

Stem Cell Therapy in Heart Failure

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Abstract. Heart related disease are among leading causes of death worldwide, but there are few efficient treatments available. Stem cells possess excellent potential because therapeutic methods now enhance patient quality of life and address comorbidities. A growing corpus of research demonstrates that local cardiac stem cells are activated to rejuvenate the heart. Recent clinical trials seem to confirm that stem cell therapy for people with persistent heart failure is safe. Along with the most effective pharmacological and technology therapies, stem cell therapy may improve NT-proBNP, exercise tolerance, and cardiac function. However, following a severe heart injury, the heart's intrinsic ability to regenerate is insufficient to facilitate healing. With stem cell therapy, the risk of fatal heart attacks and strokes is reduced by 65%. In some heart failure patients, stem cell therapy has been found to lower the risk of heart attack and stroke. More research on the effectiveness and safety of these medications is needed before they can be used more frequently.

Keywords: Heart Disease, Myocardial Infarction, Stem Cells.

1. Introduction

A promising strategy for treating end-stage heart failure, a substantial cause of morbidity' and mortality, is stem cell-based therapy. A variety of sources can be used to obtain stem cells, and all have distinctive qualities that may affect how effective a treatment might be. Despite improvements in medical and catheter-based acute myocardial infarction therapy, the 1-year death rate for these individuals is still as high as 13%, and their 5-year prognosis for heart failure is still as great as 50%. A significant loss of cardiomyocytes is linked to this disorder since the left ventricle's systolic dysfunction is a significant prognostic factor and it has long been believed that the heart is a post-mitotic organ.

Adult stem cells are formed from totipotent' embryonic stem cells. Adult stem cells produce skeletal, cardiac, and hematological myoblasts. Giving adult somatic cells transcription factors allows us to get specialized cells back to their pluripotent state. Some cells can be directly injected into the area to engraft, grow, and replace damaged tissue cells. In order to urge the patient's cells to repair injured tissue, some cells secrete substances. Understanding the potency of each cell type is crucial for differentiating between therapeutic modalities of action. Multipotent adult stem cell, induced pluripotent, and embryonic stem cell lines are being used in the study of chronic HF. Success depends on stem cells' potential for revascularization, electromechanical link to beat in time with native cardiomyocytes, and ability to, engraft and survive in the host myocardium [1]. Cell therapy, according to Emerson C. Perin, M.D., Ph.D., is very effective in treating heart failure.

Findings reveal that recommendations may include combining stem cell therapy with conventional medicines, to treat persistent heart failure and lower inflammation. The consequences of injecting stem cells—also known as mesenchymal precursor cells—into the heart are investigated in this study. To add to the guideline-directed medical therapy (GDMT) for heart failure, researchers hypothesized that a single injection of healthy adult donor stem cells would reduce the number of times participants were hospitalized for heart failure-related incidents and prevent heart attacks, strokes, and death.

2. Heart failure

2.1. Heart failure's usual therapy

Shengmai is the name of the conventional treatment for heart failure. The brown pill that was given out was called the Shengmai wan. Its goals were to replenish and encourage the creation of bodily fluids while restoring a normal pulse. It has a flavor that is fragrant and just a little bit sour, bitter, and sweet. It is used in situations where there is a "qi and yin deficiency manifested by cardiac palpitations, dyspnea, hardly perceptible pulse, and spontaneous perspiration."

Traditional Chinese medicine appears to be beneficial in stabilizing the condition, enhancing cardiac function, and raising overall quality of life.

2.2. Ischemic heart failure and stem cell therapy

The first trial using stem cells to treat Ischemic, heart failure took place in 2002. Three significant randomized clinical trials with notable findings—A. STAMI, RE. PAIR-AMI, and TOP CARE-CH. D—released their findings in 2006.

