Stem Cell Research Treatment in Cerebral Aneurysm

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Publication Date: 2025/09/26

Abstract: Cerebral aneurysms represent 3-5% of the global population and the 3rd worst cause of morbidity and mortality that follows aneurysmal subarachnoid hemorrhage. Traditional surgical clipping and endovascular coiling therapies remain below acceptable standards to secondary injuries due to neurovasospasm, neuroinflammation, and blood–brain barrier disruption. This paper explores the therapeutic advances of stem cell–based therapies as novel, untapped treatments for cerebral aneurysms. Paracrine action of stem cells of mesenchymal origin, MSCs, exerts protective immunomodulatory effects through an anti-apoptotic, anti-inflammatory mechanism. This cell-free MSCs' extracellular vesicles MSC-EVs therapeutic system is safer, more stable, and penetrates the blood-brain barrier more readily. Vascular repair, re-endothelialization, and stabilization of aneurysmal walls are unique examples of integration processes by which endothelial progenitor cells EPCs are integrated using the mechanics of paracrine and integration. These cell therapies aim at the maintenance of the neurons, angiogenesis, and those that facilitate tissue repair. However, clinical implementation of preclinical results remains a challenge that has not been completed, as a result of tumorigenicity, immune removal, protocol standardization, and logistical delivery. There is an imperative to consider more detailed clinical trials, biomarker follow-up, and combination therapy discovery as presented by current evidence. The therapeutic interventions for the intricate pathophysiology of cerebral aneurysms may become safer and less self-toxic for the body through the use of stem cell research, MSCs, and EPCs along with their vesicles owing to the immunomodulation and regenerative capabilities.

Keywords: *"Cerebral Aneurysm, Subarachnoid Hemorrhage, Stem Cell Therapy, Mesenchymal Stem Cells, Extracellular Vesicles, Endothelial Progenitor Cells."*

How to Cite: Aryan Parag Gandhi (2025) Stem Cell Research Treatment in Cerebral Aneurysm. *International Journal of Innovative Science and Research Technology*, 10(9), 1717-1721. https://doi.org/10.38124/ijisrt/25sep1089

I. INTRODUCTION

The incidence rate of cerebral aneurysms is 3–5 per cent of the entire populace, and the subarachnoid hemorrhage that may result after the destruction of cerebral aneurysms (SAH) strikes 10 instead of 15 subjects per 100,000 people on a yearly basis [4]. Despite the clinical and technological advancements in neurosurgery and endovascular procedures, aneurysmal subarachnoid hemorrhage continues to be puzzling both clinically and medically, while simultaneously possessing high rates of morbidity and mortality. First, the case fatality rates stand at 35 to 50 percent, and 5 of 10 survivors endure incapacitating neurological conditions. Cerebral aneurysms also alter clinically and morphologically the architecture of the blood vessels. On the other hand, the abdominal sac of the aneurysm and the processes during and after its rupture are a pathological phenomenon that disrupts blood flow and the flow of blood downstream, which is the architecture of the vasculature of the sac; the difference between life and death is defined. Most of the damage, secondary neuroinflammation, vasodilation, vasospasm of the cerebral vessels, and rupture, belongs to the subclass of rupture.

The classical approach has been the treatment of an aneurysm by surgical clipping or by endovascular coiling, with the subsequent management of the secondary clinical issues, such as intracranial hypertension and vasospasm. The deficiencies of existing approaches prompt the quest for more worthwhile treatment modalities, particularly in the field of stem cell medicine. In contrast to all other forms of treatment, stem cell therapy has distinct mechanistic activities, which are neuroprotective and anti-apoptotic, and pro-angiogenic mobilization of tissue repair and regeneration. In this study, effective thematic literature analysis on stem cell therapy of cerebral aneurysms has been included. The author has detailed meticulously the types of treatment and types of cells utilized, the actions of the cell type and clinical therapeutic issues.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25sep1089

