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Research article

PROMISING MESENCHYMAL STEM CELL INTERVENTION FOR RELIEVING CARDIAC RECOVERY AGAINST CARDIOTOXIC INJURY MODELING WITH DOXORUBICIN: A NOVEL THERAPEUTIC APPROACH

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Doxorubicin (DOX), a commonly used anti-neoplastic agent, has been associated with significant cardiotoxic effects, which limit its clinical utility. Recent studies suggest that mesenchymal stem cells (MSCs) may offer therapeutic potential in mitigating DOX-induced cardiotoxicity through their regenerative properties. This study aimed to evaluate the cardioprotective effects of fetal kidney-derived mesenchymal stem cells (FKD-MSCs) in a DOX-induced cardiotoxicity rat model. Thirty male Sprague-Dawley rats were divided into three groups: control, sham, and treatment. DOX (10 mg/kg) was administered to the sham and treatment groups to induce cardiotoxicity. The treatment group received intraperitoneal FKD-MSCs (2 x 10^6) three times at weekly intervals post-DOX administration. Immunohistochemical analyses were conducted to assess cardiac recovery. The 5-bromo-2-deoxyuridine (BrdU) labeling technique was used to track FKD-MSC localization in the cardiac tissue. The immunohistochemical findings demonstrated a significant improvement in the treatment group compared to the sham group. The BrdU-labeled FKD-MSCs were predominantly localized in cardiac muscle tissues, indicating their successful homing and integration into damaged cardiac regions. The results of the study indicate that FKD-MSCs significantly attenuated DOX-induced cardiotoxicity in rats, suggesting their potential as a novel therapeutic approach for cardioprotection. Further studies are warranted to investigate their clinical applications in managing chemotherapy-induced cardiotoxicity.

Keywords: doxorubicin, stem cells, cardiotoxic, recovery

INTRODUCTION

Doxorubicin (DOX) is an anthracycline drug. It is an anti-neoplastic agent used to treat many neoplastic diseases in humans and animals [1]. Cardiotoxicity is a significant side

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effect that occurs during antineoplastic therapy. The rates of cardiotoxicity studied in vitro and in vivo are mainly due to the formation of free radicals, leading to cardiac apoptosis or oxidative stress in combination with immunological treatments. However, other mechanisms may also contribute to antineoplastic-induced cardiotoxicity [2].

Mesenchymal stem cells (MSCs) are multipotent stem cells that can easily proliferate in vitro and can differentiate into various cell lines. They can be easily isolated from many tissues such as bone marrow, umbilical cord, placenta, and adipose tissue [3]. Following administration, these cells have been observed to migrate to the site of injury, where they have been shown to exert paracrine effects by releasing signals that promote repair in the affected region [4]. Consequently, the therapeutic potential of MSCs in the treatment of numerous diseases remains a subject of ongoing investigation.

Stem cell therapy is a procedure in which stem cells or progenitor cells are transplanted into the heart to enhance tissue repair, neovascularization, and functional recovery after myocardial injury. The therapeutic potential of different stem cell types, including mesenchymal stem cells (MSCs), cardiac progenitor cells (CPCs), and induced pluripotent stem cells (iPSCs), in promoting cardiovascular regeneration has been a subject of ongoing research [5]. Several studies have also demonstrated the therapeutic effects of MSCs in various diseases. The administration of MSCs has shown beneficial effects on cardiac recovery in experimental cardiotoxicity models. Intraperitoneal administration of fetal kidney-derived mesenchymal stem cells (FKD-MSCs) has been shown to prevent DOX-induced cardiotoxicity in rats, as evidenced by improved histopathological findings, reduced fibrosis, and modulation of apoptosis and anti-apoptotic development [6]. In addition, various types of MSCs, when administered either locally or systemically, have been found to improve cardiac function, reduce inflammation, and ameliorate myocardial fibrosis in cases of anthracycline-induced cardiotoxicity [7]. Furthermore, bone marrow MSCs, their exosome, and vitamin E have shown therapeutic benefits in reducing cyclophosphamide-induced cardiotoxicity, with MSCs being the most effective [8]. Moreover, MSCs that have been pretreated with platelet-rich plasma (PRP) have demonstrated enhanced attenuation of DOX-induced cardiotoxicity in comparison with MSCs administered alone, with improved oxidative stress, inflammation, and cardiac apoptosis markers [9]. Overall, these findings suggest that MSC application holds promise for cardiac recovery in experimental cardiotoxicity models. However, the impact of FKD–MSCs administration in DOX-induced cardiotoxicity in rats has not been previously studied.

