Regenerative Therapy 27 (2024) 301–306

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

Mesenchymal stem cell therapy in ischemic stroke trials. A systematic review

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ARTICLE INFO

Article history:
Received 12 January 2024
Received in revised form
11 March 2024
Accepted 24 March 2024

Keywords:
Ischemic stroke
Cerebrovascular accident
Mesenchymal stem cells

ABSTRACT

Cerebrovascular accidents, also known as strokes, are the leading cause of permanent disability in society, presenting significant socioeconomic and healthcare costs. They can be caused by ischemic factors or hemorrhages, with ischemic strokes being the most common among the population. Therapies for patients suffering from this condition are limited and primarily focus on acute-phase treatment. In recent years, there has been an increase in cellular therapies, employing Stem Cells to mitigate or eliminate the consequences arising from this disease. Mesenchymal Stem Cells (MSCs) hold substantial therapeutic potential in Nervous System pathologies due to their low antigenicity and capacity to differentiate into various human tissues, such as adipogenic, chondrogenic, and osteogenic tissues. This study conducts a literature review using the “clinical trials” and “Pubmed” database, summarizing all ongoing clinical trials for ischemic strokes that utilize MSCs as treatment.
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Contents

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Peer review under responsibility of the Japanese Society for Regenerative Medicine.

https://doi.org/10.1016/j.reth.2024.03.026
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1. Introduction

Cerebrovascular accident (CVA), commonly referred to as a stroke, is a serious medical condition that affects the brain and can have devastating consequences. It occurs when blood supply to a part of the brain is interrupted due to the obstruction of a blood vessel (ischemic stroke) or the rupture of a blood vessel (hemorrhagic stroke). In both cases, reduced or interrupted blood flow results in cerebral damage due to oxygen and nutrient deprivation [1]. Ischemic strokes are the most prevalent in the population, accounting for approximately 85% of all strokes, while hemorrhagic strokes are less common but exhibit a significantly higher mortality rate [2]. Projected costs associated with ischemic strokes are estimated to reach $240.67 million by 2030 [3]. Strokes are the leading cause of permanent disability and the second leading cause of death in the adult population of developed countries. Due to population aging, a reduction in stroke incidence is not anticipated; instead, it is expected to increase over time, creating a greater socio-economic and health challenge [4].

The associated risk factors are highly heterogeneous, classifiable into modifiable and non-modifiable factors. Hypertension is the most relevant modifiable factor, while age is the predominant non-modifiable factor predisposing individuals to the disease. Additionally, male gender and a family history of stroke have been demonstrated to increase the risk [5]. Stroke symptoms can vary depending on the affected brain region, but generally include sudden weakness or numbness in the face, arm, or leg, confusion, difficulty speaking or understanding language, vision problems, dizziness, loss of balance or coordination, and severe headache. Early diagnosis and immediate treatment are crucial to minimize cerebral damage and improve prognosis. Treatment options may involve medications to dissolve blood clots (in the case of ischemic stroke) or to control blood pressure and prevent hemorrhage (in the case of hemorrhagic stroke). Rehabilitation is also a critical aspect of the recovery process, aiding patients in regaining lost abilities and adapting to limitations caused by the stroke [6].

Unfortunately, current treatments do not achieve complete remission of resulting sequelae, necessitating extensive research efforts to develop novel therapies for the disease. Improvement in animal models, adoption of new technologies, and the implementation of innovative treatments are imperative [7]. Thanks to advanced therapies, the utilization of MSCs has gained significant relevance in treating various diseases and injuries of the Nervous System due to their immense regenerative therapeutic potential in neurological medicine. MSCs can be isolated from various adult tissues such as adipose, connective, and dermal tissues, as well as fetal tissues like umbilical cord, amniotic fluid, or placental blood, among others [8]. Among these sources, obtaining MSCs from bone marrow is the most commonly employed method in literature. They are easy to isolate and manipulate in vitro. Furthermore, these cells possess low antigenicity and no tumor formation has been observed in experimental processes utilizing MSCs from adult individuals [9].

