Narrative Review Article

Current Constraints and Possibilities Using Mesenchymal Stem Cells for Regenerating Cardiac Tissues in Patients with Myocardial Infarction

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ABSTRACT

Myocardial Infarction (also commonly known as Heart attack or Cardiac arrest) is a predominant cause of mortality and hospitalization worldwide. Current treatments such as use of stents and open-heart surgery carry risks and have their own limitations. However, the use of regenerative medicine offers promising potential and effective treatment therapies using mesenchymal stem cells (MSCs) due to their potent properties and self-renewal capabilities. This literature review does a comprehensive assessment of the studies, research and clinical trials involving MSCs to find a more effective and durable cure for myocardial infarction. The studies and clinical trials conducted worldwide using both allogenic and autologous MSCs show positive signs of myocardium tissue regeneration and improvement of cardiac functions. Positive outcomes carried over a decade of preclinical and clinical trials using MSC therapies to treat myocardial infarction are very promising offering significant potential for cure. Further research and clinical trials are required to standardize protocols for administration of MSCs and provide cohesive guidance on use of optimal dosing, administration routes, and frequency to ensure safety and efficacy of this treatment.

Keywords: Myocardial Infarctions; Stem cells; Stem Cell therapy; Regenerative Medicine; Mesenchymal Stem Cell; Coronary Arteries

INTRODUCTION

Myocardial Infarction is the leading cause of death worldwide and approximately 7 million people are affected by acute myocardial infarction yearly (1). Myocardial Infarctions can be distinguished into 5 different types. Type 1 is due to formation of atherosclerotic plaque in the coronary artery and subsequent rupture leading to thrombosis and vessel occlusion (blood clot). Type 2 is due to insufficient supply of oxygen to cardiomyocytes (heart muscles). Type 3 is due to sudden cardiac death with no biomarkers available for measurements. Type 4 is due to complications during or after performing percutaneous coronary intervention procedure and Type 5 is due to complications after performing coronary artery bypass grafting (CABG) surgery (2).

Current myocardial infarction treatments include percutaneous coronary intervention with bare-metal or drug-eluting stents (DES) (3) and coronary artery bypass grafting (CABG). Despite advances, DES can fail due to thrombosis, fracture, or recoil (4), and

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with failure rates of 15–20% (5), new options such as regenerative medicine are being explored.

Regenerative medicine involves use of different types of stem cells. Stem cells can be broadly classified into embryonic and adult stem cells based on the source of origin. They can be further classified based on their differentiation property i.e. totipotent, pluripotent, multipotent, oligopotent and unipotent (6). MSCs are adult stem cells and multipotent with potential for treating myocardial infarction conditions due to their tissue repair and regeneration capabilities. Stem cells can be sourced from the same person (autologous) or from a donor (allogeneic) (7).

This research paper provides insights into the use of stem cells to treat ruptured and damaged coronary arteries and significant breakthroughs in treatment of myocardial infarction cases. Also, the paper covers reasons for myocardial infarctions, current treatments and their limitations, future treatments and MSC therapies, their administration routes and some challenges.

PATHOPHYSIOLOGY AND CONVENTIONAL TREATMENTS FOR MYOCARDIAL INFARCTION

Myocytes are muscle cells which make up the heart's myocardium (heart muscle) and are responsible for the heart's ability to contract and pump blood. Loss of myocytes can result in a myocardial infarction (8). Additionally, cardiac fibrosis characterized by the buildup of scar tissues in the heart's muscle can also lead to myocardial infarction. This excessive extracellular matrix protein builds up impacts heart stiffness, contractility and electrical conduction (9). The loss of myocyte is an irreversible process which leads to scar formation in the heart muscle and cardiac fibrosis eventually leading to heart dysfunction and failure.

Myocardial infarction is commonly treated with percutaneous coronary intervention —a minimally invasive procedure that restores coronary blood flow using stents. Each year, approximately 600,000 stents are implanted in the United States (10). Stent technology has evolved from bare-metal stents (BMS), made of stainless steel or cobalt/platinum chromium, to drug-eluting stents (DES), which use a metal scaffold coated with a drug-polymer to reduce restenosis (11).

