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Review

Mesenchymal stem cell for hemorrhagic stroke: A clinical review

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ABSTRACT

Hemorrhagic stroke, which is also called an intracerebral hemorrhage, is a cerebrovascular disease that represents a serious public health problem worldwide. Among all types of stroke, intracerebral hemorrhage causes the highest percentage of mortality and morbidity, affecting 2 million people annually, with no specific treatment established except for rehabilitation-oriented techniques.

In recent years, new alternatives have been sought to treat this type of pathology, with mesenchymal stem cell therapy gaining special relevance. These cells present a series of biological properties, including regenerative repair, neuroprotection, and immunomodulation that make them a tool with enormous potential in regenerative medicine. In this review, we are going to focus on clinical trials and clinical studies which use cell therapy with Mesenchymal Stem Cells as a treatment for patients suffering from intracerebral hemorrhage. The clinical trials found are not very numerous. It remains an area to be explored; however, existing studies suggest it is a safe therapy that yields positive neurological and functional outcomes in many treated patients. All of this makes it a very promising and encouraging therapy for patients with this type of pathology.

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Contents

1. Introduction

Cerebrovascular disease (CVA) or stroke is a major public health concern in developed countries. It is defined as a transient or permanent alteration of cerebral circulation that affects a brain area, either of ischemic or hemorrhagic origin [1]. Among them,

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intracerebral hemorrhage (ICH) is one of the most devastating types, representing 15 % of all strokes and being a leading cause of long-term disability worldwide [2,3]. Although its prevalence is lower than that of ischemic stroke, it accounts for 40 % of stroke-related deaths and leaves around 50 % of survivors dependent one year later due to severe neuropsychological sequelae, such as memory and speech impairments, and loss of independence in daily activities [4–7]. Each year, 2 million people worldwide suffer from ICH, which has a high incidence rate despite limited therapeutic options (see Supplementary Fig. 3). Currently, rehabilitation remains the only effective intervention, highlighting the urgent need for new treatment strategies [3]. Due to its impact, the World Health Organization considers ICH a public health priority.

ICH is defined as an accumulation of blood within the brain parenchyma caused by non-traumatic vascular rupture, which may remain localized or extend into the ventricular system, subarachnoid, or subdural spaces [8,9]. It is classified based on etiology into primary and secondary hemorrhages. Primary ICH is the most frequent (60 % of cases) and results from spontaneous rupture of weakened vessels due to hypertension or cerebral amyloid angiopathy. Secondary ICH arises from tumors, vascular malformations, vasculitis, drug use, liver disease, or other less common causes [8,10]. According to bleeding location, it is categorized as parenchymal (ICH), subarachnoid (HSA), or intraventricular (IVH). Depending on hematoma site, it is further classified into subcortical (basal ganglia and thalamus), lobar (cerebral lobes), cerebellar, brainstem (pons), or IVH, which often present symptoms similar to HSA (see Supplementary Fig. 4) [9].

Identifying and managing risk factors is key for both primary and secondary prevention. These are divided into modifiable and non-modifiable (Table 1) [11,12]. Hypertension is the most relevant modifiable factor, present in 60 % of cases [13]. Others include alcohol abuse, smoking, drug use, low LDL cholesterol and triglycerides, and the use of anticoagulant or antiplatelet agents. Among non-modifiable factors, age (from 55 years onward), male sex, and African-American or Asian ethnicity stand out. Cerebral amyloid angiopathy is the second most common cause of ICH. Other contributing factors include cerebral microbleeds, vascular abnormalities, tumors, and chronic liver disease [12,14,15].