Despite contradicting data regarding the advantages of stem cells on cardiac function, other clinical trials (STAR-HEAR.T, BOOST, SC. IPIO, ĆADUCEÚS, ŘEGEŇT, Focus HF, and others) demonstrate the benefits of stem cells on remodeling and function of ischemic myocardium. stem cell treatment for nonischemic heart failure Preclinical research suggest that stem cell therapy may be beneficial for persons with nonischemic heart failure. Compared to people with ischemic heart failure or healthy controls, these individuals' bone marrow stem cells' functional potential is less diminished. Additionally, circulating progenitor cells are more prevalent in dilated cardiomyopathy patients than in ischemic heart disease patients [2].

3. Stem cell

To engraft, specialize, and replace the damaged cells in a tissue, certain cells can be incorporated intravenously into the area. Certain cells release chemicals that encourage the person's cells to repair damaged tissue. To distinguish between variations in therapeutic modes of action, it is essential to comprehend the potency of each cell type. Chronic HF is being researched using multipotent adult stem cell, induced pluripotent, and lines of embryonic, stem cells.

Totipotent prenatal stem cells develop into adult stem cells. Hematological, cardiac, and skeletal myoblasts develop from adult stem, cells. We are able to encourage specialized cells to revert to their pluripotent state by providing gene transcription to mature somatic cells.

Success depends on stem cells' ability to engraft and survive in the host myocardium, as well as on their capacity for revascularization and electromechanical link to beat in time with native cardiomyocytes [1].

3.1. The Stem cell origins

A few helpful cells have been found by researchers. Adult stem cells' capacity for trans differentiation and self-renewal is lower than that of ESCs. Despite these restrictions, numerous adult stem cell populations have. been studied for use in regenerative cardiac surgery. Through a biopsy, it might be possible to obtain adult stem cells from postnatal blood, bone marrow, 'adipose tissue, skeletal muscle, and heart tissue.

3.2. Induced pluripotent stem cells from humans (iPSC)

mature cells that have been reprogrammed to become any form of human cell Similar to fetal cells, induced pluripotent stem cells beat irregularly and asynchronously. Human Ipsc' research attempts to mimic, the structure and function of the mature heart. In order to get synchronous, regular beating, it is required to convince induced pluripotent stem cells to act like adult cardiomyocytes.

Sarcomeres, mitochondria, transverse tubules, and sarcoplasmic reticulum are all closely packed together in adult ventricular myocytes to aid in contraction. The organism transitions from glycolytic to oxidative metabolism after birth, which causes the formation of this highly specialized excitation-contraction coupling machinery [3].

3.3. Hematopoietic and mesenchymal stem cells

Human bone marrow contains a wide range of cell types, including monocytes, fibroblasts, lymphocytes, adipocytes, osteoblasts, chondroblasts, and osteoclasts, as well as a small but diversified collection of undifferentiated cells. Undifferentiated stem cells include hematopoietic stem cells (HSC.s), which give rise to hem angioblasts and endothelial progenitor cells (EPCs), as well as non-hematopoietic mesenchymal precursor cells, which give rise to mesenchymal stem cells (MSCs). Cells of adults are separated from undifferentiated stem cells using density gradient centrifugation. Centrifugation produces mononuclear cells from bone marrow (BMMNCs). They are composed of committed cells at varying stages of development as well as undifferentiated HSC and MSC.

3.4. Cardiovascular stem cells (CSCs)

Beltrami found congenic, multipotent, and self-renewing cardiac stem cells in the myocardium (CSCs). In animal ischemia models, these cells differentiate into cardiomyocytes, smooth muscle cells, and endothelial cells. CSCs and their cell surface antigens Sca-1 and MDR1 are recognized by the stem cell antigen c-kit, but not hematopoietic cells. Migrating bone marrow progenitor cells exhibit c-kit but not KDR, CD31, or CD45. CSCs divide and differentiate in the cardiac myocardial niches [4].

Numerous diverse cell types with unique shapes and functions make up our body. All of these various cell types can develop from stem cells to become other, more specialized cell types. Additionally, Stem cells have the ability to regenerate themselves by dividing to create new stem cells. In general, there exist two types of stem cells [1].