Despite improved restenosis rates, DES are associated with life-threatening late Stent Thrombosis. Stent Thrombosis occurs in ~1% of high-risk patients (e.g., multi-vessel interventions) and carries a mortality rate of 22.2% (12). Acute stent thrombosis remains a serious complication despite advanced procedural techniques and dual antiplatelet therapy (13). The underlying triggers of coronary artery disease and its progression are still not fully understood but are thought to involve both genetic and environmental factors (14).

REGENERATIVE THERAPIES USING MSCS

Due to the high rate of myocardial infarction occurrences and mortalities there has been a strong need and interest to research and study the use of regenerative medicine. It offers promising potential for treatment using MSCs to repair and regenerate damaged heart tissues. MSCs multipotent property promotes biological healing in various ways which includes paracrine factors, cell-to-cell contact and immunomodulation.

Paracrine factor is characterized by MSC secreting different bioactive factors like cytokines, chemokines, hormones, growth factors, and miRNAs. These molecules are extremely potent and protect injured tissues and have properties of endogenous tissue repair and regeneration mechanism and immune-mediated phagocytosis. MSCs may x`show similarities from various sources, however there are substantial differences in their paracrine signaling markers. MSCs obtained from embryonic stem cells (ESC) seem to be a better source for neurogenic-related processes than bone marrow stem cells, which significantly slow down angiogenesis in the damaged myocardium. Another finding from clinical trials of patients with heart diseases shows that allogeneic MSCs are more effective in improving endothelial function than autologous MSCs (15).

Cell-to-Cell Contact (also known as heterocellular contact) occurs due to formation of gap junctions or tunneling nanotubes with adjacent or nearby cells. Tunneling nanotubes, which are thin membranous channels that connect cells, allow transfer of larger molecules and cell organelles. MSCs need to be in close proximity to the host cells to enable transfer of small molecules between them (15).

Once MSCs are administered to the ruptured heart tissues there are many ways as to how they work with the damaged cell. These stem cells either work directly in contact with the damaged cells or they do so through certain molecules and microvesicles. The molecules have mechanisms of immune regulation which helps regenerate the cardiac tissue that was damaged. A small

proportion (~0.07%) of bone marrow MSCs in vitro were found to generate cardiomyocyte-like cells indicating that MSCs may not always generate cardiomyocytes frequently enough for cardiac repair (16).

Immunomodulation process alerts or modifies the immune system and can result in boosting or suppressing the body's immune response. MSCs are able to influence both adaptive and innate immune responses. The immune system interacts with a variety of cytotoxic T cells, helper T cells, and natural killer cells. These cells help apoptosis (programmed cell death) from occurring. The direct contact (``heart as it increases the oxidative damage and increases cell death in the smooth muscle cells.

DELIVERY ROUTES FOR MSCS IN CARDIAC REPAIR

MSCs can be administered using different routes as illustrated in Figure 1, such as intracoronary, intra-myocardial, and intravenous. Intracoronary administration route injects MSCs into the desired zone of myocardium. This intervention procedure uses the central lumen of a special balloon catheter fixed in the coronary artery. Once properly positioned, the MSCs can be released to the targeted zone of myocardium by one of the two ways - temporarily blocking coronary flow (minimizing rapid cell washout) or maintaining coronary flow. The MSCs released via the blood cells are distributed throughout the heart via the bloodstream, potentially reaching a wider area of damaged tissue. The clinical trials use either autologous or allogenic MSCs and show mixed results of improvement in Left Ventricular Ejection Fraction (LVEF), remission, mortality rate, procedural complications, etc. (17).

