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Intra-arterial delivery of mesenchymal stem cells

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Abstract:

While treatments have been developed to combat stroke, such as intravenous recombinant tissue plasminogen activator and endovascular recanalization therapies, their ability to decrease the long-term disability that accompanies stroke is limited. Currently, stem cell research focused on mesenchymal stem cells (MSCs). MSCs are multipotent, nonhematopoietic stem cells found in the stromal fraction of the bone marrow, along with the connective tissue of most organs. MSCs are an increasingly appealing cell source due to the relative ease in which they can be retrieved, developed, and handled *in vitro*. Despite the fact that numerous paths of stem cell transport to the brain in acute ischemic stroke (AIS) exist, the intra-arterial (IA) route of stem cell transport is most attractive. This is due to its great potential for clinical translation, especially considering the growing clinical application of endovascular treatment for AIS. Here, we evaluate research examining IA delivery of MSCs to the stroke region. The results of the study revealed the maximum tolerated dose and that the optimal time for administration was 24 h, following cerebral ischemia. It is important that future translational studies are performed to establish IA administration of MSCs as a widely used treatment for AIS.

Key words:

Intra-arterial, ischemic stroke, maximum tolerated dose, mesenchymal stem cells

Introduction

In the United States, stroke is the third highest cause of death and the leading cause of long-term disability. The costs of addressing stroke were measured at an overwhelming 73.3 billion in 2010.[1] Despite the development of treatments, such as the administration of intravenous (IV) recombinant tissue plasminogen activator, which began 18 years ago, and the ever-growing number of endovascular recanalization therapies for acute ischemic stroke (AIS), their ability to reduce long-term disability associated with stroke is narrow.[2,3] Therefore, the continued discovery and development of new treatments for AIS remains imperative. To address the lack of effective treatments, several preclinical studies have been conducted over the past decade, signifying the efficacy of various types of stem cells in facilitating and improving neurological outcomes, following AIS.[4-7] Currently, mesenchymal stem cells (MSCs) stand at the forefront of clinical translation of stem cell research for stroke. MSCs are adult, nonhematopoietic progenitor cells with the ability to differentiate into a diverse number of cell lineages, including chondrocytes, osteoblasts, and neuron-like cells.[8-11]

Intra-arterial Delivery of Mesenchymal Stem Cells Shows Therapeutic Potential for Stroke

MSCs are multipotent, nonhematopoietic stem cells that are located primarily in the stromal fraction of the bone marrow, along with the connective tissue of the majority of the organs.[9-11] While it has been found that MSCs can be harvested from amniotic fluid, adipose tissue, umbilical cord, and placenta without difficulty, they are most often isolated from adult bone marrow. Due to the relative ease in which they can be obtained, developed, and manipulated *in vitro*, MSCs are an increasingly appealing cell source.[12] In addition, MSCs derived from adult tissue do not carry the risk of tumorigenicity that is present in pluripotent cells.[13] Furthermore, these stem cells have low major histocompatibility complex (MHC) 1 and no MHC II antigen expression; therefore, they are immunoprivileged, eliminating the necessity for immunosuppression in allogeneic administration of MSCs.[12,13] As a result, allogeneic MSCs from a healthy donor can be administered off-the-shelf

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very quickly without a requisite for immunosuppression. This aspect of MSCs makes them especially appealing as candidates for future translation into treatments for ischemic stroke, an illness that often presents without prior warning and whose detrimental effects may be ameliorated by prompt stem cell therapy.[14-16]

Numerous paths of stem cell transport to the brain in AIS exist. Of all possible routes, the intra-arterial (IA) route of stem cell transport is most attractive due to the great potential it holds for clinical translation, especially considering the growing clinical application of endovascular treatment in the management of AIS.[6,17-20] In addition, IA distribution of stem cells following AIS is minimally invasive and allows for better diffusion and distribution of a larger number of stem cells, both in and around the infarct area, in comparison to intracerebroventricular, intraparenchymal, and IV stem cell delivery.[21] IA transport is more efficient as it prevents the stem cells from becoming trapped in the liver and lungs, a problem that can occur with IV transport.[22] Furthermore, a prior investigation has demonstrated improved histological and functional outcomes in IA transplantation of stem cells when compared to IV delivery.[23] Nonetheless, MSCs can range from 5 to 50 μ, and this vast size range places limitations on the efficacy of IA delivery. A possible constraint for IA delivery of MSCs is the potential for regional cerebral blood flow compromise as a result of the presence of larger MSCs in the 20–50 μ size range. Therefore, while MSCs present a plausible and innovative therapy to treat AIS, the potential to worsen cerebral ischemia exists.[10]

Lower Dosage and Subacute Delivery Effectively Decreases Infarct Volume

A recent study determined the maximum tolerated dose (MTD) of IA MSCs that did not obstruct middle cerebral artery (MCA) flow, as well as defined its success and the ideal timing for delivery, following ischemic stroke. In the first part of the study, reversible MCA occlusion (rMCAo) was given to adult female Sprague-Dawley rats for 90 min, and after an hour, single doses of MSCs were administered through the IA route. The doses de-escalated (1×10^6, 5×10^5, 2×10^5, 1×10^5, and 5×10^4) to determine the MTD and address the efficacy of lower doses to treat cerebral ischemia. Through the use of laser Doppler flow signal over the ipsilateral MCA, the researchers were able to measure the percent change in mean flow. The results demonstrated that an IA MSC dose of 1×10^5 and lower did not compromise MCA flow. Hence, an IA MSC dose of 1×10^5 can be deemed MTD. In the second part of the study, the efficacy of an IA MSC dose of 1×10^5 was compared at 1 h and 24 h, following rMCAo. The results of the investigation demonstrated a significant decrease in infarct volume and improved neurodeficit score in the 24 h delivery as compared to the 1 h delivery. On the whole, this investigation established that an IA MSC dose of 1×10^5 administered after 24 h could be very safe and effective in the treatment of cerebral ischemia in a rat model.[24]