This study aimed to treat DOX-induced cardiomyopathy in rats by intraperitoneal administration of FKD-MSCs and to demonstrate the improvement of cardiotoxicity by immunohistochemical methods.

MATERIALS AND METHODS

Preparation of Fetal Kidney-Derived Mesenchymal Stem Cells

Hysterectomies were performed on pregnant Sprague-Dawley rats (day 19 of gestation) by midline laparotomy, and fetuses were obtained. The fetuses were anesthetized and euthanized with ether. Kidney samples were removed from the fetuses and stored in Dulbecco's Modified Eagle's Medium (DMEM) (Lonza, Belgium). The FKD-MSCs were prepared following the methods outlined in the researchers' previous study [6]. The obtained FKD-MSCs were then incubated in a culture medium containing 5-bromo-2-deoxyuridine (BrdU; 5 μmol/L, Invitrogen) for 48 hours before transplantation.

Experimental protocol

The rats were housed under standard laboratory conditions (21 ± 2 °C, 65% humidity, and 12 h light/12 h dark). Rats were fed standard rat chow ad libitum and provided with constant access to water. Thirty male, 10-week-old Sprague Dawley rats were randomly divided into three groups: control, sham, and treatment. To induce cardiotoxicity, 10 mg/kg DOX (Doxorubicin, 10 mg, Koçak Farma) dissolved in 0.9% NaCl was administered to the sham and treatment groups as a single injection via the tail vein.

Control group (n=10): did not receive DOX and/or FKD-MSCs. 0.9% NaCl (same volume as MSCs) was administered intraperitoneally to the rats 3 times at weekly intervals.

Sham group (n=10): received DOX only, no treatment. 0.9% NaCl (same volume as MSC) was administered intraperitoneally to the rats 3 times at weekly intervals, 7 days after DOX injection.

Treatment group (n=10): received DOX and FKD-MSCs. The rats were given 2 x 10^6 MSC injections intraperitoneally, 3 times at weekly intervals, 7 days after DOX injection.

The rats were monitored for five weeks. Rats were euthanized under general anesthesia with xylazine (Xylazinbio 2 %, 10 mg/kg, i.p., Bioveta, Ivanovicena Hane, Czech Republic) and ketamine (Ketasol 10 %, 75 mg/kg, i.p., Richter Pharma AG, Wels, Austria). Cardiac tissue samples were obtained, and immunohistochemistry was performed.

Immunohistochemical method

The indirect immunoperoxidase method was utilized to perform immunohistochemical examinations. For this purpose, the method used by Yavuz and Dinçel was modified [10]. Sections of cardiac tissue were taken from paraffin blocks and placed on polylysine slides, with a thickness of five microns. These were then deparaffinized in xylols,

rehydrated in graded alcohols, and stained according to the NovoLinkTM Max Polymer Detection System (RE7280-K) kit procedure. The removal of endogenous peroxidase activity was achieved through a series of washing steps: initially with Proteinase K for 15 minutes at room temperature, followed by three washes with de-ionized water for 5 minutes each. This was then followed by the addition of 3% hydrogen peroxide solution. They were then washed with PBS twice for 5 minutes each, Protein Block for 5 minutes, PBS twice for 5 minutes each, primary antibody (anti-BrdU) for 1 hour at room temperature, PBS twice for 5 minutes each, Post Primary Block for 30 minutes, PBS twice for 5 minutes each, NovoLink Polymer for 30 minutes, PBS twice for 5 minutes each, and incubated with DAB for 3-5 minutes at room temperature. After washing with distilled water, the sections were counterstained with Mayer's hematoxylin, changed twice in alcohol and xylol, and covered with entellan. The sections were examined under a binocular light microscope and photographed.