ICH pathophysiology is dynamic and occurs in two main phases (Fig. 1). The primary injury begins with vessel rupture and blood extravasation into the parenchyma, generating a hematoma that increases intracranial pressure and causes tissue compression, ischemia, and potentially herniation [16,17]. The surrounding area becomes edematous and infiltrated by neutrophils and activated microglia. Continued bleeding during the first hours may enlarge the hematoma, and volumes >30 ml are associated with poorer prognosis [14,18]. Secondary injury arises from the brain's response to the hematoma and its breakdown products. Blood components trigger oxidative stress, inflammation, excitotoxicity, and apoptosis [19]. Vasogenic edema forms due to clot retraction and plasma extravasation, exacerbating intracranial pressure [20,21]. Thrombin is released to control bleeding but also disrupts the blood-brain barrier, promoting neuronal damage [22–24]. Inflammatory activation by microglia and infiltrating macrophages leads to the release of cytokines (IL-1β, IL-6, IL-12, IL-23, TNF-α), chemokines, TLR4, HO-1, and other toxic agents [17]. This cascade amplifies neuroinflammation, promotes glutamate excitotoxicity, and activates caspases that trigger cell death [21]. Simultaneously, oxidative stress from neutrophil activation releases ROS, nitric oxide, and peroxynitrite, causing lipid peroxidation and structural damage [25–27]. The complement system also contributes by lysing erythrocytes, releasing hemoglobin and iron, further increasing toxicity. Ultimately, these events lead to brain atrophy and irreversible tissue loss [28,29].

Clinical manifestations depend on hematoma size and location. Common symptoms include headache, nausea, vomiting, focal signs, and rapidly progressing neurological deficits, especially in the first hours due to hematoma expansion [30,31]. Decreased consciousness or coma is common in large hemorrhages or brainstem involvement. Cerebellar hemorrhages may present with ataxia, vomiting, nystagmus, and facial paralysis. Lobar hemorrhages can lead to seizures, aphasia, or hemianopsia, and thalamic or basal ganglia hemorrhages typically cause motor and sensory deficits. IVH is often associated with attention loss [12,14,31]. ICH also carries a high burden of long-term disability, with many survivors partially or fully dependent in daily life. The socioeconomic impact is substantial, with stroke care representing 3–4 % of total healthcare costs in developed countries.

Table 1
Risk factors associated with ICH.

Modifiable risk factors
Hypertension
Smoking
Excessive alcohol consumption
Anticoagulation
Use of antiplatelet agents
Drugs
Decreased low-density lipoprotein cholesterol, low triglycerides
Non-modifiable risk factor
Old age
Male sex
Asian ethnicity
Cerebral amyloid angiopathy
Cerebral microbleeds
Chronic kidney disease
Other factors
Poor working conditions
Long sleep duration

1.1. Therapeutic options

This disease is a medical emergency that requires early diagnosis, through neuroimaging [32]. Treatment usually is based on blood pressure management, reversal of coagulopathy, intracranial pressure monitoring as well as neurosurgical interventions such as hematoma evacuation or external ventricular drainage in cases of large hematomas. Since there are so few therapeutic options, most efforts are focused on rehabilitation to overcome the disabilities caused by the damage after a ICH. These are mostly neurorehabilitation therapies, incorporating physiotherapy exercises or functional movement restoration technologies. As a result, treatment is difficult and subject to controversy [10,33].

For all these reasons, the development of an effective treatment for this type of pathology is vital and it represents a great challenge. During the last decade, the use of Advanced Stem Cell Therapies has gained great importance in the treatment of various diseases and injuries of the Nervous System, thanks to the enormous therapeutic potential in regenerative neurological medicine, as well as, in other types of diseases of cartilage, bone or diabetes, among others. Similarly, Stem Cells have been used as a treatment in ICH with positive results, both in preclinical models and in clinical trials [34,35].

The cell types most commonly used in research have been mesenchymal, neural, embryonic, or hematopoietic stem cells. Of these, the most widely used in research are Mesenchymal Stem Cells (MSCs), characterized by Friedenstein in 1976, who isolated them from bone marrow. They are defined as multipotent progenitor cells with self-renewal potential and the ability to