While intra-myocardial injection involves direct delivery of MSCs into the damaged myocardial zone. This intervention is usually carried out as an adjunct procedure during coronary artery bypass grafting (CABG) or using a catheter-based transendocardial injection. Several clinical trials using an intramyocardial delivery approach have been conducted to treat ischemic heart failure or ischemic cardiomyopathy. The trials used allogeneic or autologous MSCs with varying amounts injected directly into the damaged zone and it showed good potential due to improvements seen in the markers of heart function such as, LVEF, Left Ventricular End Diastolic Volume, as well as in scar size and tissue perfusion (17).

In case of intravenous administration, MSCs are administered intravenously using an intravenous injection prepared by suspending MSCs in a sterile solution and typically injected into a vein in the arm or hand. Since this approach injects a solution containing MSCs into the body's bloodstream through a vein, the MSCs are dispersed to all parts of the body instead of only the affected part in the heart. Hence this delivery approach is less efficient when compared to other delivery options discussed in this research paper (17).

Also, trans-endocardial injection administers MSC cells directly into the affected area of the heart using a needle tipped catheter inserted from the peripheral artery into the endocardium and led across the aortic valve. Studies suggest that this approach is the most efficient and maintains the highest efficacy of injected MSC cells thereby aiding in damaged tissue repair and regeneration of the myocardium (17).

Finally, trans-endocardial injection of MSCs is more efficient than direct intra-myocardial and intracoronary injections for patients with chronic dilated cardiomyopathy and acute myocardial infarction.

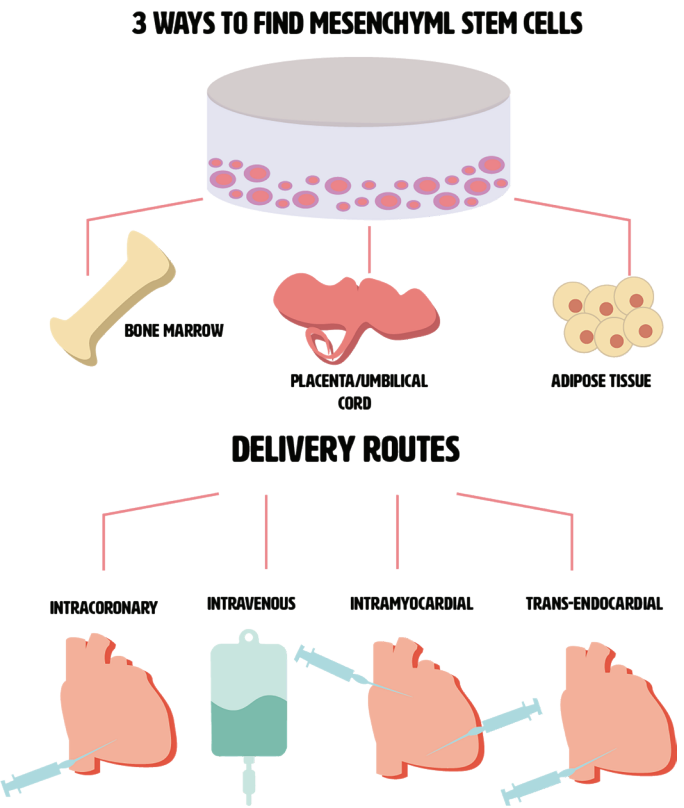

Figure 1. Demonstrates the various ways in which MSCs can be sourced and once sourced how they can administered using various delivery routes.

Overall, the administration route plays a very important role on the effectiveness and efficacy of treatment in case of both chronic and acute myocardial infarction (17).

CURRENT CHALLENGES WITH MSC THERAPIES

The clinical trials website lists and tracks a number of trials conducted worldwide on MSC therapy (18). Review of the trials surface inconsistency and variability in the efficacy of MSC therapies which may be attributed to absence of standardized protocols and challenges related to variable biological behavior. The absence of standardized protocols for MSC therapies is a significant challenge, stemming from the inherent heterogeneity of donor and tissue sources, coupled with discrepancies in cell harvesting, processing, expansion, and formulation. This variability is further compounded by the inadequate availability of standardized assays for measuring potency, quality control, and determining release criteria.

