Effects of mesenchymal stem cells with injectable scaffold on cardiac function in myocardial infarction in Rabbit

Jafari, N.[1], Sharifi, D.[1*], Dehghan, M.M.[1], Abarkar, M.[2], Hejazi, M.[3], Abbasnia, P.[1], Molazem, M.[1], Tavakoli, A.[1], Mehdinavaz Aghdam, R.[4], Ahmadi Tafti, S.H.[5], Tajik P.[1]

[1]*Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran*

[2]*Department of Clinical Sciences, Faculty of Veterinary Medicine, Islamic Azad University, Karaj Branch, Karaj, Iran*

[3]*Department of Animal Sciences, Faculty of Agriculture, Islamic Azad University, Khorramabad Branch, Khorramabad, Iran*

[4]*Nanotechnology Department, Engineering Research Institute, Tehran, Iran*

[5]*Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran*

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Correspondence
Sharifi, D.
Department of Clinical Sciences,
Faculty of Veterinary Medicine,
University of Tehran, Tehran, Iran
Tel: +98(21) 61117036
Fax: +98(21) 66438327
Email: dsharifi@ut.ac.ir

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Abstract:

BACKGROUND: Bone marrow-derived mesenchymal cells can transdifferentiate into Cardiomyocyte cells and improve heart function after transplantation. Since biomaterials can improve the cell retention in the site, cell survival and differentiation, heart tissue engineering is now being explored as an applied solution to support cell-based therapies and increase their efficacy for myocardial diseases. Chitosan in combination with Glycerol Phosphate (GP) can produce a thermo sensitive material that in body temperature can form a jellylike material. **OBJECTIVES:** The aim of this study was to evaluate the effects of a combination of autologous undifferentiated bone marrow mesenchymal stem cells (MSCs) and injectable scaffold on cardiac function improvement in rabbits after inducing myocardial infarction. **METHODS:** The Left Anterior Descending (LAD) coronary artery was ligated by No. 6-0 polyamide suture material, and autologous MSCs with injectable scaffold were injected into the margins of the infarcted zone at the time of surgery. At 4 weeks after transplantation, the cardiac function and structure was detected using echocardiography. **RESULTS:** There was no significant difference among the three groups (MI only, MI Scaffold, and MI+Scaffold+MSCs) in the Echocardiographic parameters including, heart rate (HR), Ejection Fraction (EF), Fractional Shortening (FS), Left Ventricular Diameter (LVD) and Left Ventricular Parietal Wall Diameter (LVPW). **CONCLUSIONS:** A combination of autologous undifferentiated bone marrow MSCs and injectable scaffold made of Chitosan+ Glycerol Phosphate in echocardiographic evaluation did not have a positive influence on achieving functional improvement.

Introduction

Myocardial Infarction or MI is a life-threatening event that can cause sudden cardiac arrest or heart failure. Despite numerous valuable advances in the diagnosis and treatment of heart diseases, cardiac dysfunction after MI is still the main cardiovascular problem worldwide.

Necrotic myocardial tissue after acute MI is gradually replaced by fibrotic cells that are not

contractible and will form scar tissue. Ventricular dysfunction will develop as a result of the massive cardiomyocyte loss. Although whole heart transplantation is still an option for patients with severe congestive heart failure, organ shortage and the essential need for immunosuppressive therapy are major problems of any whole organ transplantation (Wang et al., 2005).

Even though Anversa and Nadal-Ginard have reported the presence of cardiogenic stem cells in the heart tissue, their number is extremely limited, and proliferation rate is very low and not enough for the need of tissue regeneration (Anversa, Nadal-Ginard, 2002).

Recent researches showed that bone marrow-derived mesenchymal cells can transdifferentiate into Cardiomyocyte cells and improve heart function after transplantation into the margin of myocardial infarcted zone.

Among experimental animals, rabbits are more suitable than rats and mice for developing a myocardial infarction model, because the rabbit's heart lacks collateral vessels, and minimal occurrence of fatal arrhythmia and death after coronary artery occlusion has been reported in comparison with other species (Lee et al., 2002).