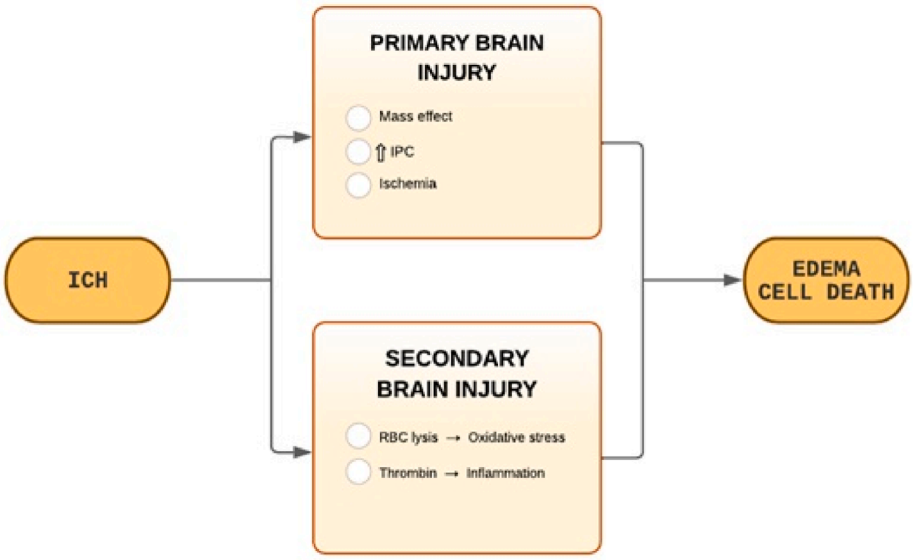

Fig. 1. ICH pathophysiology.

differentiate into different cell lineages such as osteocytes, adipocytes, and chondrocytes [6,36,37]. However, there are not specific criteria for identifying MSCs. The International Society for Cell Therapy proposed a series of markers and cellular characteristics to identify MSCs in 2006 [38]:

- Self-renewal ability.
- Multipotent, they can differentiate into osteogenic, adipogenic, and chondrogenic lineages.
- Expression of positive surface markers CD73, CD90, CD105 and negative surface markers CD14, CD34, CD45, and HLA-DR.
- Adherent growth capacity in plastic.
- Ability to expand *in vitro.*

They can be isolated from different types of tissues such as bone marrow, adipose tissue, or skeletal muscle [39]. Of all these sources, one of the most used in research is bone marrow, as bone marrow-derived MSCs are relatively easy to isolate and manipulate *in vitro* simply. Furthermore, they have low antigenicity and it has been observed that they do not cause tumor formation in preclinical and clinical models [36]. The action potential of MSCs is based on migration to the site of injury where they secrete a series of molecules and different trophic factors with immunomodulatory, angiogenic, and antiapoptotic power. This creates a microenvironment that promotes regeneration, in turn inducing the proliferation of endogenous neural stem cells [40–46]. The effectiveness of the use of MSCs therapy has been demonstrated in different preclinical studies for this type of pathology [47–51]. Experimental models, mostly in rats and mouse, have employed different sources of MSCs, including bone marrow-derived MSCs (BMSCs), umbilical cord-derived MSCs (UCMSCs), and adipose-derived MSCs (ADMSCs), with BM-MSCs being the most extensively studied [47,48]. The administration routes explored include intravenous, intracerebral, and intraventricular delivery. Generally applied in the acute or subacute phase after ICH. Intravenous administration, the most frequently used in preclinical studies, has been associated with significant attenuation of systemic and local inflammation, as well as improvement in neurological function [47–49]. Intracerebral and intraventricular administration, although more invasive, have shown superior effects on reducing hematoma volume, limiting perihematomal edema, enhancing neurogenesis, and preserving blood-brain barrier integrity [49–51].

Specifically, the therapeutic benefits observed are primarily mediated through paracrine mechanisms rather than direct cell replacement. MSCs modulate the inflammatory response by reducing pro-inflammatory cytokines (TNF-α, IL-1β) and increasing anti-inflammatory mediators (IL-10), thereby limiting secondary brain injury [47,48]. Additionally, MSCs promote angiogenesis and vascular remodeling via secretion of VEGF and bFGF, and stimulate neurogenesis and synaptic plasticity through the release of BDNF and GDNF [49–51]. In addition, to histological and biochemical improvements, several preclinical studies have reported significant motor and functional recovery following MSC administration, as evidenced by improved performance in neurological severity scores, beam walking, corner turn, and rotarod tests [52–54].

Despite these advances, the action mechanisms of MSCs need to be further studied because they are still unknown. In addition, many parameters can affect the therapeutic properties of MSCs, such as the source, cryopreservation, culture time, supplementation of the culture medium with growth factors, optimal dosage, or route of administration of the cells [55]. The main objective of this review is to critically analyze the clinical evidence available to date regarding the use of MSCs as a potential therapeutic strategy ICH.

