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Review Article

TREATMENT OF MYOCARDIAL INFARCTION BY STEM CELL BASED THERAPY

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ABSTRACT:

Purpose: Recently myocardial infarction is one of the leading causes of death worldwide. Myocardial infarction leads to the serious consequences which cause increase in mortality and morbidity. In myocardial infarction there is permanent loss of cardiomyocytes which results an irreversible loss of cardiac function. Cardiac repair requires the replacement, restoration and regeneration of heart function. Conventional therapies such as revascularization, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) prevent the additional damage to heart muscle and also reduce the risk of future heart attack. However, there is need to develop a new therapy to improve the infracted area after the myocardial infarction and also to lower the mortality rate.

Approaches: The data were collected from various sources like journal articles, internet, textbooks, related materials in library and databases such as Pubmed, Science Direct, Springer, Google Scholar and so on.

Findings: Stem cell-based therapy is found to be a much more promising therapy when compared to other available therapies. Stem cells therapy shows significantly improved heart function after myocardial infarction, therefore decline into heart failure.

Conclusion: Recently the interest is stem cell based therapies which provide the potential benefit and have ability to improve the cardiac function. In this review, we highlight the benefits of stem cells in cardiac repair.

Key Words: *Stem Cells, Totipotent, Pluripotent, Multipotent, Myocardial Infarction.*

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INTRODUCTION

Myocardial infarction is a key component of the burden of cardiovascular disease and a major cause of morbidity and mortality[1]. The incidence of heart failure following myocardial infarction is around 32.4 million worldwide every year[2]. Myocardial infarction is a medical term related to heart attack which focuses on the myocardium (the heart muscle) and the changes that occur in it due to the clogging of the artery. The main change that occurs is necrosis (death) of myocardial tissue[3].

Most common treatment available for myocardial infarction involves the thrombolytic therapy – uses of the drug like antiplatelets, antithrombotic, vasodilator, ACE inhibitor etc. to break blood clots, reduction of cardiac workload and pain control[2].

Currently the standard treatment for myocardial infarction is revascularization therapy including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) and has become an intervention of choice[4]. The main aim of such procedure is to restore the blood flow to the ischaemic myocardial and limiting the size of infract. This reduces the early complications and improves the survival rates.

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Both of these treatments have limited result as they can only interrupt an ongoing process. However these treatments have low ability to improve cardiac function that has been deteriorated as a result of damage caused by myocardial infarction[3,5].

Based on these facts, myocardial infarction remains an important health issue. Hence there is a need to develop a new cost effective treatment for myocardial infarction[4].

Stem cell therapy has recently been developed which offers much more promising outcome when compared to other conventional therapy for myocardial infarction. Stem cells have remarkable potential to introduce new cell into damaged tissue in order to treat disease. They also have the ability to differentiate into cardiomyocytes. So the stem cell therapy can be considered as a highly prospective therapy in the treatment of myocardial infarction.

In this review, the future aspects and the uses of different types of stem cells for treatment of myocardial infarction has been discussed.

1. STEM CELLS

Stem cells are mother cells having three common defining characteristic[6]:

1. Self renewing : Ability to divide indefinitely and renew themselves through mitotic cell division.
2. Dynamic : Ability to differentiate into specialized cell types.
3. Clonogenic : Ability to produce an exact duplicate.

They are found in multicellular organisms and can become cell of the blood, heart, bone, skin, muscle, brain and many others[5]. According to their possibilities for differentiation, stem cells are categorized into :

Table 1: Different categories of Stem cells

S.NO	TYPES	WHAT IT CAN BE	EXAMPLE
1.	Totipotent cells (Toti: Whole)	Each cell can develop into new individual	Cell of embryo of 1-3 days
2.	Pluripotent cells (Pluri: Many)	Each cell can give rise to any type of cell in body (over 200)	Cell of blastocyst 5-14 days
3.	Multipotent cells (Multi: Several)	Cell differentiate and can form a number of tissue types	Fetal tissue, cord blood, adult cells

Based on the existence the stem cells, it can also be subdivided into:

1. **Embryonic stem cells:** The term "Embryonic stem cells" as they suggest are obtained from Embryo. These are the pluripotent stem cells derived from blastocyst (inner cell mass) in early stage implantation. Pluripotent stem cells have the potential to form 220 types of cell from three germ layers - ectoderm, mesoderm and endoderm, and have ability to give rise to most somatic cell linkage, including cardiomyocytes[7]. Embryonic stem cells are obtained from the blastocyst, until the embryo becomes a hollow ball of 150- 200 cells and is hardly visible to naked eye. It is an in vitro fertilization process, where the cells are obtained from the interior ball which causes the death of the embryo. During the process, the embryonic stem cells differentiate into myocytes with the structural and functional properties of cardiomyocytes which h host the cardiac cells[8]. The preclinical studies in several rodents suggest that when the embryonic stem cells are transplanted into infracted myocardium, embryonic stem cells derived cardio myocytes engraft and improve the myocardial performance in the rodent. Due to this, characteristic embryonic stem cell becomes an attractive cell sources for cell transplantation therapies for many diseases including myocardial repair[4]. But there is an ethical issue regarding the use of embryonic stem cells.

2. **Human umbilical cord cells:** Cord blood is a sample of blood relatively collected from a newborn baby's umbilical cord. Human umbilical cord blood cells are non invasive process which shows no risk to mother and baby. It's a richer source of haematopoietic (blood) stem cells and progenitor cells which are rarely found in bone marrow which act as a precursor to blood cells. Human umbilical cord blood cells are more potent than bone marrow cells. Primitive heamatopoietic stem cells derived from human umbilical cord blood cells have approximately 4% higher frequency of CD3+, CD38-, CD 133+ cell. These are easier to collect than bone marrow cells and stored in frozen until needed. It also shows the less immune rejection and complications than bone marrow such as Graft versus host disease. Additionally, they have myogenic and angiogenic properties which help to repair

muscle cell and endothelial cell, indicates that they would be used for repairing the damaged myocardium. In the various preclinical studies in animal model of acute myocardial infarction, the intra myocardium injection of human umbilical cord blood cells has shown significant reduction in the infract size. It shows the safety profile in successful clinical transplantation[9].

3. **Fetal cardiomyocytes:** Fetal cardiomyocytes are the multipotent cells which are able to replicate and differentiate into cardiac myocytes because these already have similar phenotype to cardiac cells. As the cells are cardiac in origin, these cells might have mechanical and electrophysiological compatible sources of cells for transplantation. Some of the preclinical studies in animal model have suggested improving Left Ventricle function. The use of immune suppression is necessary because the cells have the immunogenicity characteristic. But there are some ethical issues regarding the use of these cells[10].

4. **Induced pluripotent stem cells (IPSc):** Today, induced pluripotent cells are the most clinically practice topic in stem cell research. These are artificially produced by reprogramming the adult cells to embryonic cells with the introduction of different gene. Different genes used for induction of pluripotency are OCT3/4, SOX2, C-myc, K1f4, NANOG, LIN28, etc. Induced pluripotent stem cells are thought to be therapeutically equivalent to embryonic stem cells because these share many similar characteristic such as embryoid body formation, teratoma formation, potency and differentiability[7]. The induced pluripotent cells were produced by insertion of viruses with different genes. However, the induced pluripotent stem cells and embryonic stem cells have similar characteristics, are able to derive cardiac myocytes that can be subsequently used for studies in cardiac differentiation[10]. Hence it can be concluded that the induced pluripotent stem cells might be potential cell sources for the treatment of acute myocardial infarction[4]. These cells are produced from skin fibroblasts and hence do not create any ethical controversies.

5. **Resident cardiac stem cells:** The resident cardiac stem cells are also known as cardiogenic progenitor cell (CPCs). These cells are found in heart and are able to differentiate into different lineages like myocardial cells and vascular smooth muscle. These cells are comprised of less than 1% of cells in the heart. According to their expression of surface marker they are subclassified into c-kit, Scal-1 and Isl-1 cells. The resident cardiac stem cells are produced from the cardioblast during embryogenesis. c- kit cardiogenic stem cells have the capability for self renewal, clonogenicity and able to develop into more than one mature cell or tissue type[11]. These cells can differentiate into myogenic, vascular endothelial and smooth muscle lineages in vitro. It shows the beneficial effect in terms of reducing the infarct size and improving left ventricular function in animal model of myocardial infarction[12]. It serves as a new significant treatment opportunity for cardiac repair.