3.5. The first is Adult stem cells

Adults' bone marrow, brains, and skin contain adult stem cells. Cells that have been lost due to injury or normal aging can be replaced by adult stem cells. For instance, hematopoietic stem cells in the bone marrow can develop into several types of blood cells that can circulate throughout the body. Bone marrow contains mesenchymal stem cells, which can develop into muscle, bone, or fat cells [5].

3.6. The second is Pluripotent stem cells

In the human body, pluripotent' stem cells can develop into any form of cell. These stem cells are present in the human embryonic development process in nature. The term "embryonic stem cells" refers to these [6,7]. Examples of pluripotent stem cells are ESCs and iPSCs (PSCs). All three embryonic germ layers are produced by these cells. Although the two cell types differ slightly in potency, the fundamental distinction is their origin. PSCs can be identified in a gradual and controlled manner. This enables researchers to generate cardiac progenitor cells (CPCs).

3.7. How does heart disease respond to stem cell therapy

The heart's tissue is harmed by heart disease. After this damage has been done, the heart frequently has a difficult time healing. Researchers have started to investigate utilizing stem cells to repair the harm caused by heart disease to assist in the restoration of heart function. The research is still in its early phases, though. Studies on this therapy have employed both adult stem cells and pluripotent stem cells. One of the adult stem cell types, mesenchymal stem cells, have yielded some of the most optimistic outcomes. Stem cells can be administered by doctors using a variety of techniques. These consist of: A heart-directed injection, Implantation within the coronary arteries, and IV rehydration solution [1,7].

Intramyocardial injection occurs during open-heart surgery, bypass surgery, or pacemaker implantation. A catheter injects cells into the coronary artery. It enters a groin blood artery and passes

through the heart. Intravenously, cells are injected into a vein. Most stem cells exit the body soon with these procedures. One possibility is growing them into a patch that goes directly to the wounded heart [8].

3.8. Improve SC homing, survival, and engraftment in damaged hearts

Intravenous, intracoronary, epicardial, endocardial, and coronary sinus injections are available for SC delivery. Intravenous injection is the least invasive method, but cells can be retained in the lungs. Intracoronary catheter injection is preferable after a MI. Trans endocardial administration with a catheter is trans endocardial and epicardial, both of which are invasive but effective. Coronary sinus delivery provides access to infarcted, and ischemic tissue, although it is not always possible. The heart was only partially accessed by intracoronary or bolus injections of the SCs used in clinical studies. 90% or more of the injected cells perish by apoptosis. Research is being done on alternative delivery techniques, like synthetic tissue constructed on a biodegradable scaffold. Although the patch can shrink and expand, its toxicity and thickness are disadvantages. There has only been a slight improvement in cardiac function. A recent study found that cardiomyocyte progenitor cells support cardio genesis and cardiomyocyte function. It is necessary to use safer and more efficient SC delivery materials.

3.9. Homing

Homing is the flow of SCs from endogenous and extracellular sources through blood or tissue in order to replace or restore damaged tissue. The cardiac cytokines SDF-1, MCP-3, and GRO-1 temporarily rise after a MI and act as chemoattractant for SCs. These mediators aid SC homing to infarcted tissue after an acute MI. Numerous homing factors emerge after a MI. SDF-1, the most well-studied homing factor, is only briefly expressed by injured cardiac tissue after a MI, but MCP-3 is only temporarily expressed. In preclinical investigations, genetically altering these components in delivered SCs enhanced SC homing. SDF-1 distribution to the heart, for instance through cell-based gene therapy gene transfer or protein-enhanced homing of SCs, led to revascularization and improved cardiac function. These, however, have not been studied in humans. It has been demonstrated in animal experiments that modifying cells to increase the expression, of SC homing factors or their receptors in cardiac tissue increases SC homing from the BM to the damaged heart [8].