The most commonly used technique for MI induction is coronary artery ligation through a left lateral thoracotomy (Ypsilantis et al., 2006). Previous researches have shown that after this operation, the heart will gradually undergo hemodynamic and morphologic alterations that will cause some degree of heart failure. These alterations include decreased cardiac output (CO) and increased filling pressures (Kompa, Summers, 2000).

Animal models of MI are typically used to answer two types of questions, either (i) does the intervention (drug or genetic modification) protect the myocardium against ischemic changes, or (ii) for the same initial injury (ischemic injury or hypertrophic stimuli), does the intervention affect the future development of cardiac tissue remodeling or change the severity of heart failure (Philipp et al., 2005).

Although the heart function after cell-based therapies has improved, unsatisfactory cell retention in the site and survival of the transplanted cells are still problems in these techniques. Since biomaterials can improve the cell retention in the site, cell survival and differentiation, heart tissue engineering is now being explored as an applied solution to support cell-based therapies and increase their efficacy for myocardial diseases. Most of the progress in the field of cardiac tissue engineering has been made in the last decade. Among different types of techniques in the cardiac tissue engineering, the approach of injectable cardiac tissue engineering is more clinically appealing because it is less invasive than that of in vitro engineered cardiac tissue or epicardial patch implantation (Wang et al., 2010).

Chitosan is a Chitin-Derived aminopolysacharide. Since Chitin is a natural polymer, chitosan is a biocompatible, biodegradable and antibacterial biomaterial that can support wound healing. For this reason, this biomaterial is used in long-term medical applications. Because of biocompatibility and hydrophilic surfaces of chitosan, it can empower cell adhesion, proliferation, and differentiation. This polymer in combination with Glycerol Phosphate (GP) in a mild acidic condition can produce a thermo sensitive material that in body temperature can form a jellylike material. Therefore Chitosan-based biomaterials can be widely used in drug release, cellular encapsulation and tissue engineering (Marchandy et al., 2009; Wang et al., 2010).

The aim of this study was to evaluate the effects of a combination of autologous undifferentiated bone marrow mesenchymal stem cells (MSCs) and injectable scaffold made of Chitosan Glycerol Phosphate on cardiac function improvement in rabbits after inducing myocardial infarction.

Materials and Methods

Preparation of MSCs: A total of five to eight milliliters bone marrow was obtained by bone marrow aspiration needle from five healthy white New Zealand rabbits. 3000 IU heparin was used for each sample for the anti-thrombosis procedure. Bone marrow was immediately transferred to cell culture laboratory and the mononuclear cells (BM-MNCs) and red blood cells were separated by centrifugation with Ficoll gradient at 400 g for 40 min. Then BM-MSCs were washed with buffered PBS two times (400 g for 10 minutes) and finally the cells were cultured in DMEM culture medium that included 20% Fetal Bovine Serum (FBS) and transferred to 25

cm2 flasks. The flasks were incubated in an incubator with 95% air, 5% carbon dioxide and 37^{o}C temperature. The culture medium was changed every 3 days. The non-adhesive mononuclear cells and red blood cells were washed away in the first culture medium changings, but the adhesive cells grew and after 5-7 days formed colonies. The Mesenchymal stem cells (MSCs) were passaged to a 75 cm2 flask by trypsin/EDTA 0.25% before they grew to completely cover the bottom of the flask (Wang et al., 2005).

Preparation of the scaffold: Different concentrations of chitosan (1-2% w/v) with glycerol phosphate (5-20% w/v) were evaluated and finally the best combination with regard to the biocompatibility, gelation time and PH was selected (Wang et al., 2010). The chitosan powder with 80% DDA (Degree of Deacetylation) and low molecular weight was sterilized by autoclaving at 126^{o}C for 20 min. Sterilized chitosan powder with a quantity of 0.225 g was issolved in 9 mL of 0.1M hydrochloric acid (HCl) to make the first solution. Subsequently 1.5 g glycerol-phosphate salt was dissolved in deionized water to make the second solution. The glycerol phosphate-deionized water mixture was then sterilized using a 0.2-µm filter (Triple Red Laboratory, UK). The final solution was made by mixing these two solutions so that the final volume was 15 mL. Solutions of chitosan-hydrochloric acid and glycerol phosphate-deionized water were chilled in an ice bath for 15 min to avoid gelation after mixing. To prepare the injectable solution, the glycerol solution was added drop wise to the ice cold chitosan solution with continuous stirring. After testing different combinations of chitosan and glycerol-phosphate, the solution with 1.5% Chitosan and 10% glycerol-phosphate had the best gelation time for cardiac tissue engineering applications (Wang et al., 2010).

