



RECENT UPDATES OF STEM CELL THERAPY IN SPONTANEOUS INTRACEREBRAL HAEMORRHAGE PATIENTS: A LITERATURE REVIEW STUDY

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ABSTRACT

Background: Spontaneous intracerebral haemorrhage (sICH) is a severe neurological condition with high disability and mortality rates globally. Effective therapeutic strategies to overcome the acute and long-term problems caused by sICH are still lacking. Mesenchymal stem cell (MSCs) therapy with the neuroprotective and neuroregenerative properties has the potential to overcome the complex brain injury mechanisms caused by sICH. **Objective:** This review highlights the recent pre-clinical and clinical findings about MSCs therapy in sICH case and their mechanisms in promoting neurological recovery. **Methods:** This is a literature review study. Study reports available from various accredited database such as PubMed and Google Scholar are collected using the following keywords: (“stroke” or “intracerebral haemorrhage”) and (“stem cell”). **Results:** From 199 published studies found, 184 studies were irrelevant to the topic and excluded. Thus, 15 articles relevant to the topic were reviewed for the analysis and synthesis process. Pre-clinical studies proved that MSCs therapy can resolved the secondary brain insult caused by sICH and improved the brain functional and clinical status. The clinical studies proved that MSCs therapy are safe and well tolerated in human bodies. There were also beneficial MSCs therapy effects in sICH patients. However, the clinical studies results were still lacking and some were inconclusive. **Conclusion:** The preclinical studies of stem cell therapy in spontaneous intracerebral haemorrhage showed promising evidences and the potential of stem cell therapy for clinical use. However, the clinical studies were still lacking. Further clinical studies are needed to confirm the neuroprotective and neuroregenerative benefits of MSCs therapy from the pre-clinical studies.

Keywords: neuroprotective, neuroregenerative, spontaneous intracerebral haemorrhage, stem cell therapy

INTRODUCTION

Spontaneous intracerebral haemorrhage (sICH) is a severe neurological condition with high disability and mortality rates globally, despite constituting only around 15% of all strokes.¹ Spontaneous ICH occurs when blood vessels rupture, leading to the leakage of blood into the cranium. This condition can be accompanied by other intracranial lesion, such as subarachnoid haemorrhage (SAH) and intraventricular haemorrhage (IVH). The sICH disrupts the glucose and oxygen delivery to the surrounding brain tissue and triggers the secondary inflammatory cascade response. The secondary brain insult could develop the complex brain injury mechanisms, including neuroinflammation, excitotoxicity, cell apoptosis, and oxidative stress.²⁻⁵ This response contributes to the expansion of the lesion and worsens patient outcomes. Unfortunately, there is a lack of effective therapeutics for this inflammatory process.⁶ The 28-day mortality rate for ICH is approximately 47%, with up to 25% of survivors facing the risk of recurrent sICH within five years. Moreover, only less than 12% of the patients

can recover and achieve independent living ability in one year after sICH. The incidence of sICH remains unyielding, particularly in low-income and middle-income countries, possibly due to the aging population and increased use of medications like antiplatelet agents, anticoagulants, and thrombolytics. Despite significant progress in preclinical research, effective therapeutic strategies to overcome the problems caused by sICH in clinical settings are still lacking.⁷

Mesenchymal stem cell (MSCs) therapy, renowned for its regenerative potential and ease of harvest from any kind of tissues, holds potential in regenerative medicine. MSCs treatment has shown encouraging results in stroke, particularly in patients with sICH who had neurological deficits, cognitive impairment, and motor dysfunction sequelae. However, challenges such as prognostic variations among subjects, the influence of pathological environments on implanted MSCs, and long-term safety concerns hinder its clinical translation. Addressing the interaction between the individual's pathological microenvironment and implanted MSCs



is crucial. This review highlights the application of MSCs therapy in sICH case across different species and their mechanisms in promoting neurological recovery. It also underscores the challenges faced by MSCs implanted in the sICH-injured brain microenvironment. Additionally, potential therapeutic methods based on MSCs are discussed, aiming for optimized clinical translation in sICH treatment.⁸

