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ORIGINAL ARTICLE

Therapeutic Role of Intravenous Mesenchymal Stem Cells Infusion in A Rat Model of Induced Acute Myocardial Infarction

Eman S. El-Shetry [a*], Adel M. Salah El-Din Taha [a], Aya M. El Gazzer [a], Mohamed Saad El-Shetry [b], Doaa M. Hendawy [c], Eman M. Borai [c]

[a] Department of Human Anatomy and Embryology, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[b] Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[c] Department of Biochemistry, Faculty of Medicine, Zagazig University, Zagazig, Egypt

***Corresponding author**
Eman S. El-Shetry
E-mail address:
eman.saad1@yahoo.com

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ABSTRACT

Background: Acute Myocardial Infarction (AMI) is a well-established cause of morbidity and mortality globally in spite of recent breakthroughs in medical therapy as reperfusion methods, implantable cardioverter-defibrillators, and ventricular assist devices. In myocardial infarction treatment, bone marrow-derived mesenchymal stem cells (BM-MSCs) are expected to demonstrate encouraging results. This study aimed to evaluate the feasible anti-inflammatory and antioxidant
role of BM-MSCs infusion in rat model with induced myocardial infarction.

Methods: Rats were randomized into an experimental (AMI) group induced by Adrenaline injection, and a control group. The (AMI) group was divided into 2 subgroups (AMI+PBS) and (AMI+BM-MSCs). The consequences of BM-MSCs infusion on cardiac inflammation and oxidative stress status were observed after 3 days of cell transplantation.

Results: BM-MSCs transplantation reduced the production of the inflammatory cytokine (TNF-a) & oxidative stress markers (MDA), increased anti-inflammatory IL-10 & antioxidant SOD, and improved histological changes in the ischemic myocardium.

Conclusions: This study provides evidence that BM-MCSs suppress oxidative stress and inflammation in cardiac tissue and relatively offer cardiac protection in AMI.

Keywords: Acute Myocardial Infarction**;** Mesenchyme Stem Cells**;** Rat Model

INTRODUCTION

Cardiovascular disease (CVD) is a major public health issue that affects a vast number of individuals all over the world. CVD has an abnormal high prevalence and it usually complicated with approximately 10% of comorbidities and 30% of the total mortality rate **[1].** Acute myocardial infarction (AMI) usually commences as a result of decreasing the blood supply of the heart. AMI encountered a dramatic decline in the number of surviving cardiomyocytes, apparent necrosis, various inflammatory responses, and remodeling myocardial processes. AMI is usually followed by a consecutive reactive remodeling of the injured myocardium with a healing by fibrous tissue. This fibrous tissue may deleteriously affects the cardiac functions with development of heart failure that poses imminent hazards to the patients' life **[2].** Clinically, thrombolysis, implantation of coronary stent or coronary artery bypass grafting have all been utilized in the management of AMI, however these therapeutic maneuvers cannot totally reduce the disease pathogenesis, restore the damage to the infarcted myocardium, or enhance the heart function. Finding a way to improve the AMI-induced heart dysfunction by regenerating the injured and non-functioning myocardium has become a mandatory research issue. Therefore, in recent decades, the scientists have directed their great attention towards management of AMI via using a new strategies, particularly using the stem cell therapy aiming to repair the injured myocardium and restore the myocardial performance **[3].**

Experimentally, stem cell therapy is one of the newest research methods for management of AMI. The stem cells are frequently tried in the regenerative medicine because of their two characteristic properties; self-renewal and potentiality to specialize into various tissues **[4]**. Actually, mesenchymal stem cells are easily extracted from the stroma of many tissues, like bone marrow, adipose tissue, muscle, and the synovial membranes. These mesenchymal cells are considered multipotent and self-renewing cells that display the surface markers like CD44, CD73, CD90, and CD105, with multilineage differentiation to adipocytes, osteoblasts, chondroblasts, and cardiomyocytes **[5].**

Of particular, bone marrow mesenchymal stem cells (BM-MSCs) are known to be the optimal and the most commonly used type of the mesenchymal stem cells being are easily accessible, non-toxic, and ethically safe with high tissue proliferation and differentiation potential. They also have minimal immunogenicity and high immunomodulatory capability along with decreasing the immune rejection effectively **[6].**

The therapeutic role of BM-MSCs is attributed mainly to their paracrine mechanism of action with production of many mediators and cytokines as vascular endothelial growth factor, interleukin 6, platelet-derived growth factor, fibroblast growth factor, hepatocyte growth factor, and insulin-like growth factor which were found to modulate the inefficient myocardial function **[7].**

BM-MSCs had been used as regenerative therapeutic tool in many CVD with promising outcomes. For instance, BM-MSCs induced myogenesis and angiogenesis in a dilated cardiomyopathy (DCM) rat model with marked improvement in cardiac dysfunction **[8]**. Also, they markedly suppressed the malignant ventricular arrhythmias in experimentally-induced myocardial infarction a rat model **[9].**

Therefore, this study was conducted to evaluate the potential effect of BM-MSCs in the management of AMI induced in a rat model via assessing the oxidative stress and the inflammatory pathways generated in the ischemic myocardium following AMI.