3.10. Changes in stem cell after transplantation

Infections with fungi can also be problematic. A few helpful cells have been found by researchers. Adult stem cells' capacity for trans differentiation and self-renewal is lower than that of ESCs. Despite these restrictions, numerous adult stem cell populations have been studied for use in regenerative cardiac surgery. Adult stem cells may be isolated from postnatal blood, bone marrow, adipose tissue, skeletal muscle, and heart tissue through biopsy. Furthermore, infections that cause very modest symptoms in people with strong immune systems can nonetheless be quite dangerous. This is because white blood cells, which are the primary immune cells in charge of combating infections, are not created in sufficient quantities right away after the transplant. Until a certain blood count is reached, antibiotics are administered to prevent infections.

3.11. Changes in the heart after transplantation

After the transplant, the artery walls of your heart can thicken and stiffen, which would cause cardiac allograft vasculopathy. The inability of the heart to adequately pump blood can result in a heart attack, heart failure, heart arrhythmias, or sudden cardiac death. One of the main problems with transplantation is the incompatibility of the grafts with the recipient organs.

3.12. Is FDA approval granted for heart disease stem cell therapy?

The FDA did not approve stem cell treatment for cardiac disease. However, researchers are conducting clinical trials to examine stem cell therapy for heart disease. Only hematopoietic stem cell

transplants used to treat blood disorders, including leukemia and multiple myeloma, are currently approved by the FDA as stem cell-based medicines. A 2020 study on mice conducted by Trusted Source suggests that stem cell therapy may aid in the recovery of heart attack damage. The mice in the study underwent heart attack treatment using human stem cells.

Researchers discovered that a heart attack altered 450 different protein concentrations in the heart. However, in 65% of the proteins, stem cell treatment either entirely or partially undid these alterations. Stem cell therapy may help persons with heart failure have fewer significant cardiac events, according to data from studies that were presented at the American Heart Association's Scientific Sessions 2021 Trusted Source [1].

The study comprised 537 heart failure patients; 261 had stem cells injected into their hearts, while 276 underwent fake surgery. After that, participants were monitored for 30 months. Those who got the stem cells had a 65 percent lower rate of nonfatal heart attacks and strokes than the control group. However, there was no decrease in heart failure-related hospitalizations in the stem cell group. Another significant discovery was that class 2 heart failure patients who received stem cell therapy experienced an 80% reduction in cardiac mortality [5].

Heart failure, which causes more than 10% of annual fatalities, can be successfully treated with stem cell therapy. More study is still required to evaluate whether stem cell regeneration therapy is a useful treatment option and can be regularly used in clinical practice, despite more than ten years of research [6].

The limited and erratic benefits observed to date are one of the obstacles to the widespread use of stem cell therapy in patients with cardiovascular disease; numerous studies have demonstrated that poor cell retention and survival is a contributing factor. Implementing imaging to predict cell fate in clinical trials, delivering cells with adjuvant medicines, or embedding cells in tissue engineering constructions are methods to better comprehend and solve this constraint. Strategies to enhance cell survival and retention must be found in order for stem cell therapy to have meaningful therapeutic success in patients with cardiovascular disease [9].

Pluripotent stem cells (PSCs) have the ability to develop into any form of body cell, making them incredibly promising for drug development and regenerative therapy. The field is at a tipping point, with multiple clinical trials in people presently underway around the world. This follows more than three decades of research, delays caused by PSC tumorigenicity and inefficiencies in differentiation processes, as well as delays in the development of new technologies. These first-in-human trials are dominated by ocular disorders, and Phase I/all results reveal promising safety and potential efficacy evidence. Furthermore, the emergence of induced PSC (iPSC) technology, which enables the generation of a number of cell-based illness models from genetically predisposed persons, makes it possible for drug discovery [10].