Myocardial infarction induction and MSCs plus scaffold transplantation: Fifteen 2.5-3 kg adult male purebred New Zealand white rabbits were hospitalized one week before the operation in standard animal house in the Faculty of Veterinary Medicine, University of Tehran. After performing control echocardiography, the animals were randomly divided into 3 groups: the scaffold treated group (5 cases), consisting of MI model with injectable biodegradable scaffold injected into the margin of MI region; the cell plus scaffold group (5 cases), consisting of MI with MSCs and scaffold injected into the same place; and the control group (5 cases), consisting of MI model with cell-free Phosphate-Buffered Saline (PBS) injected into the MI region.

The animals were anesthetized with intramuscular administration of ketamine hydrochloride 10% (40 mg/kg) and xylazin hydrochloride 2% (5mg/kg). Maintenance of anesthesia was performed by Isoflurane inhalation through tracheal tube. Under general anesthesia, left lateral thoracotomy was accomplished via forth intercostal space. After Pericardiotomy, craniolateral surface of myocardium was exposed (Zhang et al., 2007). LAD coronary artery was ligated by using 6-0 polyamide suture with round needle on beating heart (Wang et al., 2005). After 5 seconds, the cyanosis and color change were visible in distal parts of the ligation on lateral surface of the myocardium (Ypsilantis et al., 2006). 15 minutes after the ligation, 10^{6} autologous MSCs and scaffold (totally 0.1 mL) were transplanted by injecting into the border area of the cyanotic myocardium by using needle No.25 (group C). In scaffold group (group S), after MI induction, the myocardium received the same volume of scaffold only, and in control group (group I), MI was induced by the same method, then the myocardium received the same volume of PBS (Wang et al., 2005).

Cardiac Function Assessment: Echocardiography on all rabbits was performed right before, immediately after, and 4 weeks after the operation using a 4-8 MHz phase-array probe of SonoSite Micromaxx set. The left side of thorax was completely shaved and echocardiography performed on right lateral recumbency starting by short axis view of cordatendinia muscle and followed by right parasternal short axis in ventricular level to evaluate myocardial thickness. Right after this view the probe was rotated 90 degrees at the place to obtain parasternal long axis view. Measurements of both the left ventricular end-systolic (LVES) and left ventricular end-diastolic (LVED) volumes plus endocardial area of the left ventricle were reduced. By use of the mentioned measurements, left ventricular ejection fraction (LVEF) and fractional shortening (FS) were calculated. Echocardiographic examinations were performed with simultaneous electrocardiography (ECG) recording by the ultra-

sound machine for exact determination of cardiac phase (Figure 1) (Zhang et al., 2007).

Data analysis: Data are expressed as mean ± standard error (SE). Analysis system software SPSS 11.0 and repeated measures analysis of variance test were used for all analysis. A level of $p<0.05$ was considered as significant difference.

Results

Ejection Fraction in all 3 groups decreased after the surgery and increased after 4 weeks, but still not to the normal value. According to repeated measures ANOVA Test, these alterations had no significant difference among these 3 groups ($p>0.05$) (Table 6) (Figure 2).

FS in all 3 groups decreased after the surgery and increased after 4 weeks, still not reaching the normal value. According to repeated measures ANOVA Test, these alterations had no significant difference among these 3 groups as well ($p>0.05$) (Table 2) (Figure 3).

HR was increased after the operation in all 3 groups. In group I and S after 4 weeks the HR decreased, still not reaching the normal value. In group S it had no decrease even after 4 weeks. According to repeated measures ANOVA Test, these alterations had no significant differences among these 3 groups ($p>0.05$) (Table 3) (Figure 4).

LVD in group S had no change after the surgery, however, it decreased during the 4 weeks. In group C and group I there was a slight increase after the surgery but it decreased after 4 weeks. These changes had no significant difference among the 3 groups according to the mentioned test ($p>0.05$) (table 4) (Figure 5).