Possibilities for Future Clinical Applications

The primary obstacle to IA transport of MSCs is the potential for vascular obstruction in small capillaries and arterioles by larger MSCs.[10] The findings by Yavagal *et al.* represent key information on the dose–response relationship in maintaining the safety of IA transport of allogeneic IA MSCs and decreasing blood flow compromise in the MCA, following IA MSC injection by lowering IA dose. In addition, the results also signify that lower safe doses of MSCs are much more effective when given through the IA route at 24 h.[24] The results from this investigation establish a foundation for future translational studies to introduce IA allogeneic MSCs as an innovative treatment for AIS in the first 24 h, following ischemic stroke.

Considering the growing use of catheter-based endovascular treatments for AIS, IA transport of stem cells holds remarkable possibilities for future clinical translation. In a previous clinical trial, IA delivery of bone marrow mononuclear cells (BMMCs) into the affected MCA was proven to be safe in the 3–7 days, following MCA strokes in 20 patients.[25] In prior clinical investigations of intracoronary transplantation of MSCs following acute cardiac failure, IA transport of MSCs has been effectively executed.[26,27] In view of the incredible potential for clinical application, further preclinical investigations focused on overcoming critical translational obstacles in IA transport of stem cells, including MSCs in stroke, are essential in bringing this treatment to patients.

Another obstacle that stands in the way of clinical translation is determining the proper speed of injection. While this study decreased the speed of injection to three times slower in comparison to previous studies, no alleviation of the undesirable effect on blood flow in the MCA was identified.[10] It has also become evident that the speed of cell injection used in rats cannot be exactly translated to humans due to their vast size differences. In addition, whereas microcatheters are very effective in allowing good blood flow around them in the internal carotid artery and are readily available for clinical use, the polyethylene 10 used in rodent studies is very snug. Further testing into injection speed will need to be done before complete clinical translation can be achieved.

In the investigation conducted by Yavagal *et al.*, the animals that received IA MSCs at the MTD of 1×10^5 at 24 h following rMCAo demonstrated superior neurologic improvements at 1 month in comparison to the control group that received IA saline, along with results from other studies that administered MSCs through the IV route. In addition to superior neurologic improvements, results from the study demonstrated a greater reduction in the infarct area in the IA MSC_24 h group than in the IA Phosphate buffered saline (PBS)_24 h.[24] This reduction of the infarct area within the IA MSC_24 h group mainly occurred in the penumbral area, revealing MSC-mediated neuroprotection to be the most probable mechanism of treatment. Results from other studies support the benefits of this mechanism, demonstrating elevated levels of anti-apoptotic factors in the periinfarct region of animals treated with MSCs.

Although prior investigations have presented the advantages of IA autologous BMMCs and fetal-derived neural stem cells, the findings of Yavagal *et al.* suggest that allogeneic MSCs administered through the IA pathway are very effective in alleviating neurological damage after ischemic stroke without

the requisite for immunosuppression.[28] Their discovery of higher safety and efficacy at the MTD in comparison to higher doses is remarkable and reveals the necessity for cautious dose escalation studies to translate IA MSC therapy to the bedside.[24] In addition, a prior investigation revealed the advantages of the IA route versus the IV route of transport of autologous BMMCs, demonstrating the increased efficacy of the IA group.[23] These authors' findings certify the advantages of the IA route and also further support the superiority of the IA over the IV route through evaluation of both routes effects on functional recovery.[24]

The ideal timing of IA stem cell administration following AIS has yet to be determined. In the study conducted by Yavagal *et al.*, they found that administration of allogeneic IA MSCs at 24 h resulted in a great decrease in infarct volume. However, this was not the case for the MSCs given at 1 h, following ischemic stroke. The fact that a decrease in infarct volume did not occur in the IA MSC_1 h group reveals that neuroprotection is not substantial when MSCs are administered at this hyperacute timing, following cerebral ischemia. Currently, IA stem cells are given via intracarotid catheters immediately following endovascular reperfusion therapy in patients suffering from ischemic stroke in the hopes of avoiding a second procedure to administer stem cells. However, the results of Yavagal *et al.*' study suggest that administration of stem cells in the hyperacute phase is useless as it is not the optimal timing for treatment. Further clinical trials should be conducted to test the administration of cells in the first couple of days, following cerebral ischemia and not combined with IA thrombolytic therapy.

In summary, administration of MSCs at MTD of 1×10^5 through the IA route will not obstruct MCA blood flow. In addition, administration of MSCs during the subacute period will more effectively stimulate neuroprotection following cerebral ischemia. Considering the gravity of these findings, further translational studies must be conducted to cement IA administration of MSCs as a widely used treatment for AIS.

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Conflicts of interest
There are no conflicts of interest.

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