3.13. Effectiveness in a clinical trial

Stem cells may restore cardiac tissue. In most studies, they reduced deaths and hospitalizations. Their hearts operated better, and their quality of life was better [11]. In a clinical trial, patients were randomly assigned to receive either their stem cells or donated cells. They were watched for mortality, heart attack, stroke, increasing heart failure, and severe arrhythmias. After 12 months, all patients were alive. Researchers wanted to know if a patient's immune system would reject allogeneic (donated) stem cells as foreign. 3.7% of patients who received donated cells responded. During cardiac catheterization, the cells were injected once. Mesenchymal stem cells are less likely to cause an immunological response and rejection than other stem cells. They rebuild muscle and minimize inflammation. Allogeneic and autologous patients were classified by stem cell dosage.

Twenty, 100, and 200 million cells were evaluated. The lowest dose of 20 million cells improved the heart's pumping function and reduced scar tissue, says Peter Johnston, M.D., a Johns Hopkins assistant professor of medicine and research co-author.

After stem cell therapy, several patients could walk farther in a six-minute test and reported enhanced quality of life in a 12month questionnaire.

Current medicines try to reduce the heart's strain and make patients feel better, but none can repair the heart or reverse heart attack damage. Greenblatt says the next steps are to compare the therapy with a placebo, determine if repeated doses improve outcomes, and examine the safety and effectiveness of stem cell therapy in patients with various forms of heart failure. Gerstenblith continues, "Our data promote continued development of allogeneic stem cell treatment." [6].

To restore ventricular function, coronary arteries are infused with bone marrow or umbilical cord blood stem cells or the heart is given an injection of these cells. Initially, it was believed that injured cardiomyocytes would be replaced by stem cells. Despite the possibility that stem cells could have paracrine effects that improve heart function, the subsequent study reveals that stem cells do not mature into cardiomyocytes that are functional. In 2019, Curfman There may be a tiny pool of stem cells in each self-renewing organ that can adjust to the normal turnover of tissue-specific cells. Insufficient tissue-specific cells cannot be produced after injury by this small pool of stem cells. This implies that bone marrow stem cells (BMSCs) are drawn from a central source and guided to the injured organ or tissue [12].

4. Regenerative therapy's rationale

Specific characteristics of stem cells allow for differentiation. multipotent, congenic, unipotent, and self-renewing Based on their anatomical make-up, functioning, cell surface indicators, transcription factors, and protein expression, stem cells can be divided into different groups. Stem cells are divided into groups according to their place of origin. In some aspects, adult stem cells are different from embryonic stem cells (ESCs).

By regenerating blood arteries and cardiomyocytes, stem cell therapy enhances heart function. Immature progenitor cells are infused into an infarct to promote the growth of new blood vessels and heart muscle cells. According to animal studies, the performance of the LV is improved along with a considerable regeneration of new blood vessels and cardiomyocytes. In 2018's human clinical trials, this goal was utterly missed. The complicated and poorly understood processes of angiogenesis and cardio genesis require certain physiologic conditions, growth factors, progenitor cell morphologies, and cell densities.

Human clinical trials were conducted after studying stem cells in animals to discover if they might repair damaged hearts' blood vessels and cardiac muscle. There have been studies on cell morphologies, cell-preparation methods, delivery mechanisms, injection volumes, postinfarct administration times, and the optimum milieu or clinical setting to deliver the cells.

Several grams of heart tissue, which contains 20 million cardiomyocytes per gram, are killed by a typical MI. Uncertainty exists over the precise number of stem cells needed to regenerate an infarct. Clinical trials using bone marrow cells have included more than 3000 patients from around the world (BMCs). Although bone marrow does not normally produce cardiomyocytes, the majority of "first-generation" clinical studies employed bone marrow-derived cells.

Clinical trials of the first generation were useful and provided a wealth of knowledge. Cell treatment is secure and efficient. Unknown is the bare minimum benefit to humans. Humans have not yet witnessed true cellular regeneration, such as the growth of new blood vessels or cardiomyocytes as a result of stem cell transplantation. Released cytokines, chemokines, and growth factors have paracrine effects that influence internal healing mechanisms, decrease apoptosis and fibrosis, and improve contractility. The aim of stem cell treatment is brought into focus through clinical learning [4].