Heterogeneity of donor and tissue-source caused due to MSCs derived from different donors or tissue sources, (bone marrow, adipose, umbilical cord, dental pulp etc.), exhibit different phenotypic and functional properties thereby impacting their therapeutic performance (19). The inconsistent functional properties make the interpretation of its clinical efficacy difficult to assess and compare the results of various studies (20). Whereas discrepancies in cell harvesting, processing, expansion, and formulation is caused due to varying protocols for isolation, culture media, passage strategy, cryopreservation, and thawing can lead to substantial alterations in cell viability, potency, gene expression, and immunomodulatory capability (21). Moreover inadequate standardized assay for potency, quality control, and release criteria are caused due to absence of agreed-upon potency or functional assays, non-standardized readouts of T-cell suppression, secretome assays etc.making it challenging to compare the outcomes (22).

In addition the biological challenges arise primarily from immunological incompatibility. Under inflammatory in-vivo conditions, MSCs may upregulate major histocompatibility complex (MHC) class II and costimulatory molecules, provoking host immune recognition and rejection and thereby reducing their survival and engraftment.

Overall absence of universal guidelines for use of MSC therapy to treat myocardial infarction makes it very challenging for wider clinical adoption.

CLINICAL TRIALS USING MSCS

MSCs have been investigated in clinical trials for over two decades covering over 1000 plus trials. Table 1 lists trials conducted in a clinical setting using different types of MSCs, patients health condition and frequency

Table 1. Clinical Trials using MSCs to treat Myocardial Infarction which captures trial size, treatment efficacy and any adverse outcomes

Stem Cell Type	Number of Patients	Treatment Efficacy	Adverse Events	References
WJ-MSCs	70 (single intervention = 20; repeated intervention = 20; control group = 25)	LVEF increase LVESD decrease	No Adverse Events Reported	26
WJ-MSCs	116 (WJ-MSC = 58 Placebo = 58)	LVEF increase LVESD decrease LVESV decrease	WJ-MSCs: Rehospitalization for heart failure: 1.7% Ectopic tissue formation: 1.7%	27
Cardiopoietic cells (conditioned MSCs)	271 (Cardiopoietic cells = 120 Control = 151)	The primary endpoint was neutral for the whole population Significant improvement in patients with an LVEDV of 200–370 mL	Cardiopoietic cells Any AE: 20.8% Any serious AE: 14.1% Death: 8.3% Control Any AE: 5.3% Any serious AE: 1.2% Death: 8.2%	28

AE - adverse event; AD-MSC—adipose-derived mesenchymal stem cell; WJ-MSCs—Wharton Jelly-derived mesenchymal stem cell; LVESV—left ventricular end-systolic volume; LVEDV—left ventricular end-diastolic volume.

of transplantation.

Starting with the initial trial, a single blind, randomized and multicenter trial which included 70 randomized patients, younger than 65 years with LVEF < 40%, who were treated using percutaneous coronary intervention and into their 3- 7 days of AMI treatment. These patients were administered single or repeated (after 10 days interval) intracoronary infusion of Wharton's Jelly-derived Mesenchymal Stem Cell (WJ-MSC) and sub-divided into 3 groups: n= 20 single intervention, n= 20 double intervention, n=25 control group. The primary endpoint was the 6-month LVEF improvement as per cardiac magnetic resonance (CMR) imaging. Before the trial, the mean baseline Ejection Fraction (EF) was ~ 40% in all three groups measured by CMR. By the end of the trial, while all patients experienced a rise in EF, however the most significant change was seen in the repeated intervention group. Single MSC transplantation (n = 20) improved the EF by 4.54 ± 2%, and repeated intervention (n = 20) did so by 7.45 ± 2% compared to the control group (n=25) when measured by CMR imaging (P < 0.001); when evaluated by echocardiography, these values were 6.71 ± 2.4 and 10.71 ± 2.5%, respectively (P < 0.001) (23).