2. Methods

The search for clinical trials investigating the use of MSCs for the treatment of ICH was carried out by consulting major bibliographic databases, including PubMed and ClinicalTrials.gov. The search strategy employed the following keywords: "*mesenchymal stem cell*," "*hemorrhagic stroke*," and "*cell therapy*" and *"clinical trial"*. The search was conducted without restrictions on publication date and included all articles available up to December 2024.

Inclusion criteria encompassed all human studies regardless of age (including newborns), sex, sample size, or trial phase, that evaluated MSC administration in patients with ICH or IVH. Studies were included irrespective of the administration route (intracerebral, intravenous, intraventricular, intra-arterial) or treatment window (acute to chronic phases), as long as they provided a follow-up period assessing the therapeutic effect ranging from days to several years.

The only exclusion criterion was the inclusion of patients with SAH, which was excluded because it involves bleeding into the

subarachnoid space without direct parenchymal involvement. In contrast, ICH and IVH cause direct injury to the brain parenchyma and trigger secondary cascades, including neuroinflammation, oxidative stress, and blood-brain barrier disruption. These pathophysiological processes are closely aligned with the therapeutic mechanisms attributed to MSCs, particularly their immunomodulatory, neuroprotective, and pro-angiogenic effects [8,9].

The selection process involved screening titles and abstracts, followed by full-text evaluation of eligible studies. A total of 15 records were initially identified. Of these, 14 were considered eligible and included in the final qualitative synthesis: 6 clinical trials and 2 observational clinical studies (Table 2), and 6 ongoing trials (Table 3). One study was excluded because it focused on a case report involving subarachnoid hemorrhage, which fell

Table 2
Summary of MSC cell therapy trials and studies in ICH patients.

Patients number/Age	Stem cell type	Stroke subtype and timing	Dose/Route of Administration	Follow-up	Results	Reference
24 patients 38–58 years old	BMNCs (autologous) and UCMSCs (allogeneic)	ICH After 6 h	180×10^6 cells Intracranial route	Up to 5 years	Safety Neurological and functional improvement (BI, NIHSS, and MBI scale índices)	[2]
Newborn babies 24–36 weeks	UCMSCs (allogeneic)	IVH After 7 days	$5–10 \times 10^6$ cells Intraventricular route	36–46 weeks	Safety No improvement (ventricular parameters)	[57]
12 patients 20–60 years old	BMSCs (autologous)	ICH and IS 3 months-1 year	$50–60 \times 10^6$ cells Intravenous route	8–24 weeks	Safety No improvement	[58]
100 patients/39–74 years old	BMSCs (autologous)	ICH After 1 day	1.4×10^6 cells Intracerebral route	Up to 6 months	Safety Neurological and functional improvement (BI and NIHSS scale índices)	[59]
9 patients 41–59 years old	BMSCs (autologous)	ICH After 1 year	45.7×10^6 (0.85×10^6/kg) cells Intravenous route	1–5 years	Safety Motor and cognitive improvement (BI, FIM and GCS scale índices)	[60]
4 patients 40–50 years old	UCMSCs (allogeneic)	IS and ICH Last 3 months	20×10^6 cells Intra-arterial route	Up to 6 months	Safety No improvement	[61]
10 patients 42–87 years old	Combined OECs, SCs, NPCs (autologous) and UCMSCs (allogeneic)	ICH and IS 6 months-20 years	OECS 1×10^6 o OECs ($1–2 \times 10^6$) + NPCs ($2–4 \times 10^6$) cells Intracerebral route NPCs ($2–5 \times 10^6$) cells o NPCs ($2–5 \times 10^6$) + SCs (2×10^6) cells Intrathecal route UCMSCs ($10–20 \times 10^6$) cells Intravenous route	6 months-2 years	Safety Neurological and functional improvement (BI and NIHSS scale índices)	[62]
2 patients 51 and 52 years old	BMSCs (autologous)	ICH 8 months-1 year	20×10^6 cells Intraventricular route	3 months-1 year	Safety Improvement (NIHSS scale índices)	[63]

* MSCs: mesenchymal stem cells, BMSCs: bone marrow mesenchymal stem cell, UCMSCs: umbilical mesenchymal stem cells, MNCs: bone marrow mononuclear cells, OECS: olfactory cells, SCs: Schawn cells, NPCs: neural progenitor cells, iNCS: induced human peripheral blood neural stem cells, ICH: hemorrhagic stroke, IS: ischemic stroke, IVH: intraventricular stroke, BI: Barthel scale, NIHSS: initial clinical scale on neurological severity in stroke, FM: functional Independence measurement scale, GCS: Glasgow Coma Scale, mRS: modified Ranking Scale, MBI: Modified Barthel Index Scale.

