⁷ Specifically, the number of implanted cells given varies based on the implantation route. The intravenous route received a median dose of 2.5 (0.5–8) million cells, and the intracerebral was received 0.5 (0.1–5) million. Meanwhile, the intracerebral ventricular, intra-arterial, and intranasal routes received 0.5 (0.2–2) million, 1.5 (1–2) million, and 1 million cells, respectively.²⁴

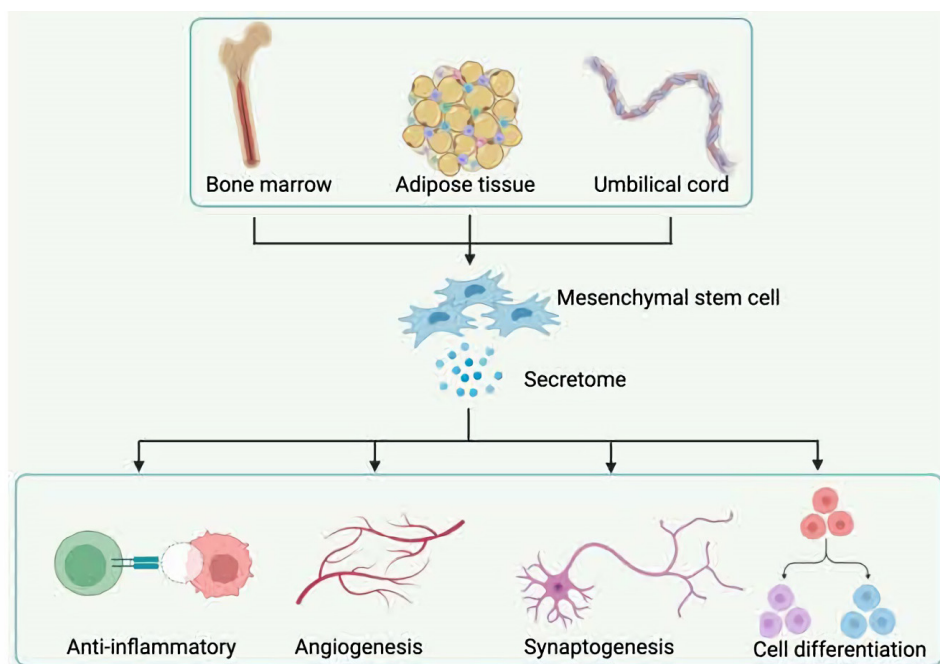


Figure 3. MSCs functions.

Currently, limited clinical trials are investigating the treatment for hemorrhagic stroke. A study including four patients with brain hemorrhages used a combination of cell types. These comprised umbilical cord mesenchymal, olfactory unsheathing, neural progenitor, and Schwann cells, which showed neurological enhancement.²⁵ Animal studies using NSCs and MSCs showed significant improvements in function and structure. Based on the results, MSCs had a greater positive impact on the modified neurological severity score (NSS).²⁶ Another analysis conducted on 26 patients who received MSC treatment for hemorrhagic stroke showed significant improvement. Furthermore, for two weeks after post-MSCs transplantation, CT scans showed accelerated hematoma reabsorption.²⁷

Previous studies showed that MSC treatment in the acute phase, within one month of ICH, provided favorable outcomes. The improvement could be observed in mobility and intellectual impairments, including language and mental activities. Zhu et al. compared 110 patients with MSCs transplantation and 96 controls. The results showed a significant recovery, based on the National Institutes of Health Stroke Scale (NIHSS), Barthel index, and modified Rankin Scale (mRS), in the transplanted group. The difference continued for approximately 12 months post-transplantation.³¹

Chang et al retrospectively investigated patients who received autologous BM-MNCs, allogeneic human umbilical cord blood cells, or control, and transplanted the cells twice (two- and three-weeks post-hemorrhage removal surgery), through the drainage tube inserted into the hemorrhagic cavity. The result showed that a lower NIHSS score was found in the transplanted group despite the patients having similar backgrounds. This suggested that hematoma evacuation with intracavity stem cell transplantation could accelerate the recovery.³² However, the effectiveness of MSC treatment in the chronic phase of ICH is still difficult to discuss because of the limited trials in the ICH chronic phase. In response to the challenge, several studies have shown promising results in improved motor functions and mechanisms.^{24,32}

CONCLUSION

In conclusion, the patient achieved good results in terms of body mobility, balance, and voluntary movement of the upper and lower right limbs. Furthermore, stem cell treatment for hemorrhagic stroke has promising outcomes for the future, combined with additional therapies to enhance clinical improvement.

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CONFLICT OF INTERESTS

All authors declare that they have no potential or actual conflicts of interest to disclose regarding the content of this article.

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