MSC characterization is based on their capacity for adhesion to plastic, differentiation into osteogenic, adipogenic, and chondrogenic lineages in vitro, and their ability to express or lack certain differentiation cluster (DC) markers—positive for CD73, CD90, and CD105, and lacking CD34, CD45, CD34, CD14 or CD11b, CD79α or CD19, and HLA-DR surface molecules [10,11].

1.1. Ischemic strokes

Ischemic stroke, also known as an ischemic cerebrovascular accident, is an acute cerebrovascular condition that occurs when blood supply to the brain is interrupted due to the obstruction of a cerebral artery, resulting in oxygen and nutrient deficiency in that area. This obstruction can be caused by a blood clot or reduced blood flow due to artery narrowing. It can manifest suddenly and lead to a variety of symptoms, including weakness or paralysis on one side of the body, difficulty speaking or understanding language, vision problems, dizziness, and loss of balance [12].

Current therapies for ischemic strokes primarily target the acute phase of the disease, aiming to achieve tissue reperfusion as soon as possible to minimize cerebral damage. This can be achieved through the administration of thrombolytic medications that dissolve blood clots or through endovascular procedures such as thrombectomy, involving mechanical clot removal [13]. After the acute phase, the patient enters a chronic phase where effective treatments are significantly diminished, with rehabilitation being one of the treatments offering partially significant improvement for these patients [14].

2. Search strategy

Several clinical trials have been conducted or are ongoing to evaluate the use of MSCs in the treatment of ischemic stroke. This review provides an overview of the studies recorded on http://clinicaltrial.gov and https://pubmed.ncbi.nlm.nih.gov (accessed on 31 July 2023) with the aim of identifying all articles reporting the use of MSCs as treatment for cerebral infarctions. Pediatric patients and trials without data updates for more than two years were excluded. Currently, we have identified fourteen relevant clinical trials (Table 1), from which we will summarize the combined protocols.

3. Results

3.1. Cerebral infarction localization

Regarding the location of the stroke, considerable heterogeneity was found in the studied clinical trials. The most predominant location is in the territory of the middle cerebral artery (MCA), consistent with the literature as the area most prone to ischemic strokes. 5 out of the 14 studied clinical trials restrict treatment to this area. Two trials focus on the anterior cerebral artery territory, one on the carotid artery, and another trial on the cerebral parenchyma area. Notably, five clinical trials do not limit a specific stroke area for patient inclusion.

3.2. Acute/chronic phase

Upon analyzing the clinical trials, it is observed that almost all of them, 13 out of 14 identified trials, solely focus their treatment on one phase of the stroke. Only one clinical trial does not limit the disease phase for treatment but restricts the timeframe to three years from stroke detection. Among the 13 trials solely focused on one disease phase, 11 trials are centered on treatment during the acute phase of the disease. Only 2 clinical trials are indicated for the chronic phase of stroke.

3.3. MSC source of acquisition

7 out of the 14 existing clinical trials for ischemic stroke treatment utilize MSCs obtained from umbilical cord for patient treatment. The second most employed source of MSCs is bone marrow, present in four out of the 14 trials. The use of MSCs from adipose tissue has only been employed in 2 out of the 14 identified trials. Notably, one trial does not specify the source of MSC acquisition.

Table 1
Clinical Trials included in the Study.