6. **Skeletal myoblasts:** Skeletal myoblasts, also termed as "Satellite Cells", normally reside between the basement membrane and sarcolemma of individual muscle fibers. These actually are unipotent (tissue committed) precursor cells[13]. These cells have capability to proliferate and are fused with other cells to repair damaged muscle tissue with response to injury. Skeletal myoblasts were the first cells to be studied in preclinical and clinical trial because of their autologous origin cell sources for regenerating the infracted myocardium. In preclinical studies the transplantation of skeletal myoblasts into the model of myocardial infarction showed the potency of replacing the cardiomyocyte loss and improving the cardiac function. A recent study also shows the significant reduction of myocardial fibrosis, apoptosis and the improvement of left ventricular ejection fraction against pacing induced canine heart failure model. Apart from benefits, some studies also suggest that there is the risk of ventricular arrhythmia. More studies should be carried out regarding the use of skeletal myoblasts cells[14].

7. **Bone marrow derived stem cells:** Bone marrow derived stem cells, are also known as

bone marrow progenitor cell (BMPCs). Bone marrow stem cells have received much attention after the landmark trial published by Orlic et al. which reveals that the bone marrow cells are able to renew the infracted myocardium in mouse model[10]. These cells are easily available, autologous origin, and able to multiply cells with the ability to transdifferentiate into cells of diverse phenotype. Bone marrow cells can be characterized by specific cell surface markers such as CD34, lineage marker, c-kit and stem cell antigen-1 (Sca-1). It includes the cell population of Haemopoietic Stem cell (HSCs), Endothelial Progenitor cells (EPCs) and Mesenchymal Stem cells (MSCs)[5].

7.1. Haemopoietic Stem cells (HSCs): Hematopoietic stem cells are immature cells that can develop into all type of blood cells and can be isolated from bone marrow by selective sorting of a particular set of surface receptors (Linage-, c-kit+, Sca-1+, CD34lo, CD 38hi)[15,16]. Several preclinical studies in animal model of acute myocardial infarction indicate that transplantation of Haemopoietic Stem cells can differentiate into cardiomyocytes and coronary vessels, hence it regenerate the 68% of infracted myocardium. Overall the transplantation of haemopoietic Stem cells demonstrates to improve the cardiac function. However, the mechanism remains the controversial more studies should be carried out regarding the use of Haemopoietic Stem cells[13].

7.2. Mesenchymal Stem cells (MSCs): Mesenchymal Stem cells are also termed as Bone marrow stromal cells. These cells are multipotent cells which reside in bone marrow, muscle, skin and adipose tissue[4]. These cells are normally distinguished into osteocytes, chondrocytes and adipocytes. It represents a rare population of cells with the absence of Haemopoietic Stem cells marker CD34 and CD133[13]. Some preclinical studies in animal model with acute myocardial infarction suggested that the in vivo transplantation of Mesenchymal Stem cells have demonstrated to improve the cardiac function by differentiating into cardiaomyocytes and endothelial cells. Where the transplantation of Mesenchymal Stem cells into rodent against porcine or canine model of myocardial infarction resulting cardiac regeneration by reduction of the infract size and improving ventricular function. It regenerates the myocardium upto 80% and normalizes the cardiac function which shows the great potential regarding the use of Mesenchymal Stem cells[17].

7.3. Endothelial Progenitor cells (EPCs): Endothelial Stem cells can be isolated from either bone marrow or peripheral blood which is the functional precursor of endothelial cells. These cells have phenotypic and functional characteristic similar to the fetal angioblast. They express as the cell surface marker such as CD34+, AC 133+, c-kit, vascular endothelial growth factor receptor 2 (VEGF2)[18]. In preclinical studies, transplantation ex vivo expanded Endothelial Stem cells in animal model with acute myocardial infarction, improves the left ventricular function and inhibit fibrosis. However there was no changes in the infract size but it shows the significant therapeutic benefit by reduction in collagen deposition and apoptosis of cardiomyocytes[5]. No major complication such as arrthymia, emboli or inflammation has been noted. Hence, it shows the safety profile in successful clinical transplantation to improve cardiac function.

Method of delivery

In the past decade, the stem cells therapy has generated the much excitement and shows the significant progress in the clinical use[10]. The main goal of cells delivery in any organ system is to deliver the appropriate cells to the interested area at the appropriate time to achieve the best patient result shown in Table 2. A huge work has been done for identifying and characterizing the best method for

stem cell delivery which are based on the different pathophysiologic mechanism to avoid the different complication. In the following, we will discuss the currently available methods of stem cells delivery[19].