The next multicenter trial involved 116 patients who experienced acute stent thrombosis-elevation myocardial infarction and were five to seven days after successful reperfusion therapy. The patients were randomly assigned and divided in two groups to receive an intracoronary infusion of WJ-MSCs or placebo into the infarct artery. The primary endpoint of safety was the incidence of adverse events within 18 months, which were monitored and quantified. The endpoint of efficacy included tracking changes in heart muscle viability and blood flow in the infarcted region over four months, and overall LVEF over 18 months. Viability and perfusion were assessed with F-18 FDG-PET and 99mTc-SPECT, and LVEF was measured with two-dimensional echocardiography. During 18 months of follow-up, adverse event rates and laboratory tests (including tumor, immune, and blood markers) were similar between groups. However, the WJ-MSC group showed greater improvement: myocardial viability and perfusion in the infarcted area increased more than with placebo (viability 6.9 ± 0.6% vs. 3.3 ± 0.7%, P < 0.0001; perfusion 7.1 ± 0.8% vs. 3.9 ± 0.6%, P = 0.002 at four months). At 18 months, LVEF rose by 7.8 ± 0.9% compared with 2.8 ± 1.2% in placebo (P = 0.001), and reduction in left ventricular end-systolic and end-diastolic volumes were also significantly greater in the WJ-MSC group (P = 0.0004 and P = 0.004, respectively) (24).

The last trial, a multinational, randomized, double-blind, sham-controlled trial was conducted at 39 hospitals. Of 484 patients with symptomatic ischemic heart failure on standard therapy, 348 underwent bone marrow harvest and MSC expansion. Those with >24 million expanded cells (315 patients) were randomized to receive endomyocardial cardiopoietic cell delivery using a retention-enhanced catheter (157) or a sham procedure (158). Procedures were completed in 271 patients (120 cell therapy, 151 sham). The primary efficacy endpoint was a hierarchical composite (mortality, worsening heart failure, quality of life, 6-minute walk distance, left ventricular end-systolic volume, and ejection fraction) at 39 weeks. The primary outcome was neutral (Mann–Whitney estimator 0.54; 95% CI 0.47–0.61; P = 0.27). Exploratory analysis showed a potential benefit in patients with baseline left ventricular end-diastolic volume 200–370 mL (Mann–Whitney estimator 0.61; 95% CI 0.52–0.70; P = 0.015). Serious adverse events were similar between groups; sudden or aborted cardiac death occurred in 1 (0.9%) cell-treated patient vs 9 (5.4%) sham patients (25).

The treatment efficacy from the trails shows a positive outcome in cardiac functions such as increasing LVEF and decreasing Left Ventricular End-Systolic Diameter (LVESD) with minimal adverse events.

ANALYSIS AND DISCUSSION

Myocardial Infarction is a leading cause of death worldwide with about ~0.1% of the world population affected by it. Current forms of treatments include use of stents and open-heart surgery. Use of stents have a high failure rate of ~15-/20% stent failure due to multiple reasons such as late stent thrombosis, fracture, compression, recoil or prolapse. Open heart surgery has a failure rate of up to 5% depending on the patient's health condition and type of procedure.

The loss of myocytes and scar formation leading to myocardial infarction has potential to be repaired using regenerative medicine with the use of MSC treatment. MSCs exhibit regenerative properties such as paracrine signaling, cell-to-cell contact, immunomodulation and migration/homing thereby aiding in myocardial tissue repair, improving cardiac functions and reducing inflammation. Paracrine signalling triggered by release of bioactive molecules such as cytokines, chemokines, growth factors, hormones and microRNA's promote tissue repair, reduce inflammation, support angiogenesis

and modulate immune responses thereby exerting a therapeutic effect. On the other hand, cell-to-cell contact of MSCs with nearby host cells forming gap junctions or tunneling nanotubes in form of thin channels that allow the transfer of small molecules, large proteins, and organelles supporting tissue repair. Additionally, the immunomodulation process can modify the immune system, either boosting or suppressing its activity. By influencing both innate and adaptive immunity, MSCs can thereby alter immune response to protect damaged tissues.