CLINICAL TRIAL NUMBER	Nº Pacientes	MSC SOURCE	AUTOLOGOUS/ ALLOGENEIC	ADMINISTRATION ROUTE	OBSERVATIONS	PHASE	LOCATION	DOSAGE	STATUS	REFERENCE
NCT01678534	19	Adipose Tissue	Allogeneic	Intravenous	No	Acute	Measurable neurological focus	One dose of 1×10^6/kg	Completed with 1 publication	[15]
NCT04811651	Estimated 200	Umbilical Cord	Allogeneic	Intravenous	No	Acute	Anterior cerebral infarction	One dose of 100×10^6	Recruiting	[16]
NCT05697718	18	Umbilical Cord	Allogeneic	Intravenous	No	Acute	Anterior cerebral infarction	Three study groups with a single dose of $5 \times 10^7/10 \times 10^7/20 \times 10^7$	Recruitment completed	[17]
NCT05292625	Estimated 48	Umbilical Cord	Allogeneic	Intravenous/ Intrathecal	No	Acute	Not mentioned	Two doses of 1.5×10^6/kg spaced 3 months apart in each group	Recruiting	[18]
NCT05850208	Estimated 60	Bone Marrow	Autologous	Intravenous	No	Subacute, Chronic and Sequelae stage, time $\leq$3 years	Middle Cerebral Artery	Two doses of 1×10^6/kg	Recruiting	[19]
NCT04097652	Estimated 9	Umbilical Cord	Allogeneic	Intravenous	No	Acute	Cortical Infarction	Dose escalation (high, medium, low)	Recruiting	[20]
NCT04280003	Estimated 30	Adipose Tissue	Allogeneic	Intravenous	No	Acute	Non-Lacunar Infarction in Middle Cerebral Artery territory	One dose of 1×10^6/kg	Recruiting	[21]
NCT02605707	20	Bone Marrow	Autologous	Intravenous	Three study groups: MSCs, Endothelial Progenitors, and control	Acute	Middle Cerebral Artery	Three study groups: MSCs, Endothelial Progenitors, and control. Two doses of 2.5×10^6/kg spaced one week in MSCs and Endothelial Progenitors groups. |	Completed with 3 publications	[22]
NCT04590118	Estimated 60	Not mentioned	Allogeneic	Intravenous	No	Chronic	Not mentioned	Three study groups with a single dose of 0.5×10^6, 1×10^6, 2×10^6	Recruiting	[23]
NCT05008588	Estimated 15	Umbilical Cord	Allogeneic	Intranasal (conditioned médium)/ intraparenchymal MSCs	Conditioned medium	Acute	Not mentioned	Three study groups: CM and MSC combined, MSC, and control. 3 cc of conditioned médium for 3 consecutive days and intraparenchymal transplantation of 20×10^6 MSCs in CM and MSC combined group. A single dose of 20×10^6 in MSCs group. Control group receives standard treatment.	Recruiting	[24]
NCT04093336	Estimated 120	Umbilical Cord	Allogeneic	Intravenous	No	Acute	Middle Cerebral Artery	One dose of 2×10^6/kg	Recruiting	[25]
NCT04434768	Estimated 14	Umbilical Cord	Allogeneic	Intravenous/Intra-arterial	No	Acute	Unilateral middle cerebral artery	One intravenous dose or one intravenous dose followed by low or high intra-arterial infusion.	Recruiting	[26]
NCT00875654	31	Bone Marrow	Autologous	Intravenous	No	Acute	Right or left carotid artery	Three study groups: control group, group with one dose of 100×10^6 MSCs intravenous and group with one dose of 300×10^6 MSCs intravenous	Completed with 2 publications	[27]
NCT01297413	38	Bone Marrow	Allogeneic	Intravenous	No	Chronic	Not mentioned	Dose escalation. Patients receive a dose between 0.5×10^6 - 1 × 106/kg	Completed with 1 publication	[28]

3.4. Autologous/allogeneic

A characteristic of MSCs is their low antigenic load, especially concerning the HLA-II molecule. Due to this feature, MSCs have become an increasingly used therapeutic option for various pathologies. Upon analyzing the 14 active clinical trials, we find that 11 clinical trials focus on treatment using allogeneic MSCs, while 3 clinical trials employ an autologous treatment protocol in their description.

3.5. Administration route

More than 78% of the studied trials choose the intravenous administration route as the most relevant option for treating patients. This route offers technical simplicity compared to local routes, such as the intraparenchymal route found in a single clinical trial. Notably, dual administration is found in two clinical trials, combining the intravenous route with either the intrathecal or intra-arterial route, respectively. In both trials, the intravenous route remains a part of the study.

3.6. Dosage

Regarding the administered dosage and regimen, differences are found among the studied trials, both in the number of doses and the quantity of MSCs to be administered. In terms of the number of doses, 10 out of the 14 clinical trials have a single dose outlined in their protocol. The remaining 3 trials use a two-dose regimen in their protocol. Additionally, there are trials that adjust the cell quantity based on patient weight, with this criterion found in half of the studied trials (7 out of 14). 5 out of the remaining 7 trials have fixed dosages without considering patient weight. The two remaining trials do not specify the exact dosage to be administered in the study or the criteria to be followed.