Table 3
Summary of ongoing MSC cell therapy trials in ICH patients.

Patients number/Age	Stem cell type	Stroke subtype and timing	Dose/Route of Administration	Follow-up	Results	Reference
20 patients 40–80 years old	UCMSCs (allogeneic)	ICH 3 months-5 years	20×10^6 cells Intravenous route	Up to 1 year	Ongoing	NCT02283879
12 patients Over 18 years old	BMSCs (autologous)	ICH After 3 days	$0.5–5 \times 10^6$/kg Intravenous route Intravetricular route	1–108 days	Safety Ongoing	NCT03371329
300 patients Over 18 years old	BMSCs (autologous)	ICH After 6 months	Not reported Intravenous route intranasal route	3 months-1 year	Ongoing	NCT02795052
30 patients 40–70 years old	BMSCs (autologous)	IS and ICH 3 months-5 years	$2–4 \times 10^6$ cells Intracerebral route	Up to 1 year	Ongoing	NCT01714167
100 patients 30–75 years old	UCMSCs (allogeneic)	ICH After 5 days	Not reported Intracerebral route	Up to 1 year	Ongoing	NCT04074408
Not reported 30–65 years old	iNCS (autologous)	IS 12 months-5 years	Not reported Intracerebral route	Up to 1 year	Ongoing	NCT03725865

*MSCs: mesenchymal stem cells, BMSCs: bone marrow mesenchymal stem cell, UCMSCs: umbilical mesenchymal stem cells, iNCS: induced human peripheral blood neural stem cells, ICH: hemorrhagic stroke, IS: ischemic stroke.

outside the scope of this review. The selection process is summarized in the PRISMA flow diagram (Fig. 2) [56].

3. Clinical trials

After many years of conducting preclinical trials on the use of Cell Therapy with MSCs in different animal models, showing positive results in both safety and efficacy for this pathology, the transition was made to designing clinical trials to determine the potential for neurological and functional recovery of this therapy in patients with this condition. After an extensive review of published articles, it was observed that the number of clinical trials is quite limited compared to ischemic stroke, due to the lower incidence in the population. However, there is a positive trend, with an increase in the number of clinical trials applying MSC therapy for ICH patients since 2011 in numerous countries, particularly in China, confirming the efficacy and effectiveness of this therapy.

Currently, despite this small advancement, many of the trials are still ongoing. A total of 6 completed clinical trials have been published, along with 2 published articles covering 2 studies (Table 2), plus a series of trials in different phases of study or recruitment (Table 3). These trials have included between 2 and 100 patients, with a total of 170 treated patients. The age range spans from 20 to 80 years, and even includes newborns between 24 and 34 weeks, according to the study published by Ahn and colleagues [57].

3.1. Cell types and sources

The trials conducted to date have employed a wide variety of cell types and sources. BMSCs have been one of the primary sources, used for both autologous and allogeneic treatment, due to their accessibility and regenerative potential, as reported by several of the completed trials [58–60]. Likewise, UCMSCs have been widely used due to their lower immunogenicity and high proliferative capacity [57,61]. Additionally, some studies have explored the use of bone marrow-derived mononuclear cells (BMNCs) in combination with UCMSCs, as well as a combination of olfactory ensheathing cells (OECs), neural progenitor cells (NPCs), Schwann cells (SCs), and UCMSCs to enhance neuronal regeneration [2,62].