Table 2: Currently available methods of stem cells delivery

S.NO	NAME	TECHNIQUE
1.	Intravenous Infusion	Least invasive
2.	Direct Surgical Intramyocardial Injection	Invasive
3.	Catheter- based Intramyocardial Injection	Less invasive
4.	Intracoronary (IC) Artery Administration	Invasive
5.	Retrograde Coronay Venous (RVC) Delivery System	Invasive
6.	Engineered Monolayer Tissue Transplantation	Invasive

1. **Intravenous Infusion:** Intravenous infusion is the most applicable technique only in the patient with post acute myocardial infarction, as it is reliant on physiological homing signal which are not present in chronic heart failure[19]. It is the most simple and least invasive delivery route which shows the different option of multiple intermittent infusion treatment. Its shows the safe profile in clinical use[20,21]. But there are also some limitations that only a few cells reaches the affected area because some cell get stuck in microvasculature of the lungs, liver and lymphoid tissue[22].

2. **Direct Surgical Intra-myocardial Injection:** It is the most effective and accurate technique which uses the intra-myocardial injection to deliver the stem cells to infracted region of the heart. The location can be identified by using echocardiography and nuclear imaging[23]. It shows the safe profile by targeting localized myocardium without disturbing the surrounding tissue and vasculature[24]. But it shows a biggest disadvantage when comparing to other delivery system that it is the invasive nature of the operation with the greater risk of complication[25].

3. **Catheter-based Intramyocardial Administration:** It is the most common technique performed in patients with chronic heart failure and lesser to ischemic heart diseases[26]. The catheter-based intra-myocardial injection can be repeated if necessary because of its less invasive nature. Currently two delivery methods are available:

(1) Transcoronary venous approach

(2) Transendocardial approach[27].

3.1 Transcoronary Venous Injection: Transcoronary venous injection has been evaluated as a potential route for administration[19]. This method shows a safe profile which was first demonstrated by Thompson et al. using the transacess catheter in combination with an intravascular ultrasound. But some study shows the complication while delivering the cells to the right coronary territory[28, 29]. It shows the greater cell retention when the transcoronary venous allows the parallel cell injection.

3.2 Transendocardial Injection: This method was first demonstrated in a swine model by Fuchs et al. which shows the improved cardiac function. It directly delivers the cells through catheter based external elastic membrane[30,31]. Many clinical studies have been published shows safe profile with positive indication. No adverse complication has been observed.

4. **Intracoronary (IC) Artery Administration:** This technique is similar of that used in coronary angioplasty. Stem cells by intracoronary infusion can directly delivers the cells into infracted region by using standard balloon catheter[32]. This procedure is widely used in clinical practice for cells delivery especially for acute myocardial infarction. Two methods are used to infuse the stems cells through the catheter are: (1) Non occlusive angioplasty: Flow rates while maintaining the coronary flow.

(2) **Stop flow method:** interference with balloon occlusion.

The main advantages are its direct infusion of cells to the targeted area of good blood supply, rich in nutrient and oxygen resulting homogenous cell engraftment[33,34].

5. **Retrograde Coronary Venous (RCV) Delivery System:** In this method the cells are delivered directly to infracted region by advancing a single or double balloon catheter through coronary sinus[35]. This method is already used during cardiac surgery as a prophylactic treatment against iatrogenic myocardial ischemia[36,37]. It shows a safe profile in human subject. It indicates clinically promising utility.

6. **Engineered Monolayer Tissue Transplantation:** The main aim of engineered monolayer tissue transplantation is to regenerate the injured cardiomyocytes. It is a solution for poor cell survival that has bother most of the delivery methods previously discussed[38]. The concept of engineered monolayer tissue transplantation is to delivers the stem cell to post infarct environment. Many studies show a significant result by improving the cardiac function[39,40]. More investigation is needed to evaluate the cardiac function end point and long term survival of the transplant tissue.

Mechanism of Action

The mechanism of action of stem cell therapy for cardiac repair is the ongoing debate in clinical trial. The main motivation for stem cells therapy is to deliver the appropriate stem cells that would engraft the damaged myocardium resulting from transdifferentiation method of administration of stem cells shown in Fig1. The myocardial infarction occurs due to loss of functional myocardium due to necrosis and cardiomyocytes apoptosis[10]. The transplantation of stem cells to the post- infract myocardium shows the healing of infract tissue and also express cardiac cytokines that promotes stem cells migration and homing[41]. Paracrine secreted by stem cells have the therapeutic effect by promoting the angiogenesis, inhibition of cardiomyocyte apoptosis and regulation of inflammatory response. The paracrine signal from stem cells heals and promotes the endogenous myocardial regeneration process. Generally the potential of stem cells are affected by paracrine signaling to functional myocardial. The infusion of exogenous stem cells can engraft the exiting myocardial as functioning cardiomyocytes in post myocardial infarction. Stem cells can differentiate in endothelial cells and smooth muscle cells which regenerate the lost cardiomyocytes and increase the vascularity in the post injury zone to prevent the futher tissue damages[42,43,44].