Table 1 Comparison of Current Treatments vs. Stem Cell-Based Approaches for Cerebral Aneurysms

Treatment Method	Treatment Method	Treatment Method	Treatment Method
Surgical clipping	Physically isolates aneurysm	Effective for accessible aneurysms	Invasive, risk of complications
Endovascular coiling	Fills aneurysm sac with coils to prevent rupture	Minimally invasive	Recurrence risk, not suitable for all types
Mesenchymal stem cells	Neuroprotection, anti-apoptotic, immune modulation	Multi-target effects, regeneration	Risk of tumorigenesis, delivery challenges
EPC therapy	Re-endothelialization, vascular repair	Stabilizes vessel wall, angiogenesis	Still experimental, limited clinical data

II. PATHOPHYSIOLOGY OF CEREBRAL ANEURYSMS AND SUBARACHNOID HEMORRHAGE

➢ *Aneurysm Formation and Progression*

The diversity of factors that lead to the development of an aneurysm in the brain is varied in the manner that each factor leads to the development of the aneurysm. The gradual weakening of the walls of the blood vessel is associated with the loss of the extracellular matrix, smooth muscle cells, and chronic inflammation. The phenomenon supports inflammation, which is the most basic process in the formation of cerebral aneurysms [6]. The molecular components of an aneurysm comprise the initiation of the NF-kB pathway, induction of matrix metalloproteinase, and the subsequent dysfunction of the endothelial cells. The development of ananguism is gradual and is marked by the lack of equilibrium between destructive and repair processes [4]. The blood circulation, inflammation, and internal pressure in the body are inseparably intertwined to achieve the healthy state of the blood vessels. Nevertheless, the constantly exerted load on blood flow, inflammation, and the walls of the blood vessel causes the development of an aneurysm, which may rupture.

➢ *Secondary Injury Mechanisms Following SAH*

Following the onset of subarachnoid bleeding, the aneurysm ruptures, imparting several secondary injuries to the brain, a series of pathophysiological processes are triggered, which lead to the rupture of the brain. Primary in this category and occurring in the initial 72 hours, is the rise of intracranial pressure, reduction of cerebral perfusion, and breakdown of the blood-brain barrier. One of the key secondary complications, Delayed cerebral ischemia, is noted approximately between four and fourteen days following subarachnoid hemorrhage. The cause is thought to be the microthrombosis and the cerebral vasospasm. Activation of the microglia, meningeal and peripheral immune cell recruitment, and the consequent inflammatory response characterized by the increase of the proinflammatory cytokines and the oxidative stress, takes into account [2]. This inflammation, accompanied by white matter injury, and the long-term complications of the nervous system, including the swelling of the brain, contribute to the collapse of the neurovascular structures. The reasons for exploring cell therapy as an adopted multi-target treatment are these exploratory mechanisms.

III. STEM CELL BIOLOGY AND THERAPEUTIC MECHANISMS

➢ *Classification and Characteristics of Therapeutic Stem Cells*

The stem cells that are relevant for research purposes in relation to aneurysms are mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), and stem cells of the neural lineage [5]. Bone marrow, adipose, and even the umbilical cord MSCs derived from have proven paracrine signaling capabilities and multipotent differentiation capacity. These cells are able to modulate the immune system and, under the right circumstances, develop into neurons, endothelial cells, astrocytes, and completely different cell types. Pertaining to the brain's blood vessel ailments, the stem cell type of particular relevance is Endothelial Progenitor Cells (EPCs). ECs can break down EPCs thereby being involved in the building and repairing of blood vessels [5]. In cerebral aneurysm, their capacities are beyond cellular substitution capabilities since they have the power to regulate angiogenesis, optimize the endothelial cell performance, and stabilize vessels walls.