3.7. Efficacy

The reviewed studies address the efficacy of different therapies in patients with ischemic stroke. In the NCT01678534 trial [15], intravenous administration of allogeneic adipose tissue-derived mesenchymal stem cells (MSCs) within the first 2 weeks after stroke does not show significant differences in neurological function or associated disability, although the results are expected to help define criteria for future studies. In the NCT02605707 study [22], therapy with endothelial progenitor cells (EPCs) results in consistent improvements in neurological function and quality of life of patients over the 48 months of the study. In the NCT00875654 trial [27], MSC therapy shows significant effects in improving motor function, especially in patients with initial stroke severity, although no differences are observed in overall assessment measures. Lastly, in the NCT01297413 study [28], there is a suggested potential functional benefit of intravenous MSC therapy in patients with significant functional deficits, although further controlled studies are needed to confirm these findings. Overall, these results support ongoing research into these therapies to improve outcomes in stroke patients.

3.8. Adverse events

Out of the fourteen clinical trials studied, only four have completed their study [15,22,27,28], while the rest are still in the recruitment phase. Upon analyzing the results from these four completed trials, it is concluded that treatment tolerance was very high, demonstrating excellent safety. Only one clinical trial (NCT01297413) reported 109 serious adverse events (38 patients in the trial) of various natures such as infections, vascular disorders, or pain syndromes, of which only 2 were directly related to the investigational treatment [28]. Both events were monitored, confirming complete recovery and the absence of further safety concerns. This suggests a favorable safety profile for the treatments evaluated across different clinical trials.

4. Discussion

Clinical trials are research studies designed to assess the safety and efficacy of new therapies or treatments in humans. Several clinical trials have been conducted or are ongoing to evaluate the use of mesenchymal stem cells (MSCs) in the treatment of ischemic stroke.

It is noteworthy that the specific localization of an ischemic stroke can vary depending on individual factors, but certain areas are more prone to ischemic strokes. Ischemic strokes in the Middle Cerebral Artery (MCA) are the most common in the literature. This artery supplies blood to important parts of the brain, including the cerebral cortex, frontal lobe, parietal lobe, and temporal lobe [29]. Therefore, it is not surprising that most clinical trials, which do not limit the area of the ischemic stroke, focus on this region for treatment.

A common factor in strokes, regardless of the affected brain area, is the time elapsed since the onset of stroke symptoms. Treating stroke in the acute phase is considered critical as rapid intervention can significantly influence patient recovery and prognosis [12]. After a stroke, secondary events can occur that further damage the brain, such as the release of excitatory neurotransmitters, inflammation, oxidative stress, and associated medical complications like infections, respiratory problems, dysphagia, or deep vein thrombosis. Detecting and treating these complications early can improve prognosis and prevent the progression of additional issues [30,31].

The use of MSCs in the treatment of acute-phase stroke has been a subject of investigation and has been shown to offer several benefits. MSCs possess neuroprotective properties, meaning they can help protect and preserve damaged brain cells during a stroke. These cells can modulate the inflammatory response and reduce cell death in the affected brain area. It has been observed that MSCs can promote cell survival and stimulate the regeneration of brain tissue in animal models of acute stroke [32]. Additionally, MSCs have the capacity to modulate the inflammatory response in the brain after a stroke. They can secrete anti-inflammatory molecules and reduce the production of pro-inflammatory molecules, which can decrease brain damage caused by excessive inflammation. These anti-inflammatory effects can help limit the extension of brain damage and improve clinical outcomes [33]. Another beneficial capacity of MSCs for stroke treatment is the stimulation of neurogenesis, which can contribute to the repair and regeneration of damaged brain tissue after a stroke [34]. All these findings align with current clinical trials where, except for two trials focusing on the chronic phase of the disease, the rest of the trials aim at treating the acute phase of the disease.

Prioritizing treatment in the acute phase of stroke underscores the importance of promptly having cells available for patient treatment. Allogeneic MSC treatment for acute ischemic stroke presents an advantage over autologous treatment since autologous treatment requires time for cell processing. As previously cited, the use of allogeneic MSCs allows faster access to treatment in the acute phase of ischemic stroke. This can be crucial, as early intervention is fundamental for improving clinical outcomes [35]. Furthermore, allogeneic MSCs have been shown to have a greater ability to modulate the immune response and reduce inflammation compared to autologous cells. This is due to specific molecules

expressed in allogeneic cells that interact more effectively with the immune system [36]. Allogeneic MSCs can also exert their therapeutic effect by secreting paracrine factors such as cytokines and growth factors. These factors can promote cell survival, reduce apoptosis, and stimulate the formation of new blood vessels, favoring the recovery of damaged brain tissue [37].