Immunohistochemical scoring

Immunohistochemical scoring of the cases was performed according to the Allred system. The method used by Özgermen et al was modified and applied [11]. According to this scoring system, staining intensity and staining prevalence were evaluated in two categories similar to standard scoring systems. According to this method, the staining intensity (darkness) score was determined as 0 (no staining), 1 (weak), 2 (moderate), and 3 (intense/dark). Staining prevalence was determined based on the ratio of stained cells to all cells in the area examined as follows: 0 (no staining), 1 (> 0 – 1/100), 2 (> 1/100 – 1/10), 3 (> 1/10 – 1/3), 4 (> 1/3 – 2/3), 5 (> 2/3 – 1). The Allred score between 0-8 was determined for each case by adding the staining intensity score and staining prevalence value. To determine the score, 10 different microscope fields were randomly examined at x400 magnification and the average of the scores obtained was accepted as the score of the related case.

Statistical analysis

Statistical analyses and graphs were performed using GraphPad Prism version 10.1.2. The significance of immunohistochemical findings was determined by Kruskal-Wallis and Mann-Whitney U tests. $P < 0.05$ was considered to indicate statistically significant differences between groups.

RESULTS

The statistical results of the immunohistochemical findings are shown in Figure 1, Figure 2, Figure 3, and Table 1. The mean values of right ventricular wall (RVW), interventricular septum (IVS), and left ventricular wall (LVW) in the MSC groups were statistically determined to be 4.375, 4.200, and 4.325, respectively, and in the control groups these values were determined to be 0.800, 1.500, and 0.733, respectively. In

the DOX groups, the mean values of RVW, IVS, and LVW were 0.900, 1.117, and 1.350, respectively. According to immunohistochemical staining, RVW, IVS, and LVW of the MSC group showed the most diffuse and strong immunostaining by the anti-BrdU antibody. When all groups were compared, there was a statistically significant difference ($p<0.05$) between the MSC group and the other groups (Fig. 1).

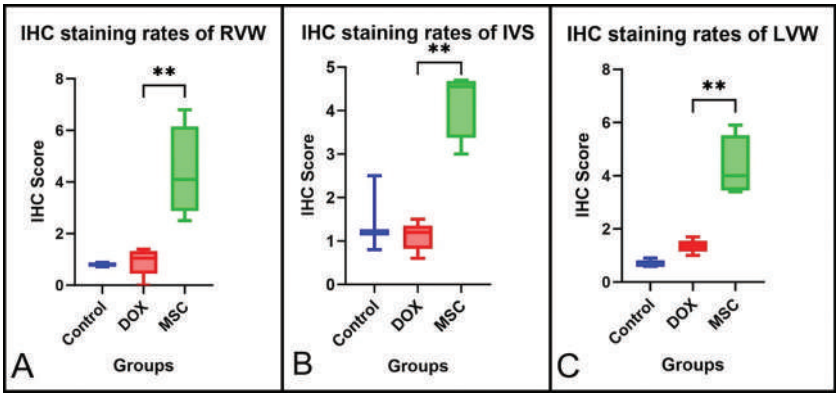

Figure 1. Immunohistochemical staining rates of the groups. **A.** Right ventricle wall. **B.** Interventricular septum. **C.** Left ventricle wall. Asterisks mean that there is a statistically significant difference between the groups.

On the other hand, differences in immunostaining were evaluated in the ventricular walls of the hearts within each group. It was found that the immunostaining of the cardiac walls was not significantly different ($p>0.05$) for all cardiac walls (Fig. 2).

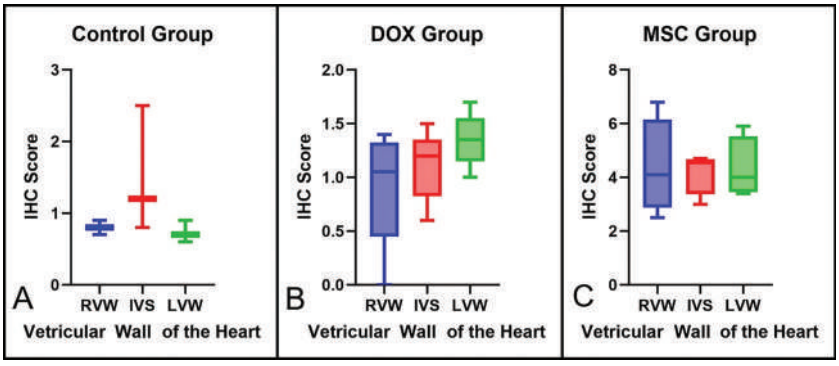

Figure 2. When the ventricular walls of the heart were evaluated, the most intense and severe staining in all three groups was observed in the heart sections in the MSC group. **A.** Control Group. **B.** DOX group. **C.** MSC Group.