LVPW increased after the surgery and during the 4 weeks after the surgery in all 3 groups and there was no remarkable difference among these groups according to repeated measures ANOVA Test ($p>0.05$) (Table 5) (Figure 6).

Discussion

The MSCs can be considered as an alternative transplant cell source in order to repair damaged myocardium after MI. When prepared donor cells were transplanted into the myocardial infarction region in the New Zealand rabbits MI model the MSCs could transdifferentiate into cardiomyocytes, inducing regeneration of vascular structures and improving cardiac function.

It had been shown that cardiac milieu (Wang et al., 2000) had positive effects on myogenesis and angiogenesis. The ischemic myocardium may produce some myogenic factors. Released myogenic factors are important in inducing immature MSCs to transdifferentiate into cardiomyocyte-like cells. However, the precise mechanism of how MSCs could differentiate into cardiomyocyte-like cells is still unknown.

To investigate the potential efficacy of MSCs implantation as well as the role of scaffold, we transplanted both scaffold and scaffold impregnated with myogenic cells into infracted myocardial area produced by ligation of the LAD in a rabbit model.

Usage of scaffolds has been accompanied with major restrictions and problems. There are still a number of questions regarding the kind of scaffold, it's physical and structural properties, and the route of application in the host tissue; however, the scaffold's structure must provide a suitable environment for cell's survival, growth, and differentiation. Transplantation of cell plus scaffold can result in some problems in cell's nutrition and growth in deep parts of the implant. On the other hand, as the graft is applied in the margin of the necrotic part of myocardium, there are still uncertainties about the cell survival in this area. In addition, for a desirable hemodynamic performance of the heart, it is necessary that all parts of the heart contract and relax coordinately. Since these kinds of grafts have no contractile properties, they can act as an overload on the infarcted myocardium.

Cell transplantation may be an alternative treatment for heart failure in the future. It is necessary, however, to understand what type of cell the potential donor cell is for cell transplantation. A long-term study showed that allogeneic cells were rejected 24 weeks after transplantation despite cyclosporine-A therapy (Li et al., 1997). Because of the consequences of immunorejection, autologous cell transplantation would be an ideal technique. Cardiac and skeletal muscle biopsies do not yield sufficient cell numbers to repair the damaged myocardium. Bone marrow contains multipotential progenitor cells such as bone marrow mesenchymal stem cells. MSCs have

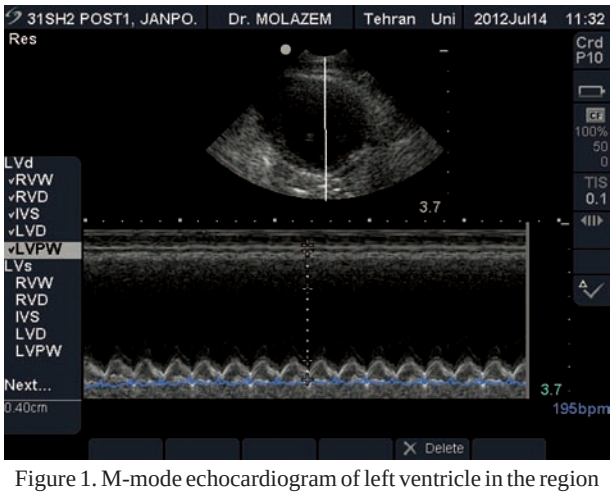

Figure 1. M-mode echocardiogram of left ventricle in the region of papillary muscles on the right lateral transverse view.

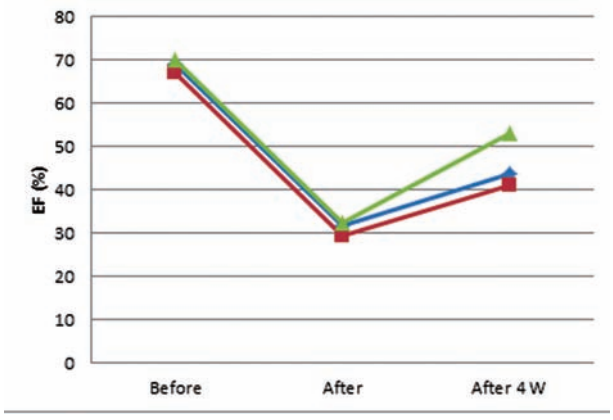

Figure 2. Ejection Fraction in all 3 groups decreased after the surgery and increased after 4 weeks, but still not to the normal value. S C I

