https://doi.org/10.48047/AFJBS.6.2.2024.1597-1604

AfricanJournalofBiological Sciences

ResearchPaper OpenAccess

Review of Mesenchymal Stem Cell Therapy on Acute Myocardial Infarction and Potential Ameliorative Effect of Atorvastatin

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Article History

Volume 6, Issue 2, April 2024

Received: 3 June 2024

Accepted: 10 July 2024

Published: 10 July 2024

doi:

10.48047/AFJBS.6.2.2024.1597-1604

Abstract: Myocardial infarction (MI) is a clinical occurrence brought on by myocardial ischemia in which there is myocardial deterioration or necrosis. Because repairing this damaged myocardium is challenging, researchers have looked into a new stem cell-based heart repair therapy. Mesenchymal stem cells (MSCs) are among the most frequently used cell type for regenerative medicine. MSCs derived from bone marrow (BM-MSCs) are a good choice for cell therapy because they are easy to acquire, have multilineage potential, and have an immunologic advantage. The findings from animal studies support the notion that BM-MSCs have anti-inflammatory, antioxidant, immunomodulatory, anti-apoptotic, and anti-fibrotic effects in cardiovascular disease. These effects significantly reduce cardiomyocyte apoptosis and remodelling effects, which help to improve cardiac function in post-infarction heart failure. In order to determine the potential of stem cell-based therapy for the treatment of MI, a number of clinical trials have been carried out to date. These clinical studies demonstrated that patients with MI who received stem cell therapy had a good safety profile and improved cardiac function. Therefore, the aim of the present study to review the role of MSCs therapy on management of acute myocardial infarction.

Keywords:*Acute Myocardial Infarction; Mesenchymal Stem Cell Therapy*

Introduction

Myocardial infarction (MI) is a clinical event induced by myocardial ischemia in which myocardial damage or necrosis is present **[1]**. The etiology of acute myocardial infarction is the imbalance between coronary blood flow and the oxygen demand that occur with a markedly increase in cardiac work or diminished blood flow, the available blood and oxygen become not enough resulting in cardiac cell ischemia**[2].** Apoptosis and necrosis of cardiomyocytes in the infarcted heart are heavily influenced by mitochondrial alterations. Mitochondrial DNA (mtDNA) is more susceptible to oxidative attack than nuclear DNA, and the mitochondria

in response to hypoxia or oxidative stress change its metabolic pathways which alters cellular protein and enzymes functions. This poorly functioning mitochondrion cannot be repaired especially with ongoing hypoxia and ROS, so the mitochondrial death pathway is activated, and the cardiomyocyte apoptosis or necrosis program is activated to eliminate the injured cells **[3].** Due to the difficulty in restoring this injured myocardium, researchers have investigated a new stem cell-based heart repair therapy **[4]**. MSCs derived from bone marrow are a good choice for cell therapy because they are easy to acquire, have multilineage potential, and have an immunologic advantage **[5].** The results obtained from animal studies are confirming the anti-inflammatory, antioxidant immunomodulatory, anti-apoptotic, and anti-fibrotic effects of BM-MSCs in cardiovascular disease that markedly result in decreasing cardiomyocyte apoptosis and decrease remodeling effects that participate in improving cardiac function in post-infarction heart failure **[6].** To date, several clinical trials have been conducted to explore the potential of stem cell-based therapy in the treatment of MI. These clinical investigations have shown that individuals with MI treated with stem cells therapy had a favorable safety profile and increased heart function [7].