These MSC characteristics that make them widely employed and useful in stroke treatment can vary depending on their source of origin. The most employed source of MSCs in the reviewed clinical trials is umbilical cord. This source has several benefits, with one of the most significant being the abundance of stem cells, facilitating obtaining sufficient quantities for therapeutic applications [38]. Additionally, its collection process is safe and non-invasive for both the donor and recipient [39]. Another widely employed source of MSCs is bone marrow, primarily due to its easy collection, processing, and lack of ethical concerns with its use as a treatment [40].

Another key factor to consider when designing a clinical trial is the dosage of MSCs to administer, regardless of their source. Cell therapy involves using living cells or their products to treat diseases or injuries. The indicated dosage of a cell therapy medication is designed to achieve maximum effectiveness in treating a specific disease or injury. Incorrect dosage can result in insufficient or no response to treatment, negatively affecting effectiveness and therapeutic outcomes. Administering the correct dosage is also crucial for patient safety. Insufficient dosage may not provide the desired therapeutic benefits, while excessive dosage can lead to serious side effects, such as adverse immune reactions or systemic toxicity. Adhering to the indicated dosage minimizes the risk of adverse effects and maximizes patient safety. Assessing the appropriate dosage also allows for optimal utilization of available resources. Cell therapy can be costly, and in some cases, cell availability may be limited. Using the correct dosage ensures that available cells are maximized, preventing waste and ensuring effective use in each patient [41].

Current clinical trials exhibit a high variety in adjusting the administered dosage. Trials with dosage based on patient weight and those with fixed dosages in their protocol are observed. Differences are also seen in the number of doses administered to patients, although most studies only propose a single dose. Notably, dose escalation is present in a significant number of trials.

Just as optimizing the dosage is necessary, an assessment of the most suitable administration route for therapy is needed. Clinical trials involve the administration of MSCs through various routes, with the intravenous route being the most common due to its key advantages. This administration allows cells to circulate through the bloodstream and reach different parts of the body, facilitating their arrival to tissues and organs needing regeneration or treatment [42]. Moreover, it is a non-invasive procedure that reduces the risk of complications and patient recovery time, thereby reducing the risk of infections associated with invasive interventions [43].

It's important to note that the majority of the clinical trials reviewed in this study are ongoing, and final results are not yet available. However, ensuring safety from the outset of the study is a key and essential step, as it not only protects individual participants but also strengthens the integrity and credibility of medical research [44]. When analyzing safety in completed trials, a very high safety profile with a high tolerance to treatment is observed. This underscores the need to prioritize participant safety throughout clinical research.

In addition to safety, treatment efficacy also constitutes an essential parameter to consider in clinical trials. Evaluating efficacy not only provides a scientific basis for decision-making in clinical practice, allowing for the selection of the most appropriate treatment for each patient, but also drives progress in medical research by generating valuable data for the development of new treatments. Furthermore, this evaluation identifies areas requiring greater resource allocation to expand research, thus contributing to improving the quality of medical care and patient well-being. With advancements in clinical trial results, new treatment options are expected for patients suffering from this disease [45].

5. Conclusions

In summary, clinical trials using mesenchymal stem cells for ischemic stroke treatment show promise, but further research is needed before this therapy can be considered a standard treatment.

Treatment in the early days or weeks after experiencing a stroke is crucial for better patient outcomes.

The use of mesenchymal stem cells in ischemic stroke treatment is an active and promising field of research, requiring additional studies to determine the optimal dosage, the best administration route, and appropriate patient selection.

The emphasis on prioritizing participant safety and evaluating treatment efficacy in clinical trials highlights the integral role they play in enhancing both the integrity of medical research and the quality of patient care.

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.

Acknowledgment

Most of the experimental work by the author in this review has been possible by grants received from the Mapfre Foundation.

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