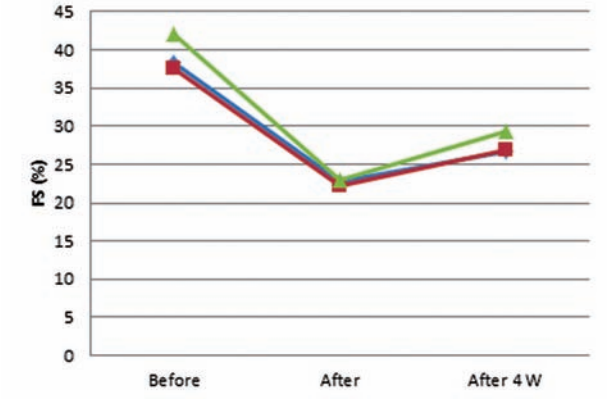

Figure 3. FS in all 3 groups decreased after the surgery and increased after 4 weeks, still not reaching the normal value. S C I

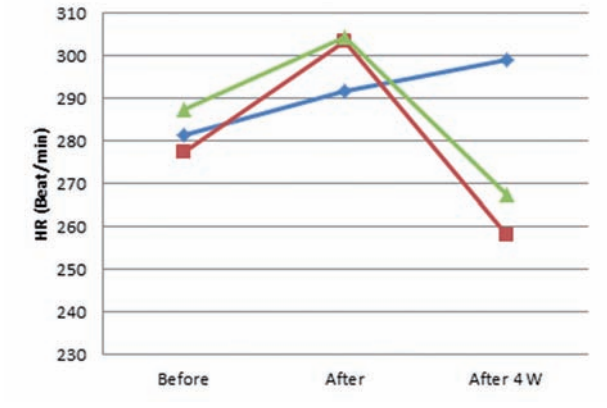

Figure 4. HR was increased after the operation in all 3 groups. In group I and S after 4 weeks the HR decreased, still not reaching the normal value. In group S it had no decrease even after 4 weeks. S C I

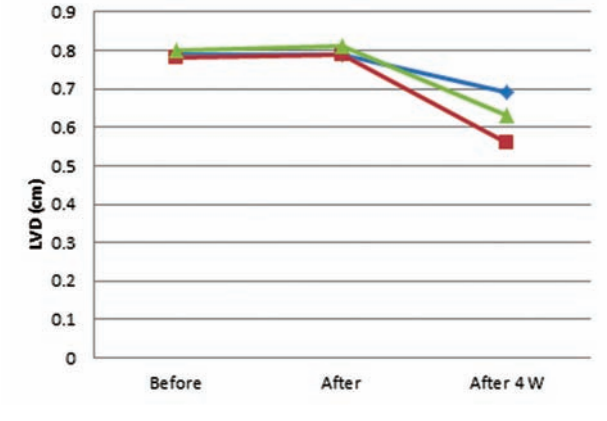

Figure 5. LVD in group S had no change after the surgery. however, it decreased during the 4 weeks. In group C and group I there was a slight increase after the surgery but it decreased after 4 weeks. S C I

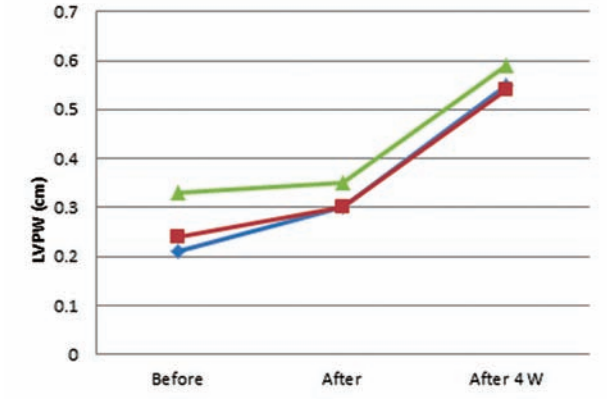

Figure 6. LVPW increased after the surgery and during the 4 weeks after the surgery in all 3 groups. S C I

significant capability for regeneration and multi-potential differentiation (Kocher et al., 2001).

