Role of stem cells in heart disease treatment

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Abstract
Introduction: Despite many advances in treatment of heart disease, particularly myocardial infarction, many patients with heart attacks suffer from chronic heart failure and are involved with this disease until death. Several therapeutic procedures including drug-therapy, heart transplantation and heart’s inside and outside equipment are used to improve the quality of life of patients, which are very expensive for patients and hospitals. By researches in genetics, tissue engineering and cell therapy, the hope to save these patients has increased. The purpose of this review study was to analyze and clarify the role of stem cells in treating heart failure.

Conclusion: Researches and clinical trials show that during 4 to 6 months after transplantation of stem cells to the heart, left ventricular function increases between 7 to 9%, end systolic volume decreases and blood supply and vessel construction promotes in infarcted region. Moreover, in prospective and case-control studies, the efficiency of this method is proved and no dangerous arrhythmia or tumor has been observed.

Keywords: Stem Cells, Nursing, Heart Disease

Introduction

Nowadays along with progress in basic sciences and tissue engineering, cell therapy is considered as a new alternative method for most of chronic, congenital and acquired diseases [1, 2]. By cell therapy universalization, in spite of longer longevity, a more healthy life is offered to human beings [3, 4]. Recently, this has led to spending millions of dollars in the field of basic cell application for treatment of various diseases and encouraging patients to use these methods in different countries [4, 5]. These methods can revolutionize the role of nurses as counselor, caregiver and a member of treatment and rehabilitation team (in each of three levels) and strengthen the need of having knowledge in this area. Nursing as an interdisciplinary science, as has been able so far to be adapted by new and updated tools and instruments and to manifest its role in this regard along with growth of science and technology more obvious than before, should pay a special attention to this therapeutic method. Therefore, nurses without any knowledge about this new therapeutic approach cannot formulate and implement an appropriate care and treatment process for the help-seekers who will benefit from these methods in future. On the other hand, nurses as the most available and most active members of the health-care team should be aware of what has been introduced as the science of the day and evolution in the conventional way of treating most diseases and have a well command of it. Thus, present study was conducted with the aim of increasing nurses’ awareness of the advantages and disadvantages of stem cell application, the latest scientific achievements in the field stem cell and the prospect of cell transplantation in damaged tissues. In the meantime, treatment of heart diseases by using cell therapy method was more attended as one of therapeutic challenges of the global community.

The history of stem cell application

Bone marrow hematopoietic cell transplantation began about 40 years ago in bone marrow malignancy and diseases such as leukemia [6, 7]. This therapeutic method was used in researchers’ minds without any particular motive, until the news of the new blood vessels growth in tumors in 1990 guided scientists, who thought that new blood vessels are made just in embryonic phase, toward the discovery of angiogenic cells and caused a great evolution in cell therapy [8]. Researchers found that there are specific types of cells in marrow which can be turned into other tissues of the body. After the discovery of angiogenic cells and their supporter and nutritional cells, it was found that the cells themselves should be also separated and evolved from the other mother cells. Research in this direction led to the discovery of "embryonic stem cells"; the research for limited transplantation of these cells began from 1998 [9]. After the study of Orlic et al. in 2001 that transplanted the embryonic stem cells to rat heart, the research increased in this field. After that, studies on various animals such as pigeons, sheep, monkeys and dogs continued and different
transplantation methods were evaluated until the Committee of Medical Ethics, with regard to the good results of animal studies, allowed the pilot implementation of this new therapeutic method on human [10]. The results of mentioned tests showed a great improve in heart function, but by the spread of the news of conducted researches, the attention of religious, moral, legal and political centers and institutions was drawn to this issue and directed the research path toward a particular way [11]. After that, the safety of marrow cells for heart was proved by Hamano et al.; then application of the stem cell transplantation along with coronary artery graft was considered and various methods, including heart muscle injection, injecting into vessels and transplantation by laser, were used and analyzed. Universities and major research centers in Europe and America began their work in the field of stem cells for treatment of congenital, acquired and chronic diseases until the number of patients in any clinical trial reached to more than 50 patients and different researchers such as Olive and Astrow focused their research on this issue [12]. Of course, due to availability and high number of patients with reduced heart muscle blood supply, a group of patients formed the first participants of the study [13]. Research continued till 2005 that U.S. Food and Drug Administration (FDA) confirmed the efficiency of cell therapy in cardiac patients and founded a unit in its administrative system for following up, development, and solving the existing challenges of this type of treatment [14, 15].