A more innovative approach was proposed by Fauzi's research group, who implemented the intraventricular

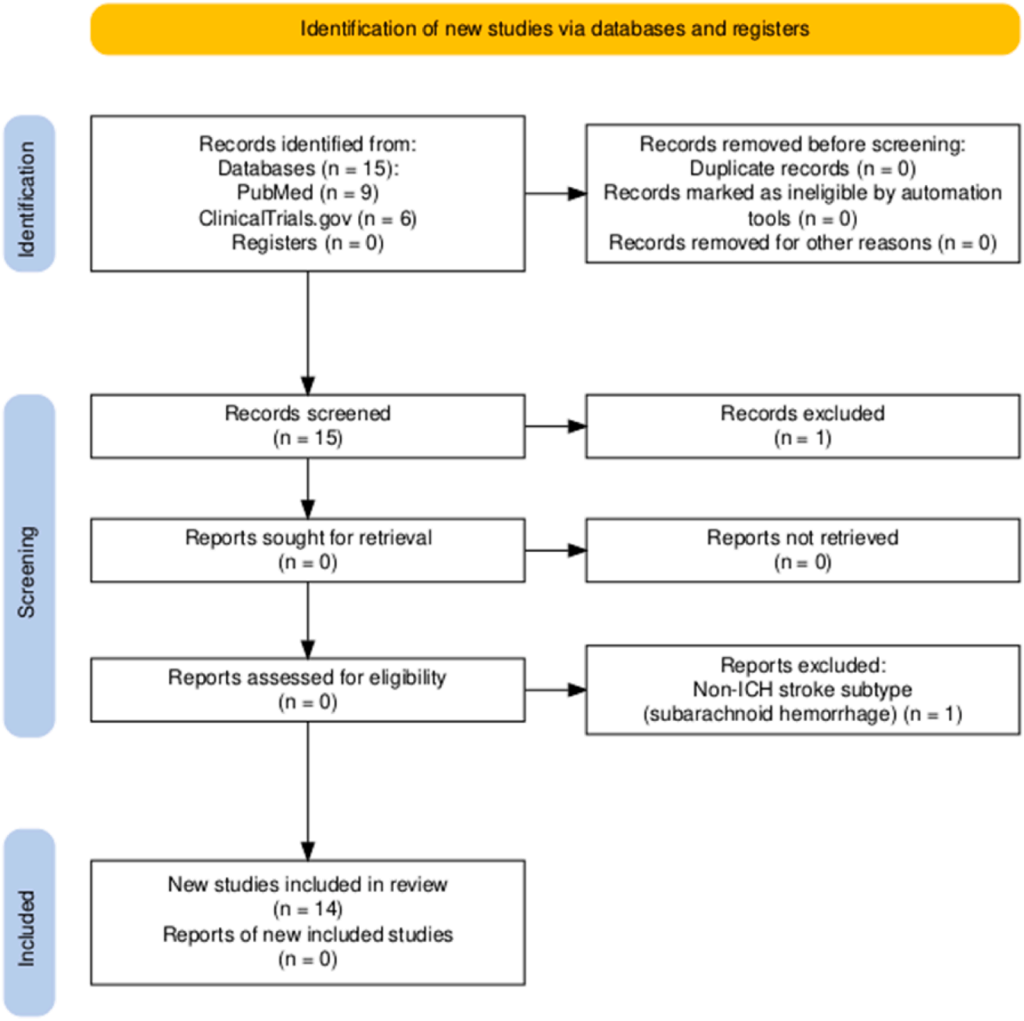

Fig. 2. PRISMA flow diagram [56].

administration of BMSCs using an Ommaya reservoir, allowing for repeated applications without additional invasive interventions [63]. In general, the choice of cell type and source has been determined by availability, safety, and therapy feasibility in each study, showing differences in therapeutic response depending on the type of cells used and their mechanism of action on the injured tissue.

3.2. Dosage, administration routes, and treatment window

Published clinical trials have explored different strategies regarding cell dosage, administration route, and the optimal timing for MSC treatment application, aiming to maximize its effectiveness and safety in ICH patients.

Regarding dosage, the number of administered cells varied significantly among studies, ranging from 1.4×10^6 MSCs in trials like the one conducted by Li and colleagues [59] to higher doses, reaching up to 1.8×10^8 in those administered by the group led by Chan [2]. This heterogeneity highlights the need to establish an optimal dose range to maximize therapeutic effects without compromising patient safety.

