AMLS Archives of Medical Laboratory Sciences

Original Article

Association between Bone Marrow Mesenchymal Stem Cell Characterizations and the Administration of Antiarrhythmic Drugs in Patients with Severe Left Ventricular Dysfunction after Off-Pump Bypass Surgery

Mansour Esmailidehaj[1], Seyed Jalil Mirhosseini[2], Zakieh Sadat Sheikhalishahi[1*]

1. Department of Physiology, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
2. Yazd Cardiovascular Research Center, Afshar Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Received: August 2019, Accepted: October 2019

Abstract

Background and Aim: Atrial fibrillation is the most common arrhythmia after coronary artery bypass grafting (CABG) and occurs in up to 30% of patients with heart failure. Mesenchymal stem cells (MSCs) can regenerate and improve cardiac function after tissue damage and are used in clinical trials. Due to the possible ability of MSCs to improve cardiac functions, in this work, we aimed to examine the probable association of the MSCs proliferation rate with the requirement for antiarrhythmic drugs in patients with severe left ventricular dysfunction after off-pump CABG.
Methods: Bone marrow samples were obtained from the sternum of 30 patients who underwent off-pump CABG at Afshar Hospital and Seyed Al-Shohada Hospital. For calculating MSCs doubling time, the cells were counted after 4, 7, and 14 days using trypan-blue color and a hemocytometer.
Results: There were no significant differences between MSCs' doubling time and the patient's age and gender. The percentage of women patients who require antiarrhythmic medicine was significantly higher than men after surgery. Also, we demonstrated that the BMSCs doubling time in female patients who received antiarrhythmic drugs was less than that of male patients who received antiarrhythmic drugs, but these differences were not significant.
Conclusion: Based on this research, we concluded that women patients who received antiarrhythmic drugs were significantly higher than men, but there was no apparent relevancy between MSCs doubling time and antiarrhythmic drugs requirement in patients with severe left ventricular dysfunction.

Keywords: Severe Left Ventricular Dysfunction; Antiarrhythmic Drug; Mesenchymal Stem Cell; Doubling Time.

[*]**Corresponding Author:** Zakieh Sadat Sheikhalishahi; **Email:** z.sheikhalishahi@gmail.com

Please cite this article as:
Esmailidehaj M, Mirhosseini SJ, Sheikhalishahi ZS. Association between Bone Marrow Mesenchymal Stem Cell Characterizations and the Administration of Antiarrhythmic Drugs in Patients with Severe Left Ventricular Dysfunction after Off-Pump Bypass Surgery. Arch Med Lab Sci. 2020;6:1-5 (e2). https://doi.org/10.22037/amls.v6.31297

Introduction

Today, despite many advances in treatment approaches, cardiac diseases are still responsible for millions of deaths worldwide, both in developed and developing societies (1). Severe left ventricular dysfunction is a condition in which the contractile strength of the myocardium is decreased, and the ejection fraction is reduced to less than 30% (2). Atrial fibrillation is the most common arrhythmia after coronary artery bypass grafting (CABG), which occurs in up to 30% of patients (3). This status is considered as unpleasant complications, including hemodynamic and thromboembolic problems and hospitalization period (4). Several antiarrhythmic drugs are commonly used to prevent atrial fibrillation after CABG. Administration of antiarrhythmic drugs reduced costs and hospitalization time and other complications (5).

The cause of atrial fibrillation is unknown, and the prevention and management of arrhythmia are crucial because it may lead to irreversible side effects. In the last two decades, novel regenerative medicine for cardiac tissue repair has been developed (6-8).

Bone marrow-derived mesenchymal stem cells (BMSCs) are non-differentiated cells that can convert to many cell types of differentiated and active cells (9, 10). The findings of many studies have claimed that under suitable circumstances, MSCs can gain primary morphological features of cardiac cells (11, 12). Numerous in vivo studies have demonstrated that MSCs may be a promising therapeutic approach for the treatment of heart disorders (13). Due to the possible ability of MSCs to improve cardiac functions, we aimed to investigate the relationship between the proliferation rate of MSCs and taking antiarrhythmic drugs in patients with severe left ventricular dysfunction after off-pump CABG.

Methods

Study design and population

Briefly, in this study, 30 patients with severe left ventricular dysfunction based on clinical findings, were randomly selected from patients referring to Seyed Al-Shohada hospital and Afshar hospital. The exclusion criteria included: patients with other heart diseases such as valvular heart disease, diabetes, and infectious diseases, and ejection fraction > 30. The study protocol was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences.

The patients filled in a written informed consent before study entry. All data were regarded as confidential.

