CASE REPORT

Application of mesenchymal stem cells in a multi-modal approach in the treatment of stroke

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SUMMARY

Stroke is a leading cause of death and disability worldwide. Despite advances in acute stroke care, many stroke survivors experience long-term neurological deficits that significantly affect their quality of life. The current standard of care for stroke rehabilitation includes physical and occupational therapy, speech therapy and pharmacotherapy. However, the limitations of these therapies have led to the investigation of alternative approaches, including the use of mesenchymal stem cells (MSCs). MSCs have been shown to promote neuronal survival, stimulate neurogenesis and modulate the immune response following stroke. This case report describes a male in his 40s with a history of right middle cerebral artery stroke in early 2015 likely from spontaneous arterial dissection of the Right ICA. He presented with residual left hemiplegia with spasticity. The patient has received a total of eight transplantations of MSCs, five via intravenous and three via intrathecal route. Patient's motor recovery was assessed during rehabilitation sessions. Post-MSC therapy, patient showed significant improvement in overall tone, power and reflex of upper and lower limb. Patient also displayed stronger and longer endurance and muscle strength. While this case report provides promising preliminary evidence for the use of MSC therapy in the rehabilitation of stroke patients, further research is needed to confirm these findings and to identify the optimal treatment protocol for MSC therapy.

INTRODUCTION

Carotid artery dissection is a condition whereby the layers of the carotid artery are spontaneously separated when a tear occurs in the intimal layer of the carotid artery creating an intramural haematoma. As a result, this potentially compromises blood flow to certain areas of the brain and can lead to a stroke.[1] A stroke especially an ischaemic stroke occurs if there is interrupted or reduced blood supply to the brain leading to lack of delivery of oxygen to the respective cells in the brain, causing cellular death to occur.[2] There are different areas of the brain that are supplied by various blood vessels, compromise of which can lead to neurological deficits in a person.

The only approved pharmacological systemic therapy for acute ischaemic stroke is intravenous thrombolysis (IVT) with alteplase, a recombinant tissue plasminogen activator (rtPA) that is usually recommended to be administered within 4.5 h of symptom onset.[3] Despite the expanded therapeutic time window, many patients still do not qualify for rtPA therapy since they present for evaluation beyond 3-4.5 hours after stroke onset. Initiating rtPA treatment beyond 4.5 hours (i.e., delayed tPA treatment) has been associated with deleterious side effects, notably, haemorrhagic transformation (HT) which could lead to high mortality in stroke patients.[4,5] Less than 5% of ischaemic stroke patients receive this treatment and still suffer post-treatment neurological deficits with no therapy available to promote recovery.[6] IVT can be administered alone or along with endovascular treatment with mechanical thrombectomy (MT), in large vessel occlusion disease. However, this technique is not yet fully developed, and the efficacy and safety of endovascular reperfusion beyond 6 hours remains controversial.[7]

MSCs are multipotent stem cell that have the ability to differentiate into various cell lineages, including chondrocytes, osteoblasts and neuron-like cells.[8] They can be easily isolated from various tissues, such as bone marrow and adipose tissue[9] and are simple to culture and expand. Due to their trilineage differentiation capacity and immunomodulatory properties, MSCs from bone marrow and adipose tissue are preferred sources for tissue engineering and regenerative medicine.[10] Furthermore, they pose low risk of tumorigenesis and require no immunosuppression following allogeneic administration due to their low expression of MHC antigens.[11] MSCs are suitable for transplantation during the acute stage of stroke and have shown substantial neurotrophic effects.[12] In addition, MSCs derived from adult tissues pose no risk of tumorigenesis and their low expression of major histocompatibility complex (MHC)-I and MHC-II antigens eliminates the need for immunosuppression following allogeneic administration.[13] They exert their therapeutic effects through several mechanisms, such as anti-inflammation, anti-apoptosis, angiogenesis and neurogenesis. As a result, they have been the focus in preclinical and clinical studies of various diseases. MSCs derived from human umbilical cord have also been shown to maintain their immunomodulatory and antioxidant activities and can differentiate into neuron-like cells.[14]

Stem cell-based therapies offer promising treatment opportunities as they are well known for their potential for trophic support and regenerative capacity after transplantation into the ischaemic brain. Apart from protecting and repairing damaged brain tissues, MSCs allow the preservation of neural tissue in the acute phase of stroke and the replacement of lost tissue in the chronic stage.[15] In the presence of injury and inflammation, MSCs are directly transplanted or homed to the damaged site. With their