After that, researches continued in Frankfurt university, Germany, Minneapolis Heart Institute, the United States, Newcastle University, England and Galway university, Ireland [16] and multinational institutions, including Traviata medical institutions (Thailand, Palestine and Hong Kong) in 2005, with the help of biotechnology and pharmaceutical companies, together with research development, took steps toward forming a stem cell bank and simultaneously, started to advertise in the field of stem cells [17, 18]. This process continued until in December 2006, International Symposium on Stem Cell Therapy for treatment of heart disease was held in Bangkok and the latest research on humans and animals were discussed. In November 2005, the comprehensive conference of stem cell therapy was held in England in which scientists presented their latest researches. In the field of cell therapy in different diseases, and different methods of stem cells therapy [19, 20].

What is a stem cell and of what resources is obtained?

Different body tissues are composed of cells which have some abilities of rebuilding their congeners cell; including heart cells and nervous system. In the meantime, there are cells in body that have a special potential for differentiation and turning into other specialized cells [21, 22]. These cells have two obvious characteristics; under the influence of appropriate conditions can be converted into other specialized cells, and are able to build their congeners basic cells and are divided during several divisions and a long time without any change [1].

1- Embryonic Mass 2 - Umbilical cord blood 3- Specific mature tissue like (marrow, muscle, venous blood). But two main sources could be introduced for them:

1- Embryonic or fetal basic cells which are obtained from the Embryonic mass that has grown to the second week.

2- Basic mature cells which are obtained from blood and bone marrow and can repair a tissue if damaged. These cells are more specialized than the embryonic basic cells. It can be stated, in order to express their differences, that the embryonic basic cells are more general and the mature basic cells are a bit more specialized and can be divided into limited tissues [10, 23, 24]. In human or animal, at the very beginning the cells are formed like a family tree and are divided in this way. Basic embryonic cells grow in vitro in a large number, are converted to anything and are also replaced by any tissue, but their safety of effect is not still specified completely; because by their overgrowth in a tissue they can be turned into a tumor or a tissue which is not targeted or the immune system may hit them back. Also, their use has been discussed in terms of ethics and religion, and is problematic; instead, the mature cells have been used in people older than thirty years. Since it is taken from the body of help-seeker himself or herself, the immune system does not hit it back and there is no need for the immunosuppressive drugs, the probability of their conversion into tumor and uncontrolled tissue is less and their use does not have any moral problem, but instead their growth will be so hard in laboratory and are not available in a large number. In addition, they are converted into fewer tissues [25, 26].

Different applications of stem cells

The legend of stem cell application for treatment of many diseases is becoming a reality and a scientific twenty years background supports this reality. Tissue
engineering experts claim that in the near future will be able to cure many diseases such as spinal cord injury, hormonal defects, Down syndrome, Acquired Immune Deficiency Syndrome, infertility, chronic hepatitis, pancreatitis, diabetes and its complications and many ischemic diseases such as congestive heart failure, unstable angina, liver ischemia, retinal ischemia, heart attacks and stroke, limb and renal ischemia [28]. At this time, research on the application of stem cells for treatment of cancers, hair and skin repair, replacement of brain cells, Alzheimers, fractures, Parkinson, bladder repair, gastrointestinal tract and muscles repair continues [19, 20, 29].

Cell therapy in heart diseases

1.1 million people in the United States suffer from heart attack each year and often after 5 years will be affected by chronic heart failure. In other words, 8.4 million people in the United States suffer from chronic heart failure and a new 400 thousand cases are added to these figures annually [26, 30]. In spite of excessive progress in pharmaceutical industry and therapeutic methods, heart diseases are considered as one of the most problematic health threatening factors in the world. This may be due to the limitation of mitoses division in heart cells [18]. About 50% of causes of chronic heart failure are the heart diseases with ischemic origin; the best medical and surgical methods such as pharmacotherapy, endocardial equipment and heart transplantation are not well responsible for these patients’ treatment due to high cost, lack of donor and immunosuppressive drugs. Chronic heart failure and the ischemic heart disease still form the most cause of mortality in the world [21, 29]. Application of stem cell for treatment of such diseases is considered as a new treatment. After cardiac infarction, the chronic heart failure or heart muscle damage (for any reason, including ischemia), heart will not have the proper contraction anymore. Pharmacotherapy, dietary restrictions, activity limitation, putting mechanical tools in the heart and heart transplantation that each one has their particular limitations are among the common therapeutic methods. The latest recommended therapeutic method is the cellular repair of heart muscle. In this method, stem cells are transferred into the heart muscle and by supplying a proper condition, it is tried to produce the new cardiac cells and to perform re-angiogenesis in the damaged area.