METHODS

This is a literature review study. Study reports available from various accredited database such as PubMed and Google Scholar are collected using the following keywords: (“stroke” or “intracerebral haemorrhage”) and (“stem cell”). The search was performed on March 2024, which includes published studies ranging from 2011-2024. The studies included were then reviewed by two independent authors to exclude any studies with irrelevant topic. Articles relevant to the topic were further reviewed for the analysis and synthesis process.

RESULTS & DISCUSSION

As many as 199 study reports from 2011-2024 were collected on March 2024, and then reviewed by 2 independent authors. As many as 189 manuscripts that irrelevant to the topic, such as: ischaemic stroke, traumatic ICH, heart problems, and non-MSCs therapy were excluded. Finally, 15 articles relevant to the topic (pre-clinical : clinical 7:8) were reviewed for the analysis and synthesis process.

Pre-clinical stem cell therapy studies

In rodent models of sICH, MSCs transplantation has shown promise in promoting neuronal recovery. MSCs, delivered via different routes such as carotid artery, cervical vein, or lateral ventricle, have been found to migrate to various brain regions including the bleeding area and hippocampus, where they differentiate into appropriate cell types, particularly neurons and astrocytes. Additionally, MSCs therapy enhances endogenous neurogenesis and differentiation, facilitating organizational restructuring and reducing tissue loss.^{1, 8} The improvement of functional recovery also followed with good safety and toxicity profile in animal model.⁵ The dose were ranging from 1×10^5 – 5×10^6 (average 6.4×10^5) for intracerebral injection delivery,

and from 1×10^6 – 8×10^6 (average 2.6×10^6) for intravenous delivery.¹

The therapeutic effects of MSCs are attributed to their trophic properties, including the secretion of neurotrophic factors like brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and glial cell-derived neurotrophic factor (GDNF), which promote neuroregeneration and functional recovery. Moreover, MSCs exhibit anti-inflammatory effects by suppressing the inflammatory cascade and down-regulating aquaporin-4 (AQP4) expression, thereby alleviating brain edema and apoptosis. Adipose-derived stem cells have also been shown to improve blood-brain barrier (BBB) integrity after ICH, further contributing to neurological recovery.^{1, 8}

In large animal models such as swine, MSC-derived exosomes demonstrate neuroprotective effects, suggesting potential clinical applications. Similarly, in primate models, MSC treatment improves neurologic deficits and microvessel density, with early intervention yielding better outcomes. However, optimal timing and delivery modes of MSCs transplantation for ICH intervention remain to be determined for successful clinical translation.¹

The combination of rodent and large animal studies provides valuable insights into the potential mechanisms and efficacy of MSCs therapy across different species, laying the groundwork for future clinical trials aimed at validating these findings in human patients. Furthermore, recent studies have explored the use of novel techniques such as hypoxic preconditioning of MSCs or priming with Rho-associated, coiled-coil containing protein kinase (ROCK) inhibitors to enhance their therapeutic potential. These approaches have shown promising results in reducing tissue loss and improving functional outcomes after sICH.^{1, 8}

Clinical stem cell therapy studies

Clinical trials investigating MSCs therapy for haemorrhagic stroke are currently scarce, with only one trial found on clinicaltrials.gov. In contrast, there are 13 trials focusing on MSCs therapy for ischemic stroke. However, despite the limited number of clinical trial studies, as many as six research articles have reported findings from completed trials and case series involving a total of 164 patients. These studies employed various sources of MSCs, including bone



marrow-derived and umbilical cord-derived MSCs.⁹⁻¹³ The MSCs therapy effective dose was $0.5-5 \times 10^8$ and the dose tolerability was 1.5×10^6 /kg of body weight based on previous clinical study.^{5,13} The studies proved that the MSCs therapy is safe and well tolerated without any related adverse events.^{5,13}