Current Management and limitation:

Because the benefits of early reperfusion therapy are best when it is administered soon after the beginning of symptoms following hospital admission. suspected patients with MI usually start therapeutic measures like aspirin, beta blockers, and antithrombotic medication at the same time with diagnostic tests like ECG and serum biomarkers. when MI is diagnosed, the main therapeutic option is the early reperfusion therapy for blocked coronary arteries, reperfusion can be achieved through mechanical or biochemical methods, including primary percutaneous coronary intervention (PPCI), coronary artery bypass graft, or angioplasty **[8]**

There is, however, a very narrow treatment window for preventing myocardial necrosis, typically 3 to 6 hours after MI onset, the success of reperfusion therapy and the degree of saved myocardium by reperfusion is markedly declined, and 12 hours after MI, the therapeutic role of reperfusion is limited, so cardiologists believe that "Time is myocardium"**[9].**

Pharmacological treatments including antiplatelet agents, beta blockers, angiotensin converting enzyme inhibitors (ACE inhibitor) and angiotensin II receptor blockers and statin are also important **[10].** Taken together, recent progress in the management of patients with an acute MI has led to a decline morbidity and mortality. Nevertheless, survivors of an MI still face a substantial excess risk of mortality as well as further cardiovascular events including angina, recurrent MI and heart failure **[11].**

The critical limit of current standard treatments for MI is that the damaged cardiac muscles and vessels could not be regenerated. The heart has been considered as a static organ and the capacity of the hearts to regenerate functional myocardium is extremely limited or absent. Not surprisingly, it has been thought that the prognosis of MI is poor while the long-term survival rate of infarct patients was even worse than that of cancer patients. Therefore, the demand for the regeneration of cardiac muscle and vessel is tremendous **[12]**

But, on the other hand, other studies reported that there are some obstacles to using stem cells as reparative therapy as, MSCs may lose biological capabilities after being isolated and cultured in vitro as the surrounding microenvironments are changed and not the same as the environment in vivo **[13].**

Or the inadequate engraftment of donor MSCs into the injured myocardium restricts their therapy reparative potential in AMI **[13].**

So MSC Preconditioning, genetic modification, and modifying MSC culture conditions are all important strategies for manipulation these obstacles, thus increasing MSC function in vitro and in vivo, and all of these processes will help increase MSC transplantation effectiveness in tissue engineering and regenerative medicine **[14].**

Stem cells as a possible therapy for the management of MI

MSCs that have been locally grafted or systematically injected have been employed for cellular therapy for a range of conditions and diseases, they have been used in many regenerative medicine, like treating

neurological condition, kidney injury, lung injury, and diabetes melliuts, including regenerative treatments to improve cardiomyocyte repair in many cardiovascular pathological conditions **[15]**

After MI, cardiac cell death and function loss with resulting fibrosis and scar formation causing ventricular remodeling eventually leads to heart failure. despite clinical advanced surgical techniques, drugs, and surgical treatments that can only reduce symptoms and slow the progression of chronic heart disease, they can't save the function of heart cells that have died. So, studies search for a new way to treat heart failure after MI. although heart transplantation stays the definitive cure for heart failure patients, this has several limitations as donor organs are limited, and it is an expensive operation. So, stem cells became a hopeful cure for heart disease a decade ago **[16].**

MSCs found to play a significant therapeutic role in CVD due to their unique characteristics and therapeutic role to control the inflammatory cascade, anti-oxidant capacity, and maintaining cells hemostasis by tight control of the apoptotic mechanism thus preventing excessive tissue degradation and improve healing **[17].**

- **Mechanism of action:**

1- Differentiation of MSCs into cardiomyocyte-like cells

The regenerative capacity of cardiac tissue is very limited and insufficient to compensate for the substantial loss of heart muscle caused by a devastating myocardial infarction or other cardiac disorders. Se regenerative therapy is a novel way to regenerate the damaged organ, MSCs have the potential to transdifferentiate into cardiomyocyte-like cells with characteristic zonal distribution in myocardial tissue that resemble cardiac myocytes if an appropriate cardiac environment is provided. Many researchers are trying to magnify this property invitro and in vivo **[18].** MSCs differentiate into cardiomyocytes and blood vessel elements that express specific cardiac markers, which integrate into the host myocardium, form gap junctions, and contribute to the restoration of cardiac function and tissue perfusion, resulting in a reduction in infarct size and reverse remodeling **[19],** In addition, when MSCs treated with exogenous Jagged1, this activates the Notch1 signaling pathway (pathway involved in cell proliferation and differentiation) thus led the stem cell to differentiate into cardiomyocyte-like cells **[20].**