METHODS

Animals and ethical approval:

Forty adult male albino rats (200-250 grams body weight) were obtained from the Faculty of Medicine's laboratory animal house in Zagazig University, Egypt. The rats were housed at 24°C and a 12-hour light/dark cycle. The rats had a free accessibility to water and fed a balanced conventional pellet diet. They were adapted for two weeks before any experimental procedure to be adjusted to the new lab. environment. The experiment was authorized by the Institutional Animal Care and Use Committee (IACUC) of Zagazig University, Egypt with a reference number (Approval no: ZU-IACUC/3/F/136/2021). The rats were treated according to the national institute of health (NIH) animal care guidelines.

Induction of AMI and Experiment protocol:

The rats were grouped randomly into 2 main groups: Control and Adrenaline-induced AMI groups.

Group I (Control group): 15 rats were supplemented with distilled water, a conventional balanced diet and phosphate buffer solution (PBS) for 2 weeks.

Group II (Adrenaline-induced AMI): 25 rats in which AMI was induced by injecting the rats subcutaneously (SC) with two doses of adrenaline (2 mg/kg once daily for two successive days with 24 hours apart) **[10]**, One day after the second dose of adrenaline, AMI was confirmed by markedly high serum cardiac enzymes (three times higher than control values); 5 rats from both groups were anaesthetized by an intraperitoneal sodium thiopental injection (45 mg/kg) **[11]**. and the heart tissue was examined for the ischemic changes then the experimental group II was further subdivided into two subgroups, 10 rats each:

Subgroup IIa (AMI untreated rats): was injected in the tail vein with 500 µL PBS per rat.

Subgroup IIb (AMI+BM-MSCs treated rats): was injected in the tail vein by 2.0×10^6 BM-MSCs /rat suspended in PBS **[12].**

After 3 days of BM-MSCs infusion, the rest of the rats from all groups (I, IIa, IIb) were sacrificed and the heart samples were collected and each divided into two parts, part for histological examination, and the other (30 mg) was homogenized for assessment of inflammatory/anti-inflammatory & oxidant/antioxidant markers.

Preparation of BM-MSCs:

The BM-MSCs were obtained from the Stem Cell and Clinical Chemistry Laboratory, Medical Biochemistry & Molecular Biology Department, Faculty of Medicine, Zagazig University, Egypt. The BM-MSCs were isolated from 6-week-old rats according to **Lennon & Caplan [13]** Bone marrow was obtained from the rats tibiae and femurs and kept with Iscove's Modified Dulbecco's Medium

(IMDM, Gibco, USA) in culture flasks containing 10% fetal bovine serum & 1% penicillin-streptomycin (Gibco, USA) in 5% CO2 incubator at 37°C. At 70-80% confluence, 0.25% trypsin-EDTA (Gibco, USA) was used to detach the cells that were sub-cultured at the ratio of 1:2. Experiments were carried out using third-passage cells, then isolated cells were identified by their plastic adherent capability and the shape of their spindles (elongated shape) which is detected by an inverted microscope [14] After 3rd passage, the BM-MSCs were washed 2 times with PBS, resuspended in culture media, and intravenously infused after AMI confirmation **[15].**

BM-MSCs labeling with (PKH-26):

Before rat injection, Paul Karl Horan 26 (PKH26) red was used to label the BM-MSCs as a fluorescence marker using Fluorescent Cell Linker Kit (Sigma, St. Louis, Missouri, USA). The cardiac tissue sections of the AMI-BM-MSCs treated rats (subgroup IIb) were examined by the fluorescent microscope (Olympus BX50F4, No. 7M03285, Tokyo, Japan) in Medical Biochemistry & Molecular Biology Department, Faculty of Medicine, Zagazig University, Egypt.