4.1. Survival/engraftment

The fact that different conditions are required for SC survival and engraftment than for homing is likely the biggest barrier to SC therapy. After a MI, supporting and cardiomyocyte cells must be replaced. Infarcted tissue may lack environmental cues that guide SCs to the cardiomyocyte lineage or paracrine factor production. In order to enhance SC migration over injured cardiac tissue, extensive

research is being done. Proteases, adhesion molecules, and integrins control SC movement across injured cardiac tissue and alter the connective tissue environment to enhance engraftment.

Several proteases affect S, C migration and engraftment in cardiac tissue. MMP-2 and MMP-9, matrix metalloproteinases, are secreted as a result of SDF-1 and other stimuli. Proteolytic enzymes such as neutrophil elastase, cathepsin G, and MMP2/9 also impair cell migration by cleaving the N-terminal region of SDF-1 or CXCR4.90. They assist in SC recruitment and enlistment as well [12].

Integrins support SC adhesion, rolling, and migration through the endothelium. HSCs express integrins and other adhesion molecules. Blocking antibodies, to VLA-4 or VCAM-1, significantly inhibited the engraftment of transplanted HSCs. Because CD18 must be expressed by EPCs in order for it to interact with EC surface ICAM-1, a CD18 neutralizing antibody hinders SC engraftment after acute MI.

4.2. Several other strategies have been proposed

Some of the techniques employed include discovering natural mediators, genetically modifying SCs, controlling the differentiation of SCs into cardiomyocytes before translation, activating growth factors (FGF-2, IGF-1a), and antiapoptotic agents. (PDGF, Bcl-1, SDF-1, and p-Akt). A challenge for SC therapy is to increase the number of cells that travel to and remain in the injured heart area [13].

4.3. Advantages and disadvantages of stem cell therapy over traditional methods

Stem cell therapy, one of many types of cell therapy, has become a successful therapeutic strategy in this field. Multipotent stem cells and pluripotent stem cells are two types of stem cells. Utilizing each of them is linked to a variety of benefits and drawbacks, according to a vast number of researches. The use of stem cell therapy as a suitable curative method for the treatment of cardiovascular disorders was suggested by numerous lines of evidence. For evaluating the effectiveness of stem cell therapy in humans, numerous clinical trials have been conducted. Although stem cell therapy is connected with significant difficulties, it appears that overcoming these difficulties could help patients with cardiovascular disorders benefit from using stem cells as an efficient therapeutic option.

5. Conclusions

Heart failure treatment has benefited greatly from the use of stem cells. The recent enrollment of thousands of participants in clinical trials signifies the change from bench to bedside research. Clinical experiments that had only moderately positive or neutral outcomes have tempered the euphoria surrounding the healing potential of stem cells. It can be a sign of clinical trials still in their early stages and a lack of understanding regarding the best cell type, cell dose, delivery technique, patient characteristics, or endogenous heart repair pathways. To mediate recovery following severe heart injury, this innate ability for regeneration is not sufficient. In order to promote myocardial repair and regeneration, the wounded myocardium should be able to draw in extracardiac stem cells after suffering an injury. In the future, sizable randomized studies are required to confirm the preliminary results, delineate the underlying mechanisms, enhance stem cell homing, and enhance patient outcomes for chronic heart failure. The preliminary nature of clinical research may be reflected in the lack of understanding regarding the ideal cell type, cell dose, distribution strategy, patient characteristics, or endogenous heart repair mechanisms. However, this innate ability for regeneration is not sufficient to give healing after severe heart injury. Therefore, myocardial repair and regeneration would benefit from the wounded myocardium's capacity to attract extracardiac stem cells after injury. Large randomized studies will be required in the future to confirm the preliminary results, illuminate the underlying mechanisms, enhance stem cell homing, and enhance chronic heart failure patient outcomes.

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