Marrow cells, fetal cells, dead donor’s heart muscle cells, the smooth or skeletal muscle cells of the individuals themselves, fetal cardiac cells, umbilical cord blood and peripheral blood of individual have been used for cell transplantation in the heart muscle, [18, 19]. It should be mentioned that there are multipower stem cells in marrow, which are also seen in peripheral blood in a small amount. A group of them which are known as generative endothelial cells (from the category of the marrow uni-nucleus cells) are very useful for angiogenesis and keeping the transplanted cells alive. By local prescription of growth factor and use of chemotherapeutic drugs, their number will increase in peripheral blood [3, 4]. Research results confirm that the best cellular resources for treatment of damaged heart muscles are skeletal muscle cells and marrow cells of the individual that must be cultivated. These cells are resistant against fatigue and ischemia. Myoblasts (skeletal muscle cells), are a set of muscle cells that are easily obtained through biopsy and marrow cells do the stimulation for angiogenesis. Myoblasts are the mature basic cells that neither the immune system excretes them, nor ethical problems exist in their use. These cells can be injected into blood vessels in the border area of the damaged part through a catheter or can be directly injected into heart muscle through open surgery or thoracoscopy (these two methods are allowed in Europe). In the method of intravascular injection that is used more for the transfer of peripheral blood or marrow stem cells, there is the risk of embolism and in direct injection into endocardium, myocardium or pericardium, which is more used for myoblast cells transfer, preparation of the electromechanical map of heart is necessary for determining cellular injection site. In this method, by ultrasound and fluoroscopy, cellular clone is being injected into the damage boundary zone, though there is a risk of cardiac rupture, especially in infarctions. Other limitations of myoblast cells are the need for a long cultivation time and the possibility of damaging during the inflammatory process [30, 31, 32, 33]. In other words, after extraction of stem cells and refining them by an in vitro re-culture, the cells are inoculated by different ways. This can be accompanied by conducting of the transplantation of new blood vessels in the heart or without them. However, the percentage of patients’ improvement that their cellular transplantation is carried out during heart blood vessels transplantation has been reported higher [34], because even the stem cells will die due to lack of sufficient blood flow. With stem cells, some materials are also injected that will improve Telomerase activity, will result in site-selection of stem cells and stimulates the stem cell growth. More
accurately, simultaneous with stem cell transplantation, angiogenic genes injection, angiogenic factors, anti-apoptosis genes, anti-oxidants and growth factors, they will improve the Telomerase activity. Factors such as GM, PGE, VEGF, SDF1 and GCSF, cytokines, cell stimulating proteins, placenta developing factors and granulocyte colony stimulation factor cause the stem cell transfer to the damaged site [35, 36]. Stem cells, under the influence of other injected materials such as β tissue factor, bone polymorphous protein, PDGF-AB factor and Azacitidine (INN) begin to grow and differentiate. Consequently, by the angiogenesis acceleration they improve the tissue oxygen-supply, activate the heart cells or replace the previous cells. In spite of the inoculation of these materials during cellular transfer, due to a phenomenon like infarction, many adhesive molecules and chemokinases move to the damaged area owing to heart cell damage and the inflammation process [37]. The most important concern of researchers in this kind of clinical trial is the lack of electrical connection of implanted cells to other heart cells which can cause arrhythmia. Therefore, automatic heart defibrillator is placed within the heart; this method has been approved as a therapeutic method [38].

The United States Food and Drug Administration (FDA) has legislated some laws in order to inoculate basic cells in heart. 1- The safety of injected compounds should be ensured; 2- The cells should not be taken from the infected tissues containing pathogenic viruses like HIV; 3- A correct approach should be used for cell inoculation that will not impair the tissue [15, 25].

In Ozbaran et al. study in Turkey, six patients with damaged heart muscle who their disease has become certain and the radiographic and clinical studies has confirmed it and also had less than 25% left ventricular ejection fraction (LVEF) echocardiography and the angiography, Dobutamine stress test, and thallium scan and positron emission tomography (PET) have been carried out for them and their heart tissue was confirmed to be alive were treated under cell therapy by coronary artery graft. Four months after surgery, the follow-up indicated that patients’ quality of life has improved compared to that of their pre-surgery and in view of USA Heart Association classification of heart failure, each one had come one class lower and had improved.

The results of echo, PET and thallium re-scan showed cardiac function improve in site of cell implant and finally the researchers recommended this treatment method for patients with advanced chronic heart failure [35].