Activating the Wnt/β-catenin signaling pathway within BM-MSC leads to an increase in the overexpression of miRNA1-2 in the MSCs, thus increasing the cell differentiation into cardiomyocyte-like cells with an increase in several genes that are involved in the reduction of cytotoxicity **[21]**

2-Immunomodulatory properties of MSCs

In both innate and acquired immunity, MSCs have been discovered to control the inflammatory response by many mechanisms as inhibiting white blood cells and neutrophile recruitment with starting the anti-inflammatory response …..

Tissue injury as pathogenesis occurs when inflammatory cells, particularly monocytes, migrate into the injured tissue as what happens after MI, these cells differentiate into macrophages, which emit a variety of inflammatory mediators such as cytokines, chemokines, and growth factors. Macrophages' primary role is to phagocyte the dead cardiac cells and neutrophils. The inflammatory mediator will activate macrophages into different types of cells with different immune functions. These cells are primarily M1 macrophages, which secrete interferon, interleukin-23, and tumor necrosis factor and enhance the inflammatory response, and M2 macrophages, which are primarily activated by T-helper (Th2-related cytokines) and boost cell proliferation and angiogenesis **[22].**

[23]found that after MSC transplantation to a rat model of MI, there is a significant reduction in the level of TNF-α, IL-1, and IL-6, and there is a marked reduction of cardiomyocyte apoptosis, which lead to a marked improvement in cardiac performance.

Also, the application of MSCs to a rat model of MI had been found to decrease the levels of CD68- positive inflammatory cells and monocyte chemotactic protein-1 (MCP-1) in cardiac cells, with also improving cardiac function**.** Additionally, the prepared medium obtained from MSCs found to decrease damage to the cardiomyocytes mediated by MCP-1**[24].**

Humoral factors in bone marrow stromal cells (BM-MSCs) prevent antigen-specific immunoglobulin M and immunoglobulin G1 from being released, preventing B-cell terminal activation **[25].** Also **[26]**show that the severity of myocarditis decreased after transplantation of MSCs with also a decrease in the number of proinflammatory monocytes.

[27] demonstrated that MSCs are shown to reduce the proliferation of T cells when cultured together, by upregulating indolamine-pyrrole 2-3-dioxygenaseleading to the consumption of tryptophan and the accumulation of its metabolites, thus decreasing T cell proliferation.

Also, NKp30, NKp44, and NKG2D receptors are inactivated on the surface of natural killer (NK) cells when cultured with MSCs, resulting eventually to inactivate NK **[28],** also **[29]**showed that MSCs decreased the surface expression of 2B4 and CD132 in NK cells inactivating them.

3-Antifibrotic effect of MSCs

Fibrosis of the heart muscle is known as myocardial fibrosis. Excess deposition of collagen generating ventricular stiffness with scar development in the myocardium leads to decreased diastolic and systolic function of the heart and that is the most common pathological event that occurs after MI **[30].**

fibroblasts help the macrophage to remove necrotic cardiomyocytes from the infarct location, resulting in ventricular remodeling, which can lead to arrhythmias and death **[31].**

MSCs was found to play a key role in reducing fibrosis through its paracrine mechanism by secreting wide range of cytokines that regulates matrix metalloproteinase, which blocks fibroblast activation and reduces extracellular matrix deposition. BM-MSCs secrete HGF, a potent fibrosis inhibitor that is thought to be the most important factor responsible for MSCs' antifibrotic effect in vitro **([32].**

MSCs also improves left ventricular remodeling and function in a mouse MI model by suppressing miR-155-mediated profibrotic signaling and hence reducing fibrosis through direct cell contact **[33].**