Culture of human bone marrow mesenchymal stem cells

Bone marrow samples (1 mL) were obtained from sternum during off-pump CABG surgery from patients with severe left ventricular dysfunction. For isolating mesenchymal stem cells from bone marrow, the aspirated samples were diluted with minimum essential medium (αMEM). Samples were centrifuged, and then, cell pellets were resuspended in α MEM containing 20% fetal bovine serum (FBS) (Gibco, USA) and 1% streptomycin/penicillin (Gibco, USA), and cultured in 25 cm^2 flasks at 37 °C in a humidified incubator containing 5% CO_2.

Doubling time of the BMSCs

For evaluating the relationship between age, gender, and the taking antiarrhythmic drugs with MSC proliferation, population doubling times for all experimental groups were assessed. Briefly, 5000 cells were seeded in 6-well plates. Cells for each well were trypsinized and counted in 4, 7, and 14 days using trypan blue color and a hemocytometer. The counted cells' outcomes were plotted for the MSCs population, and doubling times were calculated from the log phase of the growth curve.

Statistical analysis

The GraphPad Prism Version 8 software (GraphPad Software, San Diego, CA, USA) was utilized to figure out data. All results are presented as mean ± standard deviation (SD). The two groups were compared using the unpaired t-test.

Results

The relationship between age and BMSCs doubling time

Human bone marrow-derived MSCs did not differ in size and phenotype in all patients (Figure 1). In this study, 30 patients with left ventricular dysfunction were confirmed by the surgeon, which included 18 man and 12 women cases, with a median age of 60 years (range of 50–70 years). Figure 2 shows the relationship between the doubling time of BMSCs and the age of patients. There was no significant difference in the doubling time and age of patients (r^2=0.0032).

The relationship between gender and BMSCs doubling time

Figure 3 displays the mean of BMSCs doubling time in male and female patients. There was no relevant discrepancy in the doubling time in males and females. The mean ± SD in the group of men was 230 ± 69, and in the group of women was 202 ± 56.

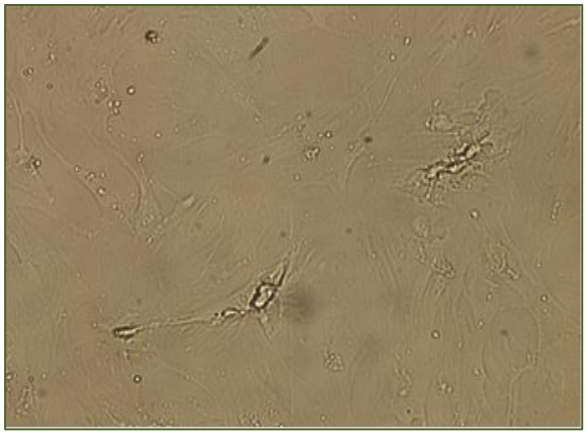

Figure 1. Bone marrow-derived MSCs after extraction and culture**.**

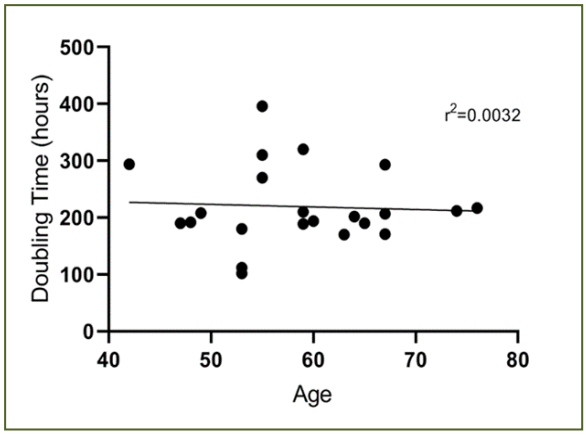

Figure 2. The relationship between the patients' age and BMSCs doubling time.

The association between taking antiarrhythmic medication and BMSCs doubling time.

Figure 4A illustrates that among 18 male patients in this study, two patients required antiarrhythmic drugs after surgery, while five female patients required antiarrhythmic drugs after surgery. Therefore, the percentage of women in antiarrhythmic drug requirements was significantly higher than men after surgery. Figure 4B possesses that the mean of BMSCs doubling time in female patients (207 ± 72) who received antiarrhythmic medication was less than that of male patients (283 ± 159) who received antiarrhythmic medication, but the difference was not substantial. Also, there was no disparity in BMSCs doubling time in man (224 ± 58) and women (198 ± 48) patients who did not receive medication.

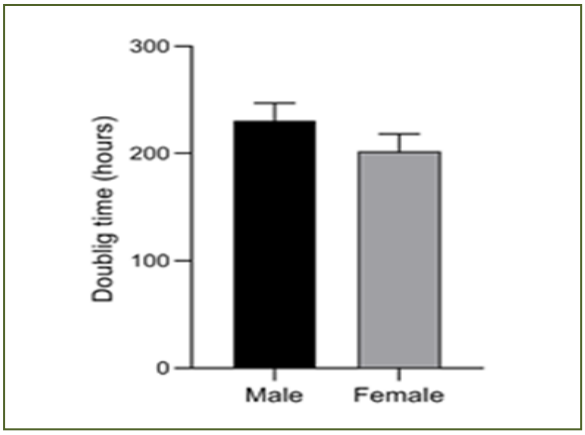

Figure 3. The relationship between gender of patients and BMSCs doubling time.