➢ *Mechanisms of Therapeutic Action*

Stem cell therapy has therapeutic effects via different mechanisms and effects, which can be defined as direct and paracrine. Direct effects include cell replacement, wherein the transplanted stem cells functionally differentiate into neural and/or vascular cells to supplant injured tissue. Newer research indicates that 'paracrine' processes are much more active during the initial treatment phase. The microenvironment gets remodeled by bioactive molecules; growth factors, cytokines, and exosomes contribute to regeneration, neuroprotection, angiogenesis, and repair, through the action of the mediators of BDNF, VEGF, and anti-inflammatory cytokines [1].

Table 2 Mechanisms of Action of Therapeutic Stem Cells in SAH and Aneurysm Repair Stem Cell Type

Stem Cell Type	Mechanism	Key Factors Involved
Mesenchymal Stem Cells	Anti-apoptotic, anti-inflammatory, BBB protection	IGF-1, HGF, IL-10, TGF-β
Endothelial Progenitor Cells	Vascular repair, angiogenesis, re-endothelialization	VEGF, cytokines, growth factors

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25sep1089

MSC-derived EVs	Cell-free therapy, microRNA delivery, oxidative stress reduction	miRNAs, mRNAs, exosomes

IV. MESENCHYMAL STEM CELLS IN CEREBRAL ANEURYSM TREATMENT

➢ *Neuroprotective Effects*

Stem cells of a mesenchymal origin have been shown to have marked neuroprotective effects in various experimental models of SAH. Kanamaru and Suzuki discuss the therapeutic stem cell in SAH through multiple mechanistic pathways, including reduction of neuronal apoptosis, preservation of the blood-brain barrier, and inflammation modulation [2]. Mesenchymal stem cells secrete protective factors that may be used to head off secondary injury cascades caused by SAH. Insulin-like growth factor-1 (IGF-1) and the hepatocyte growth factor (HGF) mediate the anti-apoptotic activity of MSCs, which are recognized to stimulate pro-survival signaling pathways in the target population of neurons and glial cells [2]. MSCs have also been found to attenuate oxidative stress due to the release of diverse pro-oxidant neutralizing enzyme systems and scavengers of free radicals, and this prevents oxidative devastation of the neuron in case of SAH.

➢ *Anti-Inflammatory Properties*

The latest discoveries reveal that MSCs possess novel immune system modulatory abilities; thus, MSCs can be applied for the treatment of subarachnoid hemorrhage. MSCs are also capable of regulating induced microglia to M2 anti-inflammatory microglia to check the outcomes of inflammation, in addition to improving tissue repair. Interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), and other key immune-regulating cytokines maintain the microenvironment at the right homeostasis [3]. In addition to microglial modulation, MSCs modulate astrocytes and glial scars, impeding neural repair and functional restoration [2]. Hence, MSCs should also be regarded as anti-inflammatory intermediates to the repair process, as they enhance the subarachnoid hemorrhage neurological outcome.

V. EXTRACELLULAR VESICLES: A NOVEL THERAPEUTIC APPROACH

➢ *MSC-Derived Extracellular Vesicles*

More recent studies have placed increased focus on MSC-EVs as a cell-free method for the treatment of subarachnoid hemorrhage (SAH). MSC-EVs can relieve SAH-related neurological deficits through the use of neuroprotection and anti-inflammatory mechanisms [4]. Multiple bioactive molecules are contained in these nano-sized sutures, so they can affect target cells to induce a cellular repair response. Besides the stem cells used, MSC macrovesicles are less related to the immune system, have lower tumor potential, are easier to bank and culture in large volumes, have better dose regulation, and are more predictable. MSC macrovesicles also move more effectively across the blood-brain barrier as compared to the parent cells, thus enabling improved navigation to and imaging of therapeutic agents to injured brain tissue [1]. Such characteristics make MSC microvesicles a novel and safer treatment method of SAH that should be directed at the need to conduct additional in-depth analysis and research.