Given the intrinsic therapeutic potential of MSCs in regenerative medicine, it is imperative to address the protocol, and biological challenges that accompany their clinical use. Protocol challenges significantly limit the consistency and reliability of MSC therapies. Donor and tissue-source heterogeneity leads to variable cell properties and unpredictable clinical outcomes. Differences in harvesting, processing, and expansion methods alter cell viability and potency, while the absence of standardized potency and quality control assays makes study results difficult to compare. Biological challenges arising after the infusion due to immunological incompatibility, where inflammatory conditions can trigger host rejection and reduce cell survival, and poorly perfused ischemic tissue, where low oxygen, nutrient deprivation, and oxidative stress create a hostile environment causing high cell death and poor engraftment.

Clinical trials for treating myocardial infarction using MSC therapy show mixed but promising results. The trial using intracoronary WJ-MSC improved the LVEF especially with repeated MSC therapy interventions. Another trial using WJ-MSC experienced better myocardial viability, perfusion, and LVEF versus placebo without added adverse events. A large multinational endomyocardial MSC trial was overall neutral but suggested benefit in patients with moderate ventricular enlargement and showed fewer sudden deaths. Overall, MSC therapy appears safe and shows meaningful improvement in cardiac function (notably LVEF and remodeling) in several trials.

LIMITATIONS

Despite extensive preclinical evidence and encouraging results from clinical trials, the wider clinical adoption of MSC therapies face several persistent challenges.

Small Sample Sizes and Short Follow-Up: Clinical trials using MSC therapy remain in early-phase (Phase I/II) studies with a few hundred participants. The small sample size limits confidence in the trial's outcomes, making it difficult to detect moderate treatment effects or rare adverse events. Follow-up periods are less than one to two years making it insufficient to evaluate long-term functional benefit or delayed complications such as tumor formation or adverse remodeling.

Patient Heterogeneity: Trial population consists of different demographics of donors or tissue sources which may influence the potency of the sourced MSCs, making it difficult to pool or compare data across studies. Without clear patient selection criteria or stratification, results become inconsistent and hard to generalize.

Lack of Standardized Dosing and Delivery: Lack of consensus on the optimal dose, frequency, or administration route (intravenous, intracoronary, trans-endocardial, intra-myocardial) of MSCs makes it difficult to evaluate the efficacy of the trials. Trials use varying doses of MSCs ranging from a few million to hundreds of millions per dose, with either single or repeated administrations. Delivery methods differ in cell retention and safety, complicating comparison between trials and making it unclear which approach maximizes benefit.

Poor Cell Survival and Engraftment: Post MSC infusion, the cells may die or fail to engraft due to ischemia, oxidative stress, inflammation, and mechanical washout from the target tissue. This can result in transient benefit rather than long-term cell repair.

Long-Term Safety Risks: Due to short follow-up periods associated with most trials, long-term safety remains uncertain. Potential risks include arrhythmia, fibrosis, ectopic tissue formation, or rare tumorigenicity. Requires persistent study of potential genomic instability resulting from the MSC therapy.

Regulatory and Manufacturing Barriers: MSC are biological products that require strict Good Manufacturing Practice (GMP) production, consistency in batch production, potency testing, and traceability. Lack of universally accepted potency assay, and culture conditions, passage number, and cryopreservation can result in varied and inconsistent cell functions. The inconsistencies and gaps make regulatory approval challenging thereby limiting large-scale access.

CONCLUSION

The use of traditional treatment methods such as stents and open-heart surgery to improve damaged

myocytes and blocked blood vessels have reached their full potential and come with its own risks, failures and need for revascularization or reintervention.

Hence, a radical approach such as the use of regenerative medicine using MSCs to address the root causes of myocardial infarction, by orchestrating a biological healing process, has emerged as a promising area in cardiology, with high potential to bring many positive and beneficial outcomes. MSC-based therapies and tissue engineering hold significant potential to regenerate damaged myocardium and improve cardiac function. In the coming years, more research and well-designed clinical trials will be essential to standardize MSC therapy protocols and establish the safety and efficacy of these treatments.

CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article.

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