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Table I: Progression of left upper and lower limb movement prior and after MSC treatment as per Medical Research Council (MRC) grading of motor power

	Movements	Before MSC therapy	After MSC therapy		
			First follow-up	Second follow-up	4 months post-treatment
Shoulder	Abduction	2/5	2/5	2/5	2/5
	Abduction	3/5	3/5	3/5	3/5
	Flexion	2/5	2/5	2/5	2/5
	Extension	2/5	2/5	2/5	2/5
Elbow	Flexion	2/5	2/5	2/5	2/5
	Extension	1/5	1/5	2/5	2/5
Wrist	Flexion	1/5	1/5	2/5	2/5
	Extension	0/5	1/5	1/5	2/5
Fingers	Flexion	1/5	1/5	1/5	2/5
	Extension	0/5	1/5	1/5	2/5
Hip	Flexion	3/5	3/5	3/5	3/5
	Extension	3/5	3/5	3/5	3/5
Knee	Flexion	3/5	3/5	3/5	3/5
	Extension	4/5	4/5	4/5	4/5
Ankle	Plantarflexion	0/5	1/5	1/5	1/5
	Dorsiflexion	0/5	2/5	2/5	2/5

Table II: Motor function assessments

Test	Before MSC therapy	After MSC therapy		
		First follow-up	Second follow-up	4 months post-treatment
Fugl-Meyer Upper Extremity Scale (FMA-UE)	51/126	80/126	82/126	95/126
Timed up and Go test (TUG)	35.29s	37.37s	35.47s	26.47s
Berg Balance Scale (BBS)	33/56	35/56	35/56	40/56

potential for tissue regeneration, migration, proliferation, rewiring of neural circuitry, physical and behavioural rejuvenation, these cells offer great regenerative potential and have been tested a treatment for stroke by promoting neurogenesis, rebuilding neural networks and increasing axonal growth.[16,17] This case study focuses on the application of MSCs in a multi-modal approach in treatment of stroke.

MATERIAL AND METHODS

The clinical case study that has been conducted involves the patient following up at Daehan Rehabilitation Hospital Putrajaya to monitor his progress for a period of three consecutive months in 2022. The diagnosis of right middle cerebral artery stroke was confirmed with a neurologist using computed tomography scan (CT scan), neurological deficits post-stroke and clinical history.

The respective inclusion criteria:

1) A confirmed clinical diagnosis of right middle cerebral artery stroke
2) A patient with residual and neurological weakness post-stroke
3) A patient that allows continuity of assessment and treatment for a year
4) A patient to accept stem cells to be used with rehabilitation

The WJ-MSC used in the stroke patients was isolated from Wharton's jelly of the umbilical cord. The stem cell isolation procedure is described in our previous case study on RP.[18] WJ-MSCs were provided by Beike 23 International Stem Cell Laboratory.

Patient received eight WJ-MSC transplantations (5×10^7 cells per session), five intravenously and three via intrathecal method using strict and sterile procedures. This would prove to add further value to the success of MSC transplantation given intravenous route targeting the systemic organs and intrathecal route targeting the cerebrospinal fluid. Further formal evaluation of patient's progress was assessed continuously by a consultant in Rehabilitation Medicine that monitored the progress.

CASE REPORT

A previously healthy male in his 40s was diagnosed with spontaneous arterial dissection of the Right Internal Carotid Artery (ICA) in 2015. Following the stroke event, patient experienced weakness in the left upper and lower limbs, with limited movement in the left upper limb and no movement over the left wrist and fingers. The left lower limb had no movement over the left ankle, with poor core coordination leading to difficulty maintaining an upright position. The patient also had a hemiplegic gait and slow cognitive processing. In addition, there was difficulty integrating motor skills and poor hand-eye coordination. Throughout standard treatment, there was no deterioration of existing neurological condition neither were there any adverse reactions documented. The patient was continuously monitored with rehabilitation, with no major changes in their diet or medication regimen.

RESULTS

Significant improvements in the patient's rehabilitation goals were observed from the initiation of MSC treatment over a period of 6 months from July 2022 till December 2022. After 2 months of intensive rehabilitation with mesenchymal stem cell (MSC) transplantation, the patient showed significant improvement in elbow extension as well as wrist and finger flexion and extension. Patient was also able to isolate muscle movements of the left shoulder as opposed to gross movement prior to treatment. The patient also regained sensation in the left lower limb and was able to extend the wrist and fingers when placed in mid-range. The left ankle was more supple and less rigid, and the patient's ability to transition from sitting to standing had improved. The patient also showed better focus and dexterity in cognitive and visual motor skills. As opposed to the time period during which the patient was solely under conventional rehabilitation, since beginning treatment with MSCs, the patient has demonstrated improvements in sensation, strength, gait and balance, requiring less effort for walking.