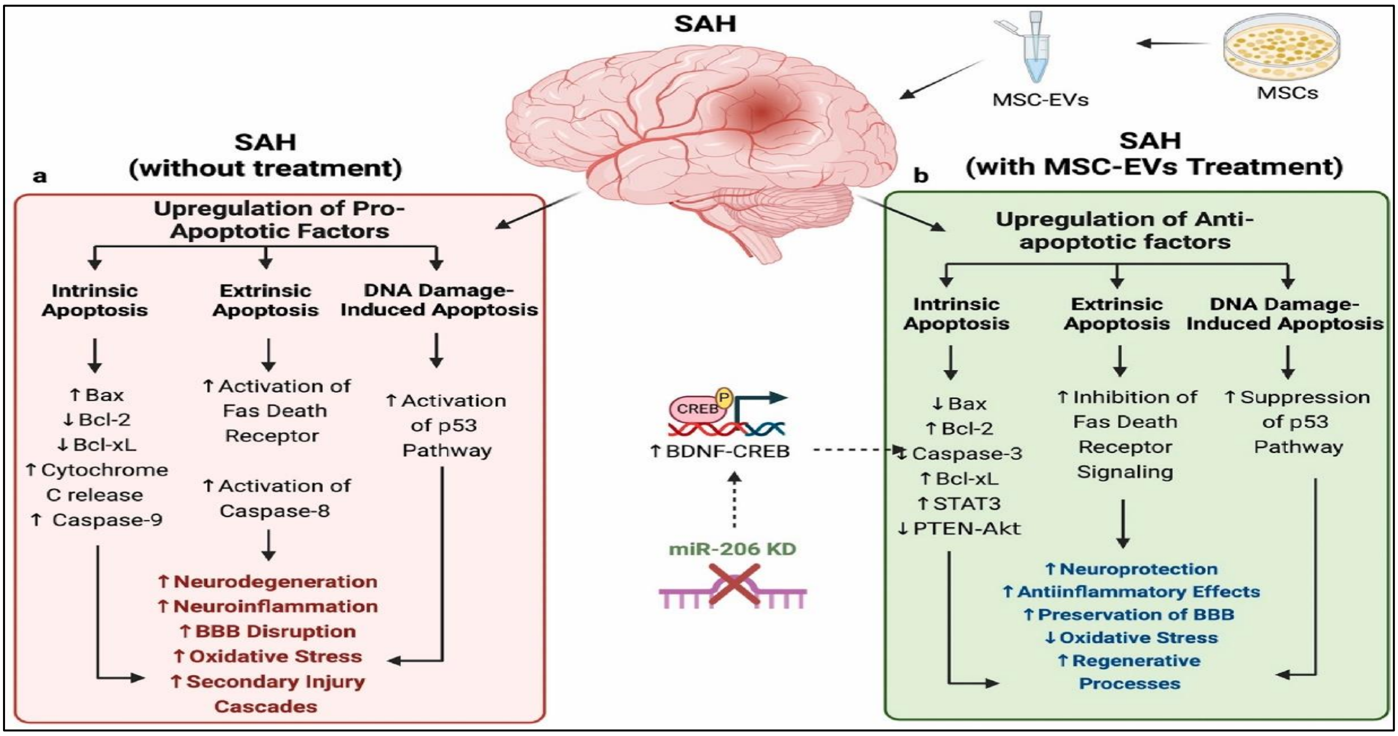

Fig 1 The Schematic Diagram of Antiapoptotic Actions of Mesenchymal Stem Cell-Derived Extracellular Vesicles (MSC-EVs) in the Subarachnoid Hemorrhage (SAH) Models.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25sep1089

➢ *Mechanisms of EVs' Action in SAH*

MSC-EVs have the capability of transporting various bioactive cellular molecules to the target cells, which can be attributed in part to its capability to transport bioactive neuroprotective and anti-inflammatory microRNAs (miRNAs), messenger RNAs (mRNAs), and bioactive neuroprotective regulatory protein assignments. As a key element, there was a distinct amount of regulatory miRNAs that are expressed on MSC-EVs that activate cell life signaling and suppress apoptotic signaling [1]. Besides the mentioned effects, MSC-EVs are also neuroprotective in other ways, such as microglial cell control in terms of classical and alternative activation, release of proinflammatory cytokines, thereby alleviating neuroinflammation. Angiogenic augmentation of MSC-EVs is also significant as it has the potential to boost cerebral perfusion and reduce the chance of delayed cerebral ischemia, which is a severe outcome of the SAH, thereby augmenting the therapeutic implications.