Positive immunostaining was observed mainly in the intracytoplasmic areas of the myocardial filaments in the MSC groups. It was observed that the staining showed a homogeneous distribution within each heart wall. The intensity and severity of

the positive staining in this group were higher than in the other groups, whereas the staining in the other two groups (control and DOX) was minimal (Fig. 3).

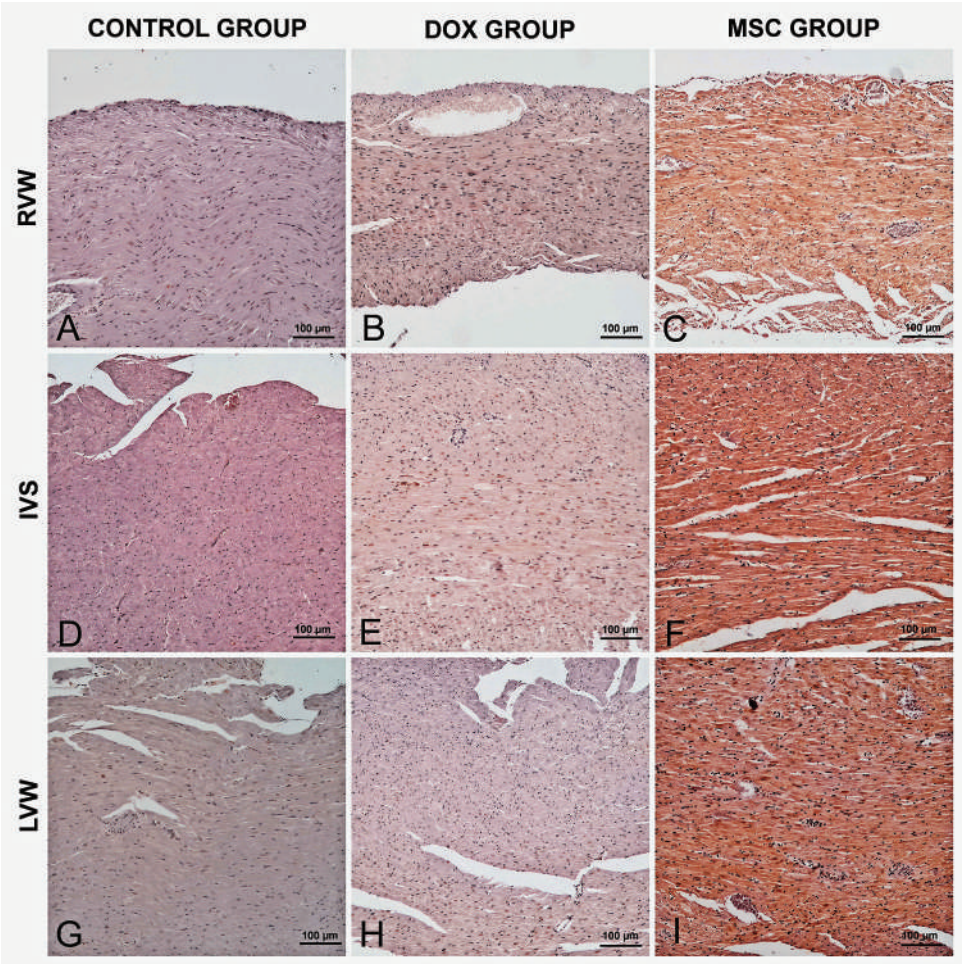

Figure 3. Immunohistochemical staining of the groups. **A.D.G.** Control Group. Negative immunostaining in the heart muscle fibers in the RVW, IVS, and LVW. DAB. x100 magnification. **B.E.H.** DOX Group. Negative immunohistochemical reactions in all three groups in the muscle filaments. DAB. x100 magnification. **C.F.I.** MSC Group. Strong positive immune reactions in the muscle fibers in all three heart walls. DAB. x100 magnification.