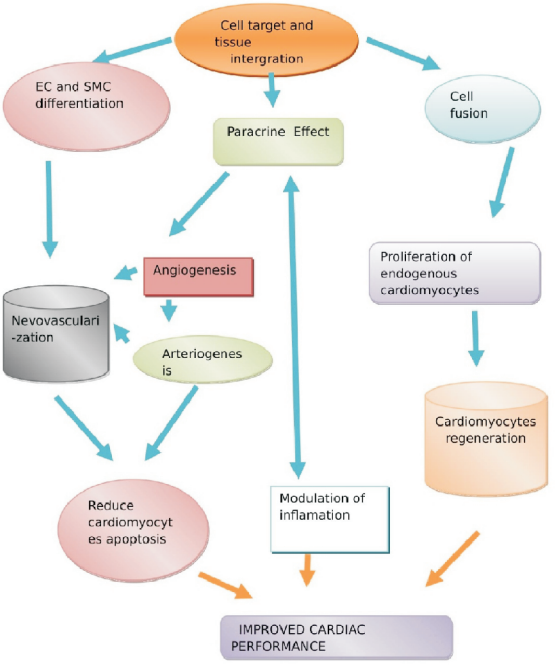

Fig. 1: Mechanism of action of stem cells.

Clinical Application and Uses of Stem Cells

Stem cells can be used in basic research and in clinical research[45]. These are:

1. Embryonic stem cells:

- Embryonic stem cells can be used in research to know how the body develop from a fertilized egg and also help to know how our adult tissues are maintained
- To study the specific signals.
- It also help to differentiate the steps required for the development of many tissues.
- For currently untreatable disease help to develop future cell based therapies.

2. Genetic Therapy: Embryonic stem cells are mostly used for gene therapy by following ways[46]:

- Therapeutic gene can be produced by using the human embryonic stem cells. These genes are

may be in active form or later activation which can differentiate into the desire cell type. Recently published data suggested that skin cells from an immunodeficient mouse were used to generate cellular therapy which shows to improve function in mouse. Hence, this can be used in treating the patient with immune deficiency.

- As embryonic stem cells can be differentiated into many cells type including expected tissue specific stem cells, they also provide constant sources of invitro cellular material. Generally the adult stem cells derived from the embryonic stem cells can be utilized for genetic manipulation technique.

1. **Drug Testing :** As the embryonic stem cells can proliferate without any restriction and differentiate into any cell types, it helps to access the unmatched tissue from human body. These cells play an important role in basic research on the differentiation and function of human tissue. These cells help to improve the safety and efficacy of human drug testing. Human heart cell lines does not exist, therefore many drug that are toxic to the human heart enters clinical trial sometimes resulting in death. Human embryonic stem cells derived the heart cells that may be helpful in identifying such drug before they are used in clinical trial by drug discovery process which provide more safe and effective treatment[47,48].

2. **Cell Based Therapies :** It is one of the most important applications of human stem cells. Stem cells can differentiate into many cells types and tissue, as they can be used for cells based therapies. However, these can differentiate into specific cells and can replace the cells and tissue to treat various diseases.

3. **Brain Damage :** In the case of brain injury recovery is rarely observed due to lack of robustness. Recently published research suggested that the administration of drug increase the stem cells division rate in rat subjected to stroke shows to improve the survival and differentiation of newly formed cells[49].

4. **Cancer :** Adult stem cells have been used to treat different cancers through bone marrow transplantation. Stem cells have potential to give rise to the different blood cells in the body and these cells are transplanted into the bone marrow of the patient, where they regenerate the blood. Recently published data suggested that injection of human neural stem cells against intracranial tumor in rodents shows to reduce tumor mass by 80 percent[50].

5. **Spinal Cord Injury :** Spinal cord injury recovery is very difficult. Recently scientists have used the adult stem cells isolated from umbilical cord and then injected into the damage part of the spinal cord which shows the positive result. But further researches are required regarding the use of stem cells in spinal cord injury[51].