Table 1. Ejection Fraction (%) (Values are means ±Std. Error).

Group	Before operation	After operation	4 Wks after operation	p-Value
S	69±3.34	31.75±2.49	43.75±5.28	p>0.05
C	67.2±3.03	29.4±1.80	41±2.96	p>0.05
I	70.25±1.43	32.25±3.35	53±1.82	p>0.05

Table 2. Fractional Shortening (%)(Values are means ±Std. Error).

Group	Before operation	After operation	4 Wks after operation	p-Value
S	38.25±4.21	22.75±2.39	26.75±2.42	p>0.05
C	37.60±1.02	22.20±1.62	26.80±3.44	p>0.05
I	42±2.79	23±2.27	29.25±2.17	p>0.05

Table 3. Heart Rate (beat/min) (Values are means ±Std. Error).

Group	Before operation	After operation	4 Wks after operation	p-Value
S	281.50±12.76	291.75±7.26	299.25±6.93	p>0.05
C	277.40±11	303.40±10.97	258.20±20.01	p>0.05
I	287.25±7.99	304.50±4.44	267.25±10.37	p>0.05

Table 4. Left Ventricular Diameter (cm) (Values are means ±Std. Error).

Group	Before operation	After operation	4 Wks after operation	p-Value
S	0.79±0.02	0.79±0.008	0.69±0.03	p>0.05
C	0.78±0.04	0.79±0.003	0.56±0.05	p>0.05
I	0.80±0.03	0.81±0.03	0.63±0.04	p>0.05

Table 5. Left Ventricular Parietal Wall (cm) (Values are means ±Std. Error).

Group	Before operation	After operation	4 Wks after operation	p-Value
S	0.21±0.01	0.30±0.01	0.55±0.11	p>0.05
C	0.24±0.01	0.30±0.009	0.54±0.14	p>0.05
I	0.33±0.03	0.35±0.04	0.59±0.14	p>0.05

Hoemann et al., in 2005 recorded positive effects of Chitosan Glycerol Phosphate plus whole blood used to promote cartilage regeneration in rabbits and proved that adding coagulating factors to this mixture can increase its solidification and effectiveness (Hoemann et al., 2005).

Many researchers have found that cultured MSCs could be induced to differentiate into myogenic cells (Tomita et al., 1999; Kocher et al., 2001), neurons, skin cells, etc. Adding 5-azacytidine (Kocher et al., 2001) into culture medium could facilitate MSCs differentiation into myogenic cells. Nevertheless, Nassiri et al. in their research concluded that although MSCs can improve cardiac function after MI induction, differentiated stem cells have no preference to undifferentiated cells (Nassiri et al., 2007). In the present study no chemicals were used to induce MSCs to differentiate into myogenic cells.

Jian- an wang et al., in 2004 proved that human bone marrow-derived mesenchymal stem cells transplanted into damaged rabbit heart will improve heart function (Wang et al., 2005).

Cardiomyoplasty by using Matrijel and other similar compounds in combination with stem cells in infarcted myocardium had positive results in several studies (Christman, Randall, 2006; Zimmermann, Eschenhagen, 2007; Volders et al., 1993).

Kofidis et al. (Kofidis et al., 2004; Kofidis et al., 2005) reported the advantages of injectable scaffolds plus stem cells transplanted into the infarcted myocardium. Usage of other kinds of biologic scaffolds like Fibrin has been reported in some other studies (Christman, Fok et al., 2004; Christman et al., 2004).

In future studies, BrdU labeled cells would help researchers to control the likely survival and transdifferentiation of injected stem cells in scaffold.

Another way to be able to accurately assess scaffold influences is to add a fourth group of MSCs only to future study. In this way researchers would be able to compare the fourth group with the MSCs plus scaffold group.