Table 1. Immunohistochemical staining scores of the groups.

	Control (Mean ± Std Error)	DOX (Mean ± Std Error)	MSC (Mean ± Std Error)
RVW	0.800 ± 0.057^{b}	0.900 ± 0.216^{b}	4.375 ± 0.892^{a}
IVS	1.500 ± 0.513^{b}	1.117 ± 0.130^{b}	4.200 ± 0.402^{a}
LVW	0.733 ± 0.088^{b}	1.350 ± 0.099^{b}	4.325 ± 0.567^{a}

Explanations: a, b– means with different superscript letters differ significantly at $p \leq 0.05$ according to Mann Whitney U test.

DISCUSSION

DOX is a highly effective antineoplastic agent in the treatment of various tumor types. However, DOX administration leads to cardiac toxicity, resulting in an increased risk of mortality, which limits its widespread clinical use in cancer patients. The most serious and dangerous side effect is cardiotoxicity, which can irreversibly alter cardiac function. DOX can cause severe cardiotoxicity and progressive myocardial failure [12]. However, the cardiotoxic side effects of doxorubicin have not prevented its use as an antitumor agent, and efforts to reduce the side effects have gained prominence.

After intravenous administration, DOX exhibits linear pharmacokinetics and is widely distributed in plasma and tissues. It is eliminated by the liver and kidneys and has a biological half-life of five minutes and 30-40 hours. DOX is cleared from plasma much faster than from myocardium [13]. This difference in clearance rates may account for the increased sensitivity of the heart to DOX.

Shivakumar et al. showed that weekly administration of DOX for 4 weeks resulted in histologic changes in the heart, kidney, liver, and testes. The toxicity group showed focal areas of interfibrillar hemorrhage, congestion, and disrupted myofibrils in cardiac sections [14]. Chen et al. investigated the effects of cumulative 15 mg/kg DOX treatment in an experimental rat model and observed myocyte degeneration, myocyte loss, myocyte atrophy, hypertrophy of residual myocytes, and increased interstitial fibrosis in histopathologic examination of myocardial tissue two weeks after DOX treatment [15]. As a precursor to the present study, Yavuz et al. reported that DOX caused vacuoles and hyaline degeneration as well as necrosis and fibrosis in cardiac tissue. They stated that MSCs used for therapeutic purposes against DOX decreased the severity of histopathologic findings [6]. In the present study, it is suggested that obtaining positive immunoreactions of anti-BrdU in the MSC group is evidence of recovery of histopathologic findings.

Multipotent stem cells can differentiate into mesoderm, endoderm, and ectoderm. Studies have demonstrated that in cultures containing appropriate growth factors, MSCs can differentiate into many cell types, including endothelial cells, cardiomyocytes, hepatocytes, neuron-like cells, astrocytes, muscle, cartilage, bone cells, and adipocytes [16].

Several animal and clinical studies have demonstrated the ability of different types of MSCs to protect and restore the myocardium against anthracycline-induced cardiotoxicity [17]. Local or systemic administration of MSCs has been demonstrated to significantly improve cardiac function, and to alleviate inflammatory responses and myocardial fibrosis [7]. Systemic transplantation of MSCs is a well-established method, but in many studies, investigators injected the cells directly into the tissue of interest. Furthermore, one study found that MSCs injected intravenously in rats were retained in the lungs. Lung retention of MSCs has not been reported in humans and was successfully prevented in rats by administration of vasodilators [18]. In a

study of 34 patients, 8-10x10^9 MSCs were infused into the infarct-related coronary artery following angioplasty, approximately 18 days after acute transmural myocardial infarction (MI) (treatment group), while 35 patients received saline (sham group). At 3 – and 6-month follow-up, an improvement in cardiac function was observed in the treatment group receiving MSCs [19]. In the first-in-human study of allogeneic MSC transplantation to cancer survivors, a total of 1x108 allogeneic MSCs derived from healthy human bone marrow were administered via 20 trans-endocardial injections. The results of this study showed that trans-endocardial injection of allogeneic MSCs is safe and feasible in patients with anthracycline-induced cardiomyopathy [20]. In our study, we preferred intraperitoneal administration of MSCs as it is a minimally invasive method that does not require anesthesia for the rats. We aimed to investigate the effects of intraperitoneally administered FKD-MSCs on DOX-induced cardiotoxicity in rats.