In a study by Hamano et al. five patients’ marrow was injected into the heart muscle during the coronary artery bypass graft. In these surgeries, taking of marrow was conducted concurrent with vascular graft. No new cardiac arrhythmias and bleeding were observed and in the next year follow-up no kind of tumor was observed in these patients and the clinical symptoms of patients had improved. For the second time, this group carried out the same treatment for other 4 patients and no tumor was observed in the heart study and no new arrhythmias were reported during the 14 months follow-up to the next year. The improvement of cardiac function during the thallium scan and echocardiography has been well specified. Other group of researchers in 2005 tested the stem cell implant through creating laser channels in the heart which their study result has not fully published yet. Astros et al. in Germany after conducting usual therapeutic measures on 10 patients with myocardial infarction performed the same surgery with the difference that marrow had been taken one day before the graft surgery and the solution containing basic unil-nucleus cells was entered the coronary vessels through artery and was injected into the damaged border region. In the next three months of follow-up, the blood supply of lesion site had increased and the cardiac function had also improved. This method can be used for people who are not able to tolerate surgeries as coronary artery graft. Despite the fact that the research about cell therapy still continues, in patients with chronic congestive heart failure this method can be used; though a greater volume of basic cells are needed for them [19, 20,36].

The other study by Bassett et al. was conducted on 60 patients with MI who were randomly selected. On average, 4.8 days were passed from the occurrence of their MI. In these patients, marrow was taken a day before surgery. At the operation day, the given cells interred the lesion site using a catheter and the solution containing cells was injected into the border of damaged region. A few months after surgery the EF average rate increased to more than 67% in the test group; while in the control group this value did not even reach 0.7%. Nevertheless, another study in South Korea by Kut et al. did not show any significant difference in the examinations of next 3-12 months in the pentad sample [20]. The blood supply was reduced to 30% and LVEF showed an increase between 15 to 57%. In addition, nuclear studies showed a 15% oxygen intake increase and 18% absorption of blood glucose in the damaged tissue compared to before operation. These results were not observed in the
control group that only underwent coronary artery bypass graft surgery [37].

**Nursing in interaction with cell therapy**

Nursing as an interdisciplinary science, has maintained its nature in spite of advances and considerable changes in different sciences. Nursing strategy is to serve all existing facilities for doing the best care of help-seeker and promoting of individual and community health [39]. Now, along with progress in the knowledge production speed in the world, nursing must maintain its independent identity and guarantee the best possible result from existing situation and accomplished changes, with timely and appropriate response, in order to better achieve its humanitarian goals. Recent advances in basic science, especially physiology and cellular and molecular sciences, has opened a new horizon in some acute and chronic diseases’ treatment which can be very hopeful, and according to experts, can create a dramatic change in medical sciences. On the other hand, such changes also have affected nursing and made the need for new nursing diagnosis unquestionable. Nursing must also be entered to the domain of these changes and new books or edition of nursing reliable sources must provide complete topics in this area. Therefore, nursing as a dynamic science and related to basic sciences, must prepare the field for use of these achievements in addition to knowing these changes and explain and determine its theoretic view toward such new approaches [40].

**Conclusion**

Most researches and clinical trials have shown that within 4-6 months after stem cells transplantation, LVEF will increase between 7 to 9%, end systolic volume will reduce and blood supply and angiogenesis in the area of infarction will improve. Even in prospective and case-control investigations the efficiency of this method has also been proved. No grown cancer mass has been observed with magnetic resonance imaging and no arrhythmia has been reported during the follow-up period.

Although it is a long time that man is aware of the existence of the body constructive unit, namely cell, and a great deal of research has been done in this field, but his unknowns are numerous about the cell function. This is deeply true about the stem cells. In view of abundant research about the use of stem cells in treating heart disease, our knowledge about the result of the researches and their conducting methods increases constantly. On the one hand, the questions in minds of most researchers have been also increased. What is the best time to transplant cells for patients with myocardial infarction? What is the best method of cell inoculation? What is the best source of stem cells? Who are the patients for transplantation? How much is the appropriate dosage of these cells’ injection? Which factors are responsible for the process of cell proliferation in cardiac tissue? What is the best way for stem cell injection to the heart? Will transplanted cells remain alive for many years? Proposing of these questions make the cellular therapy be not recommended as a comprehensive clinical method, but researchers and scientists hope for the future of this treatment method and consider it as a substitution for heart transplantation. Another important point for nursing researchers and the investigators of other fields is whether the cost of this treatment method is economical for cardiac failure patients compared to other common methods and if the existing potentials have been well used in utilization of previous methods.

**References**

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