Assay of serum cardiac enzymes:

24 hours following AMI induction, blood samples were collected via retro-orbital vein puncture in dry clean tubes. Sera were obtained by blood centrifugation for 15 minutes at 2500 rpm. By automatic pipettes, the clear sera were separated then analyzed for cardiac troponin I (cTnI) and creatine kinase MB (CK-MB) levels by enzyme-linked immunosorbent assay (ELISA) Kits (Pointe Scientific, Inc. USA).

Assay of cardiac inflammatory/anti-inflammatory & oxidant/antioxidant markers:

The obtained cardiac samples, after 3 days of BM-MSCs infusion, were kept at -20 °C, then homogenized using 5 ml cold buffer; 100 mM potassium phosphate, pH 7.0, containing 2 mM EDTA/gram tissue. After centrifuging for 15 minutes at 50,000 rpm, the clear supernatant was collected and kept at -80 °C [15] to be utilized for colorimetric assessment of the inflammatory cytokine (TNF-α in pg/ml) and the anti-inflammatory cytokine (Interleukin-10 in pg/g cardiac tissue) using ELISA kits (MyBiosource.INC) according to kit instructions. Also, the oxidative stress biomarker (MDA in nmol/g cardiac tissue) and the antioxidant superoxide dismutase enzyme activity (SOD in U/g protein) were assessed using a Rat MDA ELISA Kit (CUSABIO. INC) and rat SOD ELISA kit (CUSABIO. INC), respectively.

Histological study:

The left ventricles from each group were taken, fixed in 10% neutral buffered formalin and finally immersed in paraffin wax blocks and cut into 5 µm thick sections. H&E staining was used to stain the cardiac sections and assessing the general histopathological changes that occur in response to AMI and evaluate the improvement that may occur after BM-MSCs infusion **[16].**

Statistical analysis:

All data were analyzed using the SPSS (Statistical Package for Social Science) version 18.0. One-way ANOVA was used to compare the mean values of different groups. The post-hoc Tukey test was used for multiple comparisons. A $p<0.05$ was considered as a statistical significant value and a $p>0.05$ was considered as a non-statistical significant value.

RESULTS:

BM-MSCs characterization and Fluorescence microscope results:

Morphologically, the BM-MSCs were characterized by their fusiform shape and attachment to plastic. These cells had a spindled, fibroblast appearance after expansion **Fig. (1a).** The cardiac tissues sections showed bright dots that represented the PKH-26 labeled cells **Fig. (1b)**

Results of serum cardiac enzymes:

There was a statistical significance increase in the serum cTnI and CK-MB in the AMI rats in comparison to the control rats **(Table 1).**

Results of inflammatory/anti-inflammatory & oxidant/antioxidant markers:

Regarding the inflammatory/anti-inflammatory cytokines, the subgroup IIa (AMI untreated rats) exhibited a significant increase ($p<0.05$) in the mean value of cardiac TNF-α also, a significant reduction ($p<0.05$) in the cardiac anti-inflammatory IL-10 in comparison with group I (control rats). However, intravenous infusion of BM-MSCs in Subgroup IIb (AMI-BM-MSCs treated rats) caused a significant decrease ($p<0.05$) in the mean value of cardiac TNF-α and a significant increase ($p<0.05$) in cardiac IL-10 compared to the subgroup IIa **(Table 2).**

Concerning the oxidative stress markers, the subgroup IIa (AMI untreated rats) displayed a significant elevation ($p<0.05$) in the mean value of cardiac lipid peroxidation marker MDA and a significant decrease ($p<0.05$) in the cardiac antioxidant marker (SOD) in comparison with group I. However, intravenous infusion of BM-MSCs in subgroup IIb caused a significant decrease ($p<0.05$)

in the mean value of cardiac MDA and significant increase ($p<0.05$) in the cardiac SOD activity in comparison to subgroup IIa **(Table 3).**

Histopathological results

Regarding histopathological examination, the control group (I) showed normal cardiac tissue histology with normally arranged branching and anastomosing cardiomyocyte, normal acidophilic cytoplasm, normal large vesicular nuclei, with flat dark nuclei of fibroblasts are also seen **(Fig. 2a)**. While in the sections used to confirm AMI of the AMI (Group II) after 24 h, it showed the sign of ongoing inflammation and necrosis; in the form of waviness and wide separation of cardiac muscle fibers, hyperesinophilic cytoplasm, small dark pyknotic nuclei and marked inflammatory cell infiltration **(Fig. 2b)**. After 3 days of BPS injection, in subgroup IIa (AMI untreated rats), the signs of inflammation and necrosis is markedly increased with marked cardiac tissue destruction, waviness of muscle fibers, marked wide separation, hyperesinophilic cytoplasm, small dark pyknotic nuclei and marked inflammatory cell infiltrate are seen to be increased **(Fig. 2c)**. After 3 days of BM-MSCs infusion in the treated group IIb (AMI+MSCs), there were marked reduction in the signs of inflammation and tissue destruction in contrast to the subgroup IIb (AMI untreated rats). As preservation of the cardiac architecture were observed, hyper eosinophilic cytoplasm is not detected, minimal blood extravasation, few small pyknotic nucleus, milder interstitial edema, many normal vesicular nuclei were seen and inflammatory cell infiltrates are markedly decreased **(Fig. 2d)**.