DISCUSSION

Regenerative medicine aims to provide a solution for diseases that have been deemed incurable. Several diseases, including Parkinson's disease, spinal cord injury, polyneuropathy, myocardial infarction and stroke, have shown positive therapeutic outcomes with regenerative medicine. Despite advances in acute stroke care, many stroke survivors experience long-term neurological deficits that significantly affect their quality of life. The current standard of care for stroke rehabilitation includes physical and occupational therapy, speech therapy, and pharmacotherapy. However, the limitations of these therapies have led to the investigation of alternative approaches, including the use of MSCs.

MSCs have shown promising results in preclinical and clinical studies for the treatment of stroke. MSCs have been shown to promote neuronal survival, stimulate neurogenesis, and modulate the immune response following stroke. Microglia cells switch from a resting form to an activated state and adopt a phagocytic phenotype to secrete pro-inflammatory cytokines after a stroke event has occured.[19] MSCs increase the secretion of anti-inflammatory cytokines, such as interleukin-4 (IL-4), interleukin-10 (IL-10) and tumour necrosis factor (TNF) and reduce the expression of pro-inflammatory cytokines such as interleukin-1 (IL-1), interferon-1 (IFN 1) and TNF. By regulating these cytokines, MSCs affect several pathways involved in immune cells and immune responses, to reduce inflammation.[20] Besides that, MSCs release trophic factors such as brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor, nerve growth factor, vascular endothelial growth factor, and platelet-derived growth factor. Trophic factors are known to induce angiogenesis, increase proliferation of neurons and prevent neuronal apoptosis.[21] The regeneration of blood vessels in the brain is important for stroke patients and with MSCs pro-angiogenic effects, vascular density of ischaemic brain tissue was significantly increased.[22] MSCs allow the growth of axons, synapses and myelin of ischaemic boundary zone, improving neural function which will promoting functional recovery after stroke. MSCs which induce myelination, will in turn increase the number of oligodendrocyte cells. Oligodendrocyte cells are vital in promoting myelin growth and protecting myelin from damage.[23] The stem cell therapy in cerebrovascular conditions depends overall upon their differentiation, inflammation and ability to repair of endogenous processes. Tissue engineering and cellular replacement therapies are at the forefront of regenerative medicine. It is becoming evident that stem cell therapy is an important tool in modern neurology, with potential efficacy in neuro-degenerative disorder.[24]

Clinical studies have investigated the safety and efficacy of MSC therapy in combination with conventional therapies for stroke patients. An open-labelled observer-blind clinical trial was conducted to evaluate the long-term safety and efficacy of autologous MSCs.[25] Post-transplantation with MSCs, clinical improvement in patients was observed in the MSC-treated patient group, which was associated with the serum level of stromal cell-derived factor-1 and the degree of involvement of the sub-ventricular region of the lateral ventricle. No serious adverse effects were observed during long-term follow up of patients. The occurrence of comorbidities was similar in comparison to the control group. Based on pre-clinical findings demonstrating the potential of peripheral blood stem cells (PBSCs), researchers conducted randomised, single-blind controlled studies in patients with middle cerebral artery infarction.[26] Patients meeting the study's inclusion criteria underwent implantation of immune-sorted PBSCs. Notably, no adverse events were reported during the study procedure or the follow-up period. Over a 12-month observation period, clinical outcomes were assessed for both the PBSC-treated group and the control group. These investigations also yielded significant evidence supporting the efficacy of PBSCs in enhancing motor deficits associated with stroke, facilitating the reconstruction of injured corticospinal tracts and restoring electrophysiological activity from the brain to the limbs.

CONCLUSION

In conclusion, the application of MSCs in a multi-modal approach for the treatment of stroke represents a promising therapeutic option. Further clinical trials are needed to determine the optimal dosage, timing and route of MSC therapy for stroke treatment. However, the current evidence suggests that the combination of MSC therapy with conventional therapies can lead to significant improvements in motor cognitive functions and overall quality of life for stroke patients.

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DECLARATIONS

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