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مجله طب دامی ایران، ۱۳۹۲، دوره ۷، شماره ۱، ۱۳-۷

بررسی اثر سلول بنیادی مزانشیمی به همراه داربست قابل تزریق بر عملکرد قلبی در آنفارکتوس میوکارد در خرگوش

نازنین جعفری[۱] داودشریفی[۱*] محمد مهدی دهقان[۱] محمد ابرکار[۲] محمد حجازی[۳] پگاه عباس نیا[۱] محمد ملازم[۱] امیر توکلی[۱] روح اله مهدی نوازاقدم[۴] سید حسین احمدی تفتی[۵] پرویز تاجیک[۱]

۱) گروه علوم درمانگاهی، دانشکده دامپزشکی دانشگاه تهران، تهران، ایران
۲) گروه علوم درمانگاهی، دانشکده دامپزشکی دانشگاه آزاد اسلامی واحد کرج، ایران
۳) گروه علوم دامی، دانشکده کشاورزی دانشگاه آزاد اسلامی، واحد خرم آباد، خرم آباد، ایران
۴) گروه نانوتکنولوژی، موسسه تحقیقات مهندسی، تهران، ایران
۵) مرکز قلب تهران، دانشگاه علوم پزشکی تهران، تهران، ایران

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چکیده

زمینه مطالعه: سلول‌های بنیادی مزانشیمی در کاهش اندازه محل آنفارکته و بهبود عملکرد قلبی اثرات مثبتی دارند. به تازگی استفاده از داربست‌های قابل تزریق زیست تخریب پذیر افق‌های نوینی را در زمینه مهندسی بافت قلب گشوده است. استفاده از داربست‌های زیست سازگار و زیست تخریب پذیر می‌توانند همانند ماتریکس خارج سلولی، نقش داربست نگهدارنده‌ای را برای سلول‌ها ایفا نماید و از طریق ارتقای ارتباط میان سلول‌ها، بافت میزبان و داربست، باعث تحریک و افزایش میزان تکثیر، رشد و تمایز سلول‌ها شود. کیتوسان به دلیل زیست سازگاری و سطوح آبدوست، چسبندگی ،تکثیر سلولی و تمایز سلولی را تقویت می‌کند. این پلیمر در ترکیب با فسفات گلیسرول در یک محیط اسیدی رقیق یک ترکیب حساس به دما ایجاد می‌کند که در دمای بدن قابلیت ژله‌ای شدن دارد. **هدف:** هدف از انجام این مطالعه ارزیابی اثر تزریق سلول بنیادی مزانشیمی خودی بر گرفته از مغز استخوان به همراه داربست قابل تزریق از جنس کیتوسان گلیسرول فسفات در بهبود عملکرد قلبی متعاقب آنفارکتوس میوکارد در خرگوش بود. **روش کار:** شریان کرونری نزولی قدامی چپ قلب خرگوش توسط نخ بخیه پلی آمید ۰-۶ لیگاتور شد. سلول بنیادی مزانشیمی خودی به همراه داربست در اطراف ناحیه آنفارکته تزریق گردید. بررسی اکوکاردیوگرافیک عملکرد قلبی در سه زمان پیش از القاء آنفارکتوس، بلافاصله بعد از القاء آنفارکتوس و در پایان مطالعه یعنی ۴ هفته پس از القاء آنفارکتوس صورت پذیرفت. **نتایج :** در بررسی اکوکاردیوگرافیک ۵ فاکتور شامل Ejection Fraction (EF)، Fractional Shortening (FS)، ضربان قلب در دقیقه (HR)، ضخامت دیواره جانبی بطن چپ (LVPW)، و قطر داخلی بطن چپ (LVD) اندازه گیری شدند. نوسانات این فاکتورها در ۳ گروه در طی ۴ هفته اختلاف معنی دار نداشتند($p>۰/۰۵$). **نتیجه‌گیری نهایی:** در این مطالعه مجموعه داربست و سلول اثرات بهبود بخشی مورد انتظار را به همراه نداشته است.

واژه‌های کلیدی: اکوکاردیوگرافی، سلول بنیادی مزانشیمی، داربست

*)نویسنده مسؤول: تلفن: ۶۱۱۱۷۰۳۶ (۲۱) ۹۸+ نمابر: ۶۶۴۳۸۳۲۷ (۲۱) ۹۸+ *Email: dsharifi@ut.ac.ir*