The administration route also varied widely depending on the therapeutic strategy employed. For example, intracerebral administration showed a higher local cell concentration, while intravenous administration, although less invasive, had a potential risk of systemic dispersion. Intraventricular administration was used in the study conducted by Ahn's research group, where cells were injected directly into the cerebral ventricle, facilitating direct contact with cerebrospinal fluid and enhancing diffusion within the central nervous system [57]. Similarly, Fauzi and colleagues employed an Ommaya reservoir for repeated intraventricular MSC administration, enabling safe and controlled access without requiring additional invasive procedures [63]. On the other hand, intravenous administration was chosen in studies such as the one by Tsang's research group, where two consecutive doses of MSCs were administered, showing functional improvements in treated patients [60]. This strategy has been widely used due to its low invasiveness and ease of application, although it has the disadvantage of potential systemic cell dispersion, reducing their concentration in the affected area. To improve targeted cell delivery, Jiang and co-workers applied intra-arterial infusion directed to the middle cerebral artery, increasing MSC bioavailability in the affected region. Although promising, this approach requires a more specialized procedure and carries a potential risk of embolization [61]. Finally, direct intracerebral administration has also been evaluated in trials such as those by Li, Chang, and colleagues, where MSCs were injected into the peri-hemorrhagic region through an intracranial drainage system placed after hematoma evacuation surgery. While invasive, this method allows for a higher local cell concentration at the injury site, promoting direct integration into the damaged brain tissue [2,59].

Regarding the therapeutic window, studies differ in the timing of MSC administration. While some trials applied the therapy in an early acute phase, within hours after the stroke, as in the study by the group led by Chang [2], others, like the one by Tsang and colleagues, administered it in the chronic phase, one year after the hemorrhagic event [60]. The evidence so far suggests that early administration may offer greater benefits by modulating the initial inflammatory response and preventing secondary damage. However, MSCs also appear to have neuroprotective and regenerative effects in later stages of the disease.

In conclusion, the variability in dosage, administration routes, and treatment windows underscores the need to standardize these parameters in future clinical trials to determine the optimal protocol for MSC application in ICH treatment.

3.3. Observed outcomes in patients

The reviewed trials have shown variable results regarding MSC administration in ICH patients, with some studies reporting significant improvements in neurological and motor function, while others did not detect clinically relevant effects. However, all studies reaffirmed the safety of the therapy, showing no significant adverse effects in treated and post-treatment evaluated patients.

To assess therapy impact, researchers have employed various measurement scales to quantify neurological recovery, functional independence, and modulation of the inflammatory response. Most patients in the analyzed trials exhibited a positive response after therapy, showing varying degrees of improvement.

The study by Chen and co-workers reported neurological improvements in speech capacity, increased muscle strength and tone, improved respiratory capacity, and significant pain reduction, according to Barthel Index (BI) and NIH Stroke Scale (NIHSS) scores, with follow-up extending up to two years [62]. Li's research group found that patients exhibited improvements in NIHSS and BI scores compared to the control group six months post-treatment, with a high percentage of treated patients achieving complete neurological recovery in swallowing and language abilities, muscle strength and tone, cognitive functions, or improvements in response to stimulation [59].

In the study conducted by the group led by Chang, significant functional improvement was observed based on BI, NIHSS, and the Modified Barthel Index (MBI) scores in treated groups compared to controls after a five-year monitoring period [2]. Similarly, Tsang and colleagues observed motor and cognitive improvements based on BI and Functional Independence Measure (FIM) scores, as well as improvements in Glasgow Coma Scale (GCS) scores in treated patients after five years of follow-up [60].

However, not all trials yielded the desired results. For instance, Bashin's research group did not observe significant motor function improvements in treated patient groups compared to controls, based on Fugl-Meyer scores [58]. Likewise, Ahn and co-workers did not detect significant neurological improvements but conducted a biomarker study on injury and inflammation following intraventricular hemorrhage in preterm infants treated with UCMSCs [57].

3.4. Adverse effects

The reviewed studies on MSC use for ICH treatment have demonstrated that the therapy is safe, as none reported severe immune reactions, post-treatment infections, systemic toxicity, re-bleeding, or metabolic side effects. Only five patients in the trial conducted by Li and colleagues developed mild fever, which resolved within days with appropriate pharmacological treatment [59].