MSCs that overexpress insulin-like growth factor 1 (IGF-1) was found to be effective in reducing the fibrotic area in cases of myocarditis that occur after Trypanosoma cruzi-infected mice **[34].**

Furthermore, MSCs that overexpress miR133 can reduce fibrosis in MI by inhibiting the Snail 1 signaling pathway, which is the main regulator of epithelial-to-mesenchymal transformation (EMT), and induced fibrogenesis process that occurs usually in the developmental and disease processes **[35].**

4-Neovascularization capacity of MSCs:

The most issue that occurs with ischemia in CVD and remains unresolved is the inadequate vessel growth, as the basis of tissue repair is the growth of new blood vessels **[36].** MSCs have shown in many studies the ability in forming new blood vessels and stimulating the growth of vascular networks by endothelial cells **([37].**

On the surfaces of native, non-cultured perivascular cells, MSC markers have been found. This suggests that the blood vessel wall has a reservoir of progenitor cells that may be necessary for the development of adult stem cells **([38].**

Also, in rat models of MI, a group of in vivo researchers discovered that some transplanted BM-MSCs differentiate into endothelial cells, forming a new microvascular network and improving cardiac function **[39]**.However, some researchers think that BMSC transplantation causes angiogenesis and heart healing in MI models mostly by indirect paracrine signaling, primarily through the release of angiogenesis factors that stimulate new blood formation [40]**.**

In also MI model, by assessing the healing effects of BM-MSCs transplantation only, pure VEGF treatment, or combined VEGF treatment and BM-MSCs transplantation in rats, the results showed that the combination of VEGF treatment and BMSC transplantation had the best result in greatly increasing vascular density (80%) and decreasing collagen deposition (33%) within the myocardium with heart function improvement **[41]**. Also **[42]**showed that endogenous cardiac MSC secretes exosomes that increase capillary density and cardiomyocyte proliferation.

In addition**,** Exosomes produced from MSCs that had been cultured under hypoxic circumstances, can promote angiogenesis in-vitro model with capillary-like tube development **[43].**

5-Anti oxidant capacity of stem cells:

MSC can do direct scavenging of free radicals, increasing endogenous antioxidant defenses, immunomodulation via reactive oxygen species suppression, modifying mitochondrial bioenergetics, and transferring functioning mitochondria to damaged cells. MSCs can mediate their anti-inflammatory and cytoprotective capabilities via modifying the redox environment and oxidative stress. As MSC therapy has been shown to have antioxidant effects in a variety of disease models, including diabetic kidney, retina, sensory neurons, brain, and bone formation; chemotherapy or radiation-induced injury to the lungs, gonads, aorta, and brain; ischemic injury to the brain, heart, kidney, and liver; and traumatic injury to the spine and testis, cognitive disorders, gastrointestinal inflammation, septic injuries, and aging **[44].**

MSCs found to secrete all isoforms of SOD in many diseases3+ asteract hepatic ischemia reperfusion injury, hepatic ischemia reperfusion injury, arthritis, hepatotoxicity, and ovarian autografts **[45, 46].**

Route of stem cell delivery in AMI:

a. **Intracoronary infusion:** This method is the same that performed in coronary angioplasty. Stem cells are administered under pressure through a balloon catheter while antegrade coronary blood flow is blocked. The advantage of intracoronary administration is that cells are directly injected into locations with good blood supply, which are rich in nutrients and oxygen, both of which are required for cell viability **[47]**.

b. **Intravenous (peripheral) infusion:** It is the simplest and least invasive method but require the largest cell number to be transplanted to overcome trapping of the cells in the microvasculature of the lungs, liver and lymphoid tissues **([48],** also it is more reliable in acute tissue injury as MI or acute renal failure as it relay on physiological homing signals released at tissue injury and act as chemoattractant for stem cells **[49].**

c. **Intramyocardial injection:** is a usually more effective in chronic ischemic cardiomyopathy as chronically infarcted myocardium are unlikely to release chemoattractant signals ,so it may be more useful to use intramyocardial injection to deliver the cells to the target area **[50].**