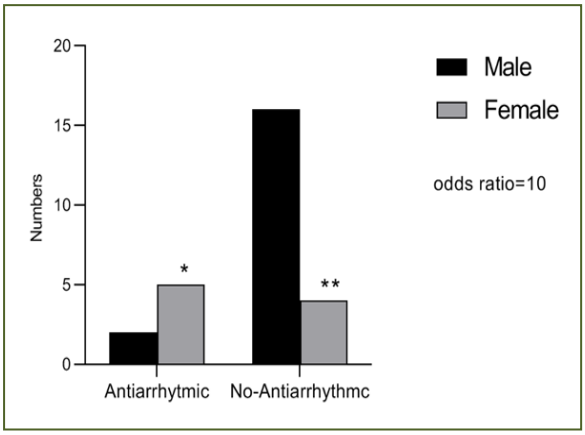

Figure 4A. The relationship between antiarrhythmic drug requirements in male and female patients.

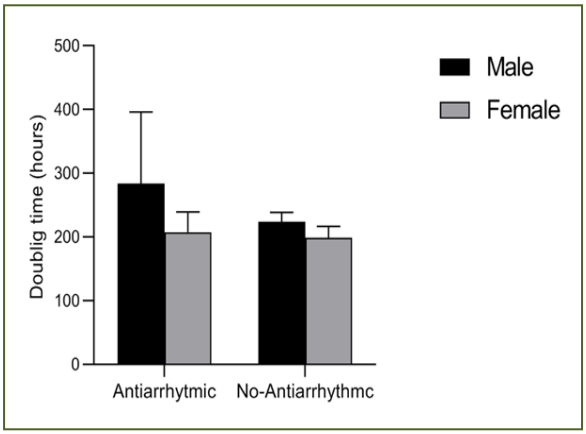

Figure 4B. The relationship between MSCs and antiarrhythmic drugs taking in in male and female patients.

Discussion

Based on our results, the percentage of women who need antiarrhythmic drugs was significantly higher than men after surgery. Our data showed that the

doubling time of BMSCs in female patients who received antiarrhythmic medications was less than that of male patients, but these differences were not substantial.

Today, despite noticeable advances in medical science, the prevalence of the cardiac disease is increasing globally (14, 15). Severe left ventricular failure after MI, a circumstance in which the reduction in blood flow and the reduction of oxygen delivery to the ventricular myocardium can cause the pump function failure and arrhythmia (16-18). Therefore, new therapeutic approaches for the treatment of heart failure should aim at reducing arrhythmia as well as improving hemodynamic function. Mesenchymal stem cell therapy is a promising option to improve cardiac function after MI (19, 20). However, some studies have shown that the injection of MSCs into infarcted myocardium increases the risk of arrhythmias. In 2011, Deguo Wang et al. reported that MSCs injection ameliorates the inducibility of ventricular arrhythmias after myocardial infarction in rats (21).

In contrast, some studies have recently reported that MSC therapy after acute MI related to reducing arrhythmias (22-24). Therefore, whether MSCs therapy causes the risk of arrhythmia is still vague. In the present study, two male patients and five female patients required antiarrhythmic drugs after surgery. The mean ± SD of doubling time of BMSCs in female patients who received antiarrhythmic drugs was less than that of male patients who received antiarrhythmic drugs, but the difference was not significant. A large number of studies have concluded that the ability of MSCs differentiation decreased with increasing age. However, some studies have shown that increasing age has nothing to do with the ability of MSCs differentiation (25). In 2011, Asumda et al. examined the relationship in age changes and MSCs in rats. They reported that with increasing age, the ability of MSCs differentiation was decreased (26). In our study, there was no significant relationship between the BMSCs doubling time and the patients' age. In female patients, the doubling time became longer with increasing age, but this doubling time was not remarkable due to the distribution of data and the number of patients. This decrement in the proliferation rate or increase of doubling time can be related to the decrease in telomere length and the activity of telomerase enzyme.

Conclusion

The results of the present study showed that there was not a clear relationship between the rate of MSCs proliferation and patients' age and gender after CABG. Based on the present research conclusion, the doubling time of bone marrow-derived MSCs in female patients who received antiarrhythmic drugs was less than that of male patients with the same situations, but these differences were not significant. This insignificancy may be due to our small number of patients, and it is suggested that the present study be performed on a larger scale.

Conflict of Interest

The authors declared that they have no conflict of interest.

Acknowledgment

Not to declare.

Funding/Support

The authors declared that there is no financial support for this work.

Ethics

The study protocol was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences with this code (IR.SSU.MEDICINE.REC.1397.199).

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