6. **Muscle Damage :** Adult stem cells are able to repair the damaged muscle after the heart attack. Heart attack is due to blockage of coronary artery, lack of oxygen and nutrients. After the attack, cells try to remodel themselves in order to pump harder because of which there is a decrease in blood flow leading to the death of muscle cells. Researchers have demonstrated that injection of bone marrow stem cells against the mice with heart attack shows to improve 33% of heart function and 66% of damaged tissue[52,53].

7. **Heart Damage :** Several clinical trials suggested that the use of adult stem cells targeting the heart disease is safe. However, no trial have proven efficacy. Recently the use of bone marrow derived stem cells and peripheral blood derived stem cells is becoming popular in targeting the heart diseases[49].

CONTROVERSIES IN STEM CELL RESEARCH:

The status of stem cell research is a controversial issue because the present state of technology requires the human embryonic cells lines which are generated by the destruction of a human embryo. Mostly the controversy focuses on embryonic stem cells. In the stem cell research mostly the embryos are discarded which believes that embryonic stem cell research violates the sanctity of life which is equivalent to murder. The most well known controversy in stem cell research has been Hwang's

claim of cloning a dog. Hwang claimed that he had already cloned 30 human embryos, but the claim now shown to be lie. Researcher claims that stem cell research has the potential to treat untreatable diseases and to alleviate suffering. Hence, still the controversy is going on regarding the use of human embryonic stem cell.

Most of the delivery methods are invasive in nature which means there is need to develop high medical equipment which makes the stem cell therapy costly. Because of the innovative nature of these treatment, more research should be carried to reduce invasive nature and the alternative methods to make it cost effective.

ETHICAL CONCERN IN STEM CELL RESEARCH:

In general, the fundamental ethical requirements that are mostly used in drug and clinical trials equally apply to cell therapy. Generally in case of embryonic stem cells research, the investigator hope to achieve is the relief of human suffering. The main ethical issues in stem cells research is the use of embryo. Embryonic stem cell research poses moral difficulties which forces us to choose between two moral principle[14]

1. To prevent or reduce human suffering.
2. To respect the value of human life

In case of embryonic stem cell research, the early embryo has to be destroyed which mean destroying a potential human life. But it leads to the discovery of new medical treatment that would reduce the suffering of many people. Therefore, many debate are still ongoing the use of embryonic stem cells. Researchers hope to find some alternative methods regarding the use of embryo[19].

Future Perspective of Stem Cell Research :

1. **Low blood supply :** This method has been developed to produce a large number of Red blood cells. In this method the hematopoietic stem cells are grown together with stromal cells, by creating an environment which mimics the condition of bone marrow and the natural site of red blood cells growth. The growth factor is Erythropoietin, added to coaxing stem cells to complete terminal differentiation to red blood cells.
2. **Gene Therapy :** Stem cell therapy shows potential benefit to treat immune deficiency diseases. Hence further research must be carried out.
3. **Baldness :** Stem cells may be used in treating the baldness through "hair multi placation" which is known as hair cloning. In this process the stem cells are collected from the existing follicles, which are multiplied in large number by culturing. After that the new follicles are implanted which have been shrunk during the aging process.
4. **Missing Teeth :** In this process the stem cells are collected from patient which are coaxed in lab to turn new tooth bud, then implanted in the gum and give rise to new tooth which take two month to grow. These cells are fused with jaw bones and release the chemical which helps nerves and blood vessels to connect with it.
5. **Deafness :** Researchers have achieved the success in regrowing cochlear hair cells with the use of stem cells which help in deafness.
6. **Blindness and Vision Improvement :** Researchers use the embryonic stem cells to grow the sheet of top potent stem cells. When these sheet are transplant against the damaged retina it shows improved vision by stimulating the neural repair. Further trials are ongoing.
7. **Bone Regeneration :** Mesenchymal Stem Cells significantly regenerate the bone defect and provides the autogenous bone graft. However, more research must be carried out regarding the use of mesenchymal stem cells.
8. **Myocardial Infarction :** Engineering techniques must be used to counteract the destructive effect of myocardial infarction

Conclusion

In general, the researcher believes that stem cells are the future of medicine. In the therapeutic world, it is most promising treatment option for the diseases which are untreatable nowadays. Stem cells therapy shows significantly improved heart function after myocardial infarction, therefore decline into heart failure. We hope to see new horizon regarding the use of stem cells in organ development and regeneration of lost tissue such as missing teeth, hair follicles and retina.

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