Several previous studies have used different labeling techniques to visualize MSCs after transplantation. Some of these techniques include membrane dyes (e.g., PKH, DiI, DiO), magnetic resonance imaging (MRI) labeling (nanoparticles Fe), DNA dyes (5-bromo-2'-deoxy-uridine, BrdU), or gene transfer labeling (adenovirus-mediated expression of enhanced green fluorescence protein (EGFP) and β-galactosidase) [21]. BrdU labeling is a frequently used technique; however, it has some limitations. BrdU is a toxic and mutagenic agent, and has been demonstrated to induce cell death and teratoma formation. Previous studies have demonstrated that it also alters DNA stability and cell cycle prolongation, and has mitogenic, transcriptional, and translational effects on the labeled cells. However, these adverse effects can be reduced by optimizing the BrdU concentration [22]. Based on the results of previous studies, we cultured the FKD-MSCs used in our study with 5μM BrdU. This concentration was determined to be optimal for labeling the MSCs without causing significant differences in cell viability.

In a study conducted in miniswine, BrdU-labeled bone marrow MSCs were injected through the coronary artery of the animals after acute MI. The optimal time window for transplantation of MSCs was determined using targeted ultrasound microbubbles loaded with SDF-1α antibody. The results indicated that the number of transplanted MSCs in the myocardium was highest in the first week [23]. In the present study, BrdU-labeled FKD-MSCs were administered intraperitoneally to rats that had DOX-induced cardiotoxicity. The rats were monitored for five weeks, and the BrdU-labeling procedure enabled the in vitro tracking of the homing of the MSCs within the cardiac tissue at the end of the experiment.

CONCLUSION

DOX has proven to be an effective antineoplastic agent for multiple types of cancer. However, its widespread use in cancer chemotherapy is limited by several systemic side

effects. However, its clinical utility is limited by systemic side effects specific to cardiac tissue, which can cause toxicity.

Stem cell therapy is a promising treatment option for DOX-induced cardiotoxicity; however, it is currently in the preclinical stage. In this context, MSCs have many properties that make them a suitable choice for the prevention and treatment of cardiac diseases, including DOX-induced cardiac injury.

In previous studies, many mesenchymal stem cells obtained from different sources and labeled by different methods were used to reduce the cardiotoxic effects of doxorubicin. The outcomes of these studies predominantly yielded positive results. The results of our study demonstrated that BrdU-labeled fetal kidney-derived mesenchymal stem cells were localized in cardiac tissue when administered intraperitoneally in the DOX-induced cardiotoxicity model in rats. Consequently, these findings suggest that FKD-MSCs could serve as a promising alternative stem cell source for the prevention of DOX-induced cardiotoxicity. A comprehensive review of the literature reveals that this study is the first and pioneering study in the field to investigate FKD-MSCs in the DOX cardiotoxicity model in rats.

This suggests that FKD-MSCs can be safely used as a cardioprotective agent. Further studies should be carried out at different times and doses, and the results should be supported by electrocardiography and echocardiography findings.

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Ethical statement

The experimental protocol was approved by the Local Animal Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital (Approval number: 2014/55).

Authors' contributions

DBBO, AEH, and OY participated in the conceptualization, methodology, validation, investigation, original draft, writing, and manuscript review. DBBO and AEH participated in the acquisition of data and analysis. OY participated in the interpretation of data. DBBO and AEH conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

There is no conflict of interest between the authors.