- **Distribution of MSCs after Systemic Infusion:**

In response to tissue damage or apoptosis, the tissues chemokines, cytokines, and growth factors are released primarily to recruit the endogenous resident stem cells for regeneration and repair, the same factors act as migratory signals for stem cells given systemically or locally**[51].** Inside the microvasculature of certain organs, interaction between chemokines (e.g. SDF-1), chemokine receptors, intracellular signaling, adhesion molecules (selectins and integrins), and proteases within the stem cell surface, allowing the cells to interact with the endothelium. Stem cells then attach to the endothelium layer and transmigrate into these tissues **([52].**

Following transfusion, researches utilizing various methods for tracking MSCs, has found an initial concentration of MSCs in the lung first, after which most MSCs travel gradually to wounded areas such as the liver, spleen, kidney, or bone marrow **[53].**

Statins as a possible therapy during the management of MI

Statins are lipid-lowering medications that are commonly used to lower the risk of cardiovascular events. In the liver, they inhibit the action of hydroxymethylglutaryl (HMG) CoA reductase enzyme, which is the limiting step in cholesterol synthesis in the liver, thus leading to inhibit the formation of low-density lipoprotein (LDL) cholesterol. Statins also reduce triglycerides synthesis but increase high-density lipoprotein (HDL). the most used statins are Lovastatin [54], simvastatin (SIM), atorvastatin (ATV), rosuvastatin (RSV), pitavastatin (PTV), fluvastatin (FLV), pravastatin (PRA), and mevastatin (MEV) **[55].**

Statins have important medicinal benefits that are unrelated to their cholesterol-lowering action, it is called pleiotropic effects. these include its Anti-apoptotic, antioxidant, anti-inflammatory, immunological, neuroprotective, and regenerative properties **[56].**

Statin was found to affect the function of many transcription factors, this is thought to be through its action as an inhibitor of HMG CoA reductase, an enzyme converting HMG CoA to mevalonate. Stoppage of mevalonate production blocks the mevalonate pathway, which is necessary for prenylation (that serves as the first critical step in protein–protein interactions) so mevalonate pathway inhibition will affect certain protein binding and interaction, thus leads eventually affecting gene expression of many pleiotropic proteins, as statin promotes MSC differentiation into osteoclast through the inhibition of protein isoprenylation.

There are mitogen activated protein kinase (MAPK) cascades that modulate a wide range of cellular functions such as proliferation, differentiation, apoptosis, and stress responses, under both normal and pathological conditions. Statin upregulates several genes involved in that pathway thus increasing the differentiation and survival of stem cells **[57].**

Also, mevalonate metabolic pathway interruption was found to cause changes in many pathways that are involved in autophagy and cell death, especially after exposure to oxidative stress, which demonstrate the possible effect of statin **[58].**

So, statins have been used recently by many researchers to demonstrate their effectiveness in increase the efficacy of stem cells. Statins have been shown to impact the biology and function of stem and progenitor cells in animals, such as enhancing cell mobilization, proliferation, and regeneration capacity **([59].**

Atorvastatin was found to inhibit cell death and increase endothelial progenitor cell proliferation via modulating the expression of cell cycle genes, including overexpression of cyclins and downregulation of the cell cycle inhibitor p27Kip. That is responsible for controlling the cell cycle **[60].**

It has been discovered that simvastatin treatment increased the expression of endothelial-specific genes and proteins in rat bone marrow MSCs (BMSCs), including von Willebrand factor, CD31, vascular endothelial-cadherin (VE-cadherin), vascular endothelial growth factor receptor-2 (VEGFR2, Flk-1), and VEGF receptor-1 (VEGFR-1, Flt-1). Simvastatin also promoted the production of capillary tube-like structures in BMSCs **[61].**

CONCLUSION:

Effectively MSCs to the target site, which is made possible in part by the use of statins, is one of the best ways to boost their therapeutic significance.

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