VI. ENDOTHELIAL PROGENITOR CELL THERAPY

➢ *EPC Characteristics and Therapeutic Potential*

Endothelial progenitor cells (EPCs) have proven to have an exceptional treatment potential, which allows them to be used to treat complex cerebrovascular pathologies, particularly useful in management. The skeptical approach of Therapeutic EPCs to biology and intracranial aneurysms includes their mechanisms and clinical applications, and EPC-based therapy forms its central material. Treatment of intracranial aneurysm EPCs has the potential to migrate and become mature endothelial cells and participate in vascular repair and remodeling [5]. The main clinical outcomes of EPCs in treating an aneurysm are the stabilization of the deteriorated arterial walls, re-endothelialization, and the recovery of endothelial activity. In addition, EPCs are able to induce vasculogenesis, new collateral vessels, augment brain blood flow, and offer alternative pathways of perfusion to patients with vascular insufficiency.

➢ *Clinical Applications and Mechanisms*

The therapy relying on endothelial progenitor cells for intracranial aneurysms works through multiple mechanisms: direct incorporation into the vascular wall, paracrine secretion of growth factors, modulation of diverse cytokines, and modification of the vascular microenvironment. Endothelial progenitor cells (EPCs) significantly promote endothelial interface repair and improve vascular stability, and thus, the chances of aneurysms enlarging and rupturing, as well as the chances of rupture, become significantly reduced [5]. Apart from the direct therapeutic application, the introduction of therapy with endothelial progenitor cells may also impact the aneurysms prophylactically, in terms of postponing their onset and progression, and, therefore, has benefits for patients with a high-risk profile. EPCs are protective of the vascular as well as the arterial walls due to the kept walls from the re-endothelialization and vascular remodeling mechanisms and their endothelial protective actions. In addition, their paracrine mechanisms of action are anti-inflammatory and pro-angiogenic, thus offering a holistic approach to the management of intracranial aneurysms.

Table 3 Challenges in Clinical Translation of Stem Cell Therapy

Challenge	Explanation	Potential Solutions
Tumorigenicity risk	Stem cells may differentiate abnormally	Preclinical testing, genetic screening
Immune rejection	Host may attack transplanted cells	Use of autologous/iPSC-derived cells
Delivery methods	Difficulties in targeting brain aneurysm site	Nanocarriers, scaffold-based delivery
Standardization	Protocols for culture, dosing not uniform	SOP development, multicenter trials
Cost and logistics	High cost, limited scalability	Banking, large-scale EV production

VII. CLINICAL TRANSLATION CHALLENGES AND CONSIDERATIONS

➢ *Safety and Regulatory Considerations*

The application of preclinical studies involving stem cells to clinical practice is limited and faces great difficulty in terms of safety, effectiveness, and obtaining approval to practice. Possible adverse outcomes involve the development of tumors/neoplasms or the potential development of malignancies triggered by collections of pluripotent stem cells. There is also the problem of immune rejection, together with unregulated differentiation of tissues, which pose serious concerns. Regulatory authorities should require the safety data collected through essential and exhaustive preclinical investigations prior to clinical testing [3]. The standard procedures of stem cell therapy should be revised and modified therapeutic stem cell procedures, as isolation, expansion, characterization, and clinical outcome should be positively achieved.

➢ *Technical and Logistical Challenges*

Stem cell therapy will play a more prominent part in clinics and practices of treatment when several aspects of practical implementation are tackled and resolved. These aspects are not in any order: stem therapy by injection, stem therapy by catheter, stem therapy by clinical therapy recommendation, cutoff instructions for dosing, preparation for treatment and cells being treated, achievement of the therapy outcome, optimization of the value of the outcomes in a specified time span, and the therapy time.