The first evidence on MSCs therapy for sICH comprehended about the administration of $5-6 \times 10^7$ autologous bone marrow (BM)-derived MSCs intravenously to patients with chronic sICH. Although functional improvements were observed post-treatment, the mean difference were not statistically significantly between MSCs-treated and control groups.¹⁰ A variety of neurological impairment scores and functional assessment scores were utilized in human studies, including the NIH Stroke Scale, mRankin scale, Barthel Index, GCS score, and Fugl-Meyer assessment. Out of the five published cases examining the MSCs therapy for sICH and evaluating the neurological function outcomes, four observed improvements in these metrics compared to control groups. Furthermore, enhancements were noted in speech, breathing, and pain reporting. Although CT scans suggested accelerated hematoma reabsorption within two weeks post-MSCs transplantation, there was a lack of statistical testing to confirm this finding. These neurological functions benefits were sustained from 6 months to 5 years after MSCs therapy, regardless of MSCs source, dosage, administration route, or treatment timing. Unlike pre-clinical studies, the human clinical trials did not confine treatment to a narrow post-stroke window; instead, they encompassed a range from one week to over a year post-stroke.¹ Notably, a study treated sICH patients with severe neurological disabilities sequelae one year post-onset, reporting improvements in functional measures at 16 weeks post-treatment and an extended Glasgow Coma Scale score enhancement at 60 weeks post-treatment using autologous bone marrow-derived MSCs.¹³

In general, nearly all studies reported minimal side effects associated with MSCs therapy. Long-term evaluations until five years post-therapy indicated a high level of tolerance to the MSCs therapy, with trials documenting few adverse events and no instances of new tumor development among participants. However, Li *et al.*, noted an exception, reporting that 12.5% of patients in their treatment group experienced a low-grade fever, which resolved within three days

without requiring pharmaceutical intervention. This result aligns with a meta-analysis of MSCs trials that identified a significant correlation between MSCs therapy and transient fever, suggesting that MSCs may possess immune-evading properties rather than being immune-privileged.¹⁴ There is no evidence linking the MSCs therapy to the development of cancer.¹² Nonetheless, further research into the long-term safety of MSCs treatment is warranted.

A phase I clinical trial study examined the biomarkers of injury and inflammation after MSCs therapy in premature infants with severe IVH. The inflammatory cytokines and growth factors were evaluated through the infant's cerebrospinal fluid (CSF) before and after intraventricular transplantation of umbilical cord (UC) blood-derived MSCs. This study proved that the UC-MSCs therapy reduced the interleukin (IL)-6 pro-inflammatory cytokine. However, there were no significant changes observed in the levels of other cytokines and growth factors.⁹ It's important to note that these results were obtained in a premature immune system, which may not accurately reflect the immune response in adults. This discrepancy underscores the necessity for further investigation in human patients or the development of improved preclinical research models. In another Phase I clinical trial by Durand and colleagues, that examined the safety and efficacy of allogenic bone-derived MSCs administration in patient with sICH, found that it is feasible and safe. Though future trial with larger sample size and placebo controlled are warranted.¹⁵

CONCLUSION

Pre-clinical studies proved that MSCs therapy can resolved the secondary brain insult caused by sICH and improved the brain functional and clinical status. The clinical studies proved that MSCs therapy are safe and well tolerated in human bodies. There were also beneficial MSCs therapy effects in sICH patients. However, the clinical studies results were still lacking and some were inconclusive. Further clinical studies are needed to confirm the neuroprotective and neuroregenerative benefits of MSCs therapy from the pre-clinical studies.

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CONFLICT OF INTEREST

There is no conflict of interest related to the materials, methods, and findings in this study.

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AUTHORS' CONTRIBUTIONS

All authors participated in the designing of the study, collecting data, analyzing and synthesize the articles.

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