In summary, the clinical trials included in this review (Table 2) show heterogeneity in stem cell type, administration route, and treatment timing, influencing outcomes. Most studies used BMSCs, with others using UCMSCs or combined cell therapies. BMSCs were generally associated with safety and, in some cases, functional improvement, especially when administered intravenously or intracerebrally. UCMSC studies showed mixed results, while combined therapies reported some functional gains. Intravenous delivery was the most common route, with safety confirmed across studies and functional improvements mainly in early treatments. Intracerebral administration was linked to better outcomes, while intraventricular, intrathecal, and intra-arterial routes showed variable or limited benefits. Treatment timing ranged from acute (within hours or days) to chronic phases (months or years). Improvements were more frequently reported

when MSCs were administered during the acute or subacute phase, with limited effects observed in chronic-phase treatments.

3.5. Ongoing trials

Among unpublished studies, patient ages range from 18 to 70 years, with treatment windows spanning from days to five years post-ICH. The MSCs used originate from bone marrow, umbilical sources, and induced neural MSCs derived from human peripheral blood. Currently, results from these trials remain unpublished, making it impossible to determine therapy efficacy at this stage, with follow-up extending up to one year post-treatment (Table 3).

4. Conclusion and future perspectives

MSC therapy has demonstrated a favorable safety profile in the treatment of ICH, with no signs of infections, immune rejection, or severe side effects reported in the clinical trials included in this review. However, the functional outcomes observed remain variable and seem to depend on factors such as the type of stem cell used, the administration route, and the timing of treatment. In particular, better neurological and functional improvements were reported in studies administering MSCs intravenously or intracerebrally during the acute or subacute phases. This may be explained by the known biological mechanisms of MSCs, including their early modulation of neuroinflammation, reduction of blood-brain barrier disruption, attenuation of secondary neuronal injury, and promotion of angiogenesis, neuroregeneration, and anti-apoptotic processes. These mechanisms align with preclinical evidence and support the rationale for early administration.

This evidence reinforces the feasibility of MSC-based therapy; however, the results regarding efficacy remain highly heterogeneous, highlighting the need for further exploration in this emerging field. While many trials have reported significant improvements in neurological function and functional independence, others have not found notable differences between treated and control groups. Current clinical evidence is still limited by small sample sizes, lack of standardized protocols, heterogeneous outcome measures, and short follow-up periods, making it difficult to compare results directly and precluding formal quantitative synthesis.

Beyond these methodological challenges, several translational barriers must also be addressed to enable widespread clinical application, including overcoming differences between preclinical models and human pathophysiology, variability in cell manufacturing and quality control, regulatory hurdles, and the complexity of large-scale cell production and delivery.

For these reasons, future clinical trials should aim to include larger patient cohorts, employ randomized controlled designs, and use standardized functional and imaging endpoints. It is also essential to extend follow-up periods to assess long-term outcomes and to compare different administration routes, cell sources, and dosing strategies to optimize therapeutic efficacy. Moreover, understanding the optimal therapeutic window is critical, as the observed improvements in acute or subacute treatments may be related to the ability of MSCs to modulate the inflammatory response and protect neural tissue during early injury stages, while administration in chronic phases appears less effective.

Additionally, there are other multiple parameters that can influence the therapeutic properties of MSCs, including the source of cell procurement, cryopreservation procedures, cultivation duration, or culture medium supplementation with growth factors. The quest for greater optimization of MSC-based therapeutic strategies has led many studies to focus on preconditioning methodologies to enhance the regenerative and reparative capacity of MSCs in damaged tissues. The type of preconditioning is tailored according to the cell type and the characteristics of the targeted damaged tissue [63]. In this regard, various studies have explored preconditioning approaches using inflammatory cytokines, hypoxia, pharmacological agents, chemical compounds, and different biomaterials to achieve, depending on the specific objective, inflammation modulation, angiogenesis stimulation, or enrichment of culture media to activate resident cells within injured tissues [64,65].

In conclusion, MSC therapy represents a promising therapeutic strategy for ICH. Its consistent safety profile and potential neuroprotective and regenerative effects justify continued clinical investigation. Translating the biological benefits observed in preclinical models into meaningful clinical improvements will require well-designed, robust trials that address both methodological and translational challenges. If these efforts are successful, MSC-based interventions could provide a novel approach to enhance recovery and reduce disability in patients suffering from ICH. Furthermore, combining MSC therapy with other complementary strategies, such as intensive rehabilitation, biomaterial applications, or preconditioning techniques, could enhance the therapeutic potential of MSCs, leading to greater neurological and functional recovery in patients, both in the short and long term.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2025.05.011.

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