The final target criterion is to overcome at all times in the clinic and in the systems, the first in the therapy value of the outcome variability in the systems of reasoning, predictable and non-repeatable, defined by the biology. To a very great degree, manageable constructs are profited by stem cells because of the difficulty in the therapeutic targets and the higher-order targets; stem cell-based in-clinic systems are costly and complicated in the conventional clinical boundary models. All sorts of impediments in the way of adopting these clinical practices abound because the economic limits of the

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25sep1089

stem cell therapy packages are very tight, and the other forms of routine treatment dominate the industry. Clinical practices that ostensibly yield such an outcome exist in tumbledown, unruly constructions of survivability, clinical stem cell engineering in which in the flow there are no molds of the nuances of the flow in making the compilation and the conveyance therewith easy and straightforward, can comfortably reside in inexpensive constructions in the pumps, contrived and set up in a way and manner to create the flow the turbulence in.

VIII. CURRENT CLINICAL EVIDENCE AND FUTURE DIRECTIONS

➢ *Clinical Trial Status*

Cerebral aneurysm stem cell therapy of cerebral aneurysms has good preclinical promise, but the therapies themselves are in the early phases. New clinical investigations of the treatment of stroke and neurodegeneration by MSC are still absent, and therefore, the studies on cerebral aneurysms have not yet been tested. The multifactorial pathophysiologic basis of aneurysmal SAH and the strategic and temporal moment of interventions needed complicate the planning of clinical studies. Early-stage clinical studies are undoubtedly important in the determination of safety and optimal treatment regimens for Phase I studies. These studies ought specifically to recruit defined patient groups having similar endpoints, such that cross-comparison and evaluation by meta-analytic analysis are simplified [2]. Biomarkers in therapeutic responses should importantly contribute to the patient's monitoring.

➢ *Future Research Directions*

Future studies should fill the holes in protocols for stem cell therapy for cell source, preparations for administration, dosing, and methods and routes of delivery. The efficacy of the treatment may be improved by stem cell use in combination therapy, either with various stem cell or various concomitant therapeutic interventions. Incorporation of the stem cells in the tissue-engineered constructs may enhance the efficacy of the treatment by providing more prolonged and localized release. Therapeutic agent-releasing nanoparticles and biomaterial scaffold materials for targeted therapy may also enhance systemic exposure while therapeutically improving the outcome [4]. Lastly, the imposition of immunogenicity and individualizing therapeutic approaches may be obviated by the development of the induced pluripotent stem cells derived from individual patient sources.

IX. CONCLUSION

The capabilities of the stem cells to repair aneurysms at the same time and maintain and regenerate the nervous system, and also serve as anti-inflammatories, are immensely useful. The stem cell literature in current use details the mesenchymal stem cells, endothelial progenitor cells, and the vesicles and their therapeutic promise. The effort in stem cells is multi-functional and multifaceted. It incorporates both in vivo multi-cell signaling (through physical cell-to-cell interaction) and isokinetic (through paracrine) signal signaling. We take them to be the endothelial progenitor cells, e.g., indispensable to the vascular repair and reconstruction engineering. The mesenchymal stem cell extracellular vesicles have also been described as resilient neuroprotective inflammatory molecules. The whole range of individual cell grafting safety concerns, logistics, and myriad complications would be out of the picture in such cell-free therapeutic usages of the EVs. The greater part of the work in the sphere of engineering safety is related to restrictions and the creation of Standard Operating Procedures (SOPs), and it is, in its turn, an insurmountable task. Such heterogeneity of the patient presentation alone, aside from the interacting and not very well-delimited pathophysiologic process in which the aneurysms occur, implies the need for a tightly defined research design and demarcation of inclusion and exclusion criteria.

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