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REFERENCES

1. Alegra CJ, Curt GA: Chemotherapy of neoplastic diseases. In Brunton, L.L. Lazo, J.S., Parker, K.L. (Eds.), Goodman & Gilman's the Pharmacological Basis of Therapeutics 2006, (pp. 1315– 1404). McGraw-Hill, New York
2. Monica L, Giancarlo, Elpidio MG, Franca A, Antonia F, Stefania P, Vincenzo T, Marina D: Animal models in studies of cardiotoxicity side effects from antiblastic drugs in patients and occupational exposed workers. BioMed Res Int 2014, 240642. https://doi.org/10.1155/2014/240642
3. Orbay H, Tobita M, Mizuno H: Mesenchymal stem cells isolated from adipose and other tissues: basic biological properties and clinical applications. Stem Cells Int 2012, 461718.
4. Luger D, Lipinski MJ, Westman PC, Glover DK, Dimastromatteo J, Frias, JC, Epstein SE: Intravenously delivered mesenchymal stem cells: systemic anti-inflammatory effects improve left ventricular dysfunction in acute myocardial infarction and ischemic cardiomyopathy. Circ Res 2017, 120(10):1598-1613.
5. Elendu C, Amaechi DC, Elendu TC, Amaechi EC, Elendu ID, Omeludike JC, Omeludike EK, Onubogu NC, Ogelle EC, Meduoye OOM, Oloyede PO, Ezeh CP, Esangbedo IJ, Adigwe AC, Akuma NM, Okafor SU: Essential information about nanotechnology in cardiology. Ann Med Surg (Lond) 2025, 87(2):748-779.
6. Orhan Y, Başak Ö, Haydardedeoğlu AE, Gungor, CD: Cardioprotective effects of fetal kidney-derived mesenchymal stem cells on doxorubicin-induced cardiotoxicity in rats. Medycyna Weterynaryjna 2022, 78 (2):79-84.
7. Lan H, Xue Q, Liu Y: The emerging therapeutic role of mesenchymal stem cells in anthracycline-induced cardiotoxicity. Cell Tissue Res 2021, 384:1-12
8. Gugjoo MB: Mesenchymal Stem cells therapeutic applications in cardiovascular disorders. in therapeutic applications of mesenchymal stem cells in veterinary medicine 2022, p. 213-245. Singapore: Springer Nature Singapore.
9. Helal OK, Mansy AE, Aly OM, Salama NA: Histological and immunohistochemical study of the possible therapeutic effect of mesenchymal stem cells, their exosomes and vitamin E on experimentally induced cardio-toxicity in adult male albino rats. Benha J Appl Sci 2020, 23(5):165-175.
10. Yavuz O, Dinçel GÇ: Expression of cox-2, hmgb-1 and cd68 in lung tissue in sheep fibrinous bronchopneumonia. Medycyna Weterynaryjna 2020, 76(1):46-52.
11. Özgermen B, Yavuz O, Haydardedeoğlu AE: Investigation of the effects of mesenchymal stem cell administration on liver recovery in experimental hepatotoxicity model. J Adv Vetbio Sci Tech 2022, 7(2):185-193.
12. Tanwar SS, Dwivedi S, Khan S, Sharma S: Cardiomyopathies and a brief insight into DOX-induced cardiomyopathy. The Egyptian Heart Journal 2025, 77(1). doi:10.1186/s43044-025-00628-0

13. Rawat PS, Jaiswal A, Khurana A, Bhatti JS, Navik U: Doxorubicin-induced cardiotoxicity: An update on the molecular mechanism and novel therapeutic strategies for effective management. Biomed Pharmacother 2021, 139:111708.
14. Shivakumar P, Rani MU, Reddy AG, Anjaneyulu Y: A study on the toxic effects of Doxorubicin on the histology of certain organs. Toxicol Int 2012, 19(3):241-244.
15. Chen X, Chen Y, Bi Y, Fu N, Shan C, Wang S, Xu J: Preventive cardioprotection of erythropoietin against doxorubicin-induced cardiomyopathy. Cardiovasc Drugs Ther 2007, 21(5):367-374.
16. Kuang Z, Ge Y, Cao L, Wang X, Liu K, Wang J, Zhu X, Wu M, Li J: Precision treatment of anthracycline-ınduced cardiotoxicity: an updated review. Curr Treat Options Oncol 2024, 25(8):1038-1054.
17. Abushouk AI, Salem AM, Saad A, Afifi AM, Afify AY, Afify H, Abdel-Daim MM: Mesenchymal stem cell therapy for Doxorubicin-induced cardiomyopathy: potential mechanisms, governing factors, and implications of the heart stem cell debate. Front Pharmacol 2019, 10:635.
18. Fox JM, Chamberlain G, Ashton BA, Middleton J: Recent advances into the understanding of mesenchymal stem cell trafficking. Br J Haematol 2007, 137(6):491-502.
19. Chen SL, Fang WW, Qian J, Ye F, Liu YH, Shan SJ, Zhang JJ, Lin S, Liao LM, Zhao RC: Improvement of cardiac function after transplantation of autologous bone marrow mesenchymal stem cells in patients with acute myocardial infarction. Chin Med J (Eng) 2004, 117:1443-1448.
20. Bolli R, Perin EC, Willerson JT, Yang PC, Traverse JH, Henry TD, Simari RD: Allogeneic mesenchymal cell therapy in anthracycline-induced cardiomyopathy heart failure patients. JACC: Cardio Oncol 2020, 2(4):581-595
21. Nagyova M, Slovinska L, Blasko J, Grulova I, Kuricova M, Cigankova V, Cizkova D: A comparative study of PKH67, DiI, and BrdU labeling techniques for tracing rat mesenchymal stem cells. In Vitro Cell Dev Biol Anim 2014, 50(7):656-663.
22. Li N, Yang H, Lu L, Duan C, Zhao C, Zhao, H: Comparison of the labeling efficiency of BrdU, DiI and FISH labeling techniques in bone marrow stromal cells. Brain Res 2008, 1215:11-19.
23. Yang L, Hu R, Yuan C, Guan L, Mu Y: Screening of the best time window for MSC transplantation to treat acute myocardial infarction with SDF-1α antibody-loaded targeted ultrasonic microbubbles: An *in vivo* study in miniswine. Open Life Sci 2023, 18(1):20220620.

INTERVENCIJA MEZENHIMALNIM MATIČNIM ĆELIJAMA ZA UBRZAVANJE OPORAVKA SRCA OD KARDIOTOKSIČNE POVREDE DOKSORUBICINOM: NOVI TERAPIJSKI PRISTUP

Deva Basak Boztok OZGERMEN, Ali Evren HAYDARDEDEOGLU, Orhan YAVUZ

Doksorubicin (DOX), često korišćeni antineoplastični agens, povezan je sa značajnim kardiotoksičnim efektima, što ograničava njegovu kliničku primenu. Nedavne studije sugerišu da mezenhimalne matične ćelije (MSC) mogu ponuditi terapeutski potencijal

u ublažavanju kardiotoksičnosti izazvane DOX-om kroz svoja regenerativna svojstva. Cilj ove studije bio je da se procene kardioprotektivni efekti mezenhimalnih matičnih ćelija preuzetih iz fetalnih bubrega (FKD-MSC) u modelu kardiotoksičnosti izazvane DOX-om na pacovima. Trideset mužjaka Sprague-Dawley pacova podeljeno je u tri grupe: kontrolnu, lažnu i grupu za tretman. DOX (10 mg/kg) je primenjen na lažnu i grupu za tretman da bi se indukovala kardiotoksičnost. Tretirana grupa je primala intraperitonealno FKD-MSC (2×10^6) tri puta u nedeljnim intervalima nakon primene DOX-a. Imunohistohemijske analize su sprovedene da bi se procenio oporavak srca. Tehnika obeležavanja 5-bromo-2-deoksiuridinom (BrdU) korišćena je za praćenje lokalizacije FKD-MSC u srčanom tkivu. Imunohistohemijski nalazi su pokazali značajno poboljšanje u tretiranoj grupi. FKD-MSC obeležene BrdU-om bile su pretežno lokalizovane u tkivima srčanog mišića, što ukazuje na njihovo uspešno naseljavanje i integraciju u oštećene srčane regione. Rezultati studije pokazuju da FKD-MSC značajno ublažavaju kardiotoksičnost izazvanu DOX-om kod pacova, što sugeriše njihov potencijal kao novog terapijskog pristupa kardioprotekciji. Potrebna su dalja istraživanja kako bi se ispitala njihova klinička primena u upravljanju kardiotoksičnošću izazvanom hemoterapijom.