Table 1: CK-MB and Troponin I levels between studied groups

Group / Variable	Group I Control	Group II AMI	t	P
CKMB (ng/ml)	**5.9±0.75**	**35.01±4.2**	**33.53**	**<0.05****
Troponin (ng/ml)	**0.049±.034**	**0.892±0.05**	**57.30**	**<0.05****

Data presented as mean ± SD, number of rats=5, SD: standard deviation, t: Independent t test, **: Highly significant ($P<0.05$)

Table 2: Effect of stem cells on Inflammatory Markers between studied groups

Group / Variable	Group I Control	Group IIa AMI	Group IIb (AMI+BM-MSCs)	t	P
IL-10 pg/ml (3^{rd} day)	**138.47±5.06**	**89.7±5.6 A**	**125.9±8 AB**	**156.009**	**<0.05****
TNF pg/ml (3^{rd} day)	**72.69 ±7.5**	**139.9 ±30 A**	**104.6 ±3 AB**	**34.97**	**<0.05****

Data presented as mean ± SD, No of rats in each group = 10 rats, SD: standard deviation, F: ANOVA test, **:Highly significant ($P<0.05$), Post hoc Tukey test, A : Highly significant versus GI, B : Highly significant versus GIIa

Table 3: Effect of stem cells on oxidative stress markers between studied groups

Group / Variable	Group I Control	Group IIa AMI	Group IIb (AMI+BM-MSCs)	t	P
SOD U/ml (3^{rd} day)	**217±7.7**	**120±9 A**	**180±7 AB**	**376.145**	**<0.05****
MDA nm/ml (3^{rd} day)	**13.75±0.71**	**25.9±1.53A**	**17.4±0.93 AB**	**314.193**	**<0.05****

Data presented as mean ± SD, No of rats in each group = 10 rats, SD: standard deviation, F: ANOVA test, **:Highly significant ($P<0.05$), Post hoc Tukey test, A : Highly significant versus GI, B Highly significant versus GIIa

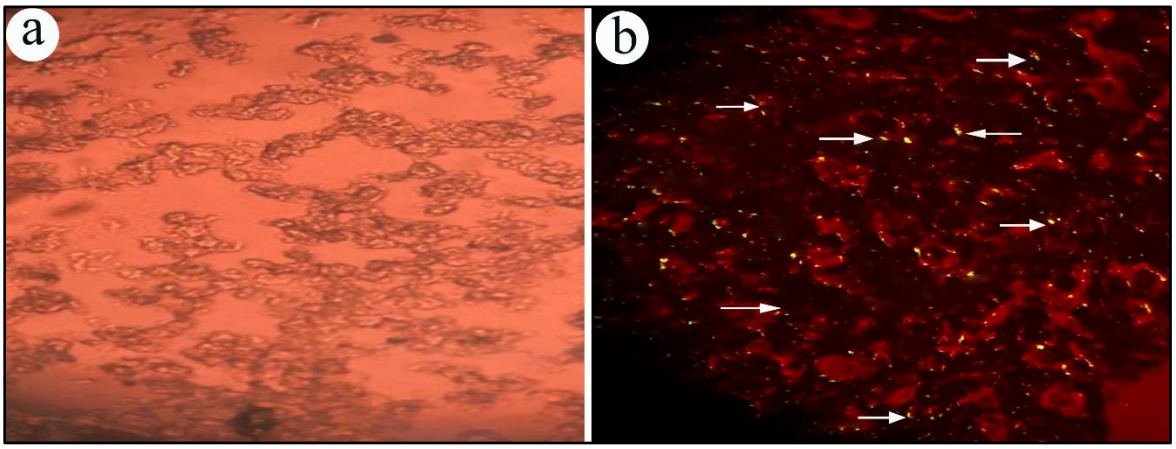

Figure 1: (a) BM-MSCs in colony formation in the 2nd week before trypsinization, (b) PKH26-labeled MSCs appearing as bright dots (arrows) in mesenchymal stem cell treated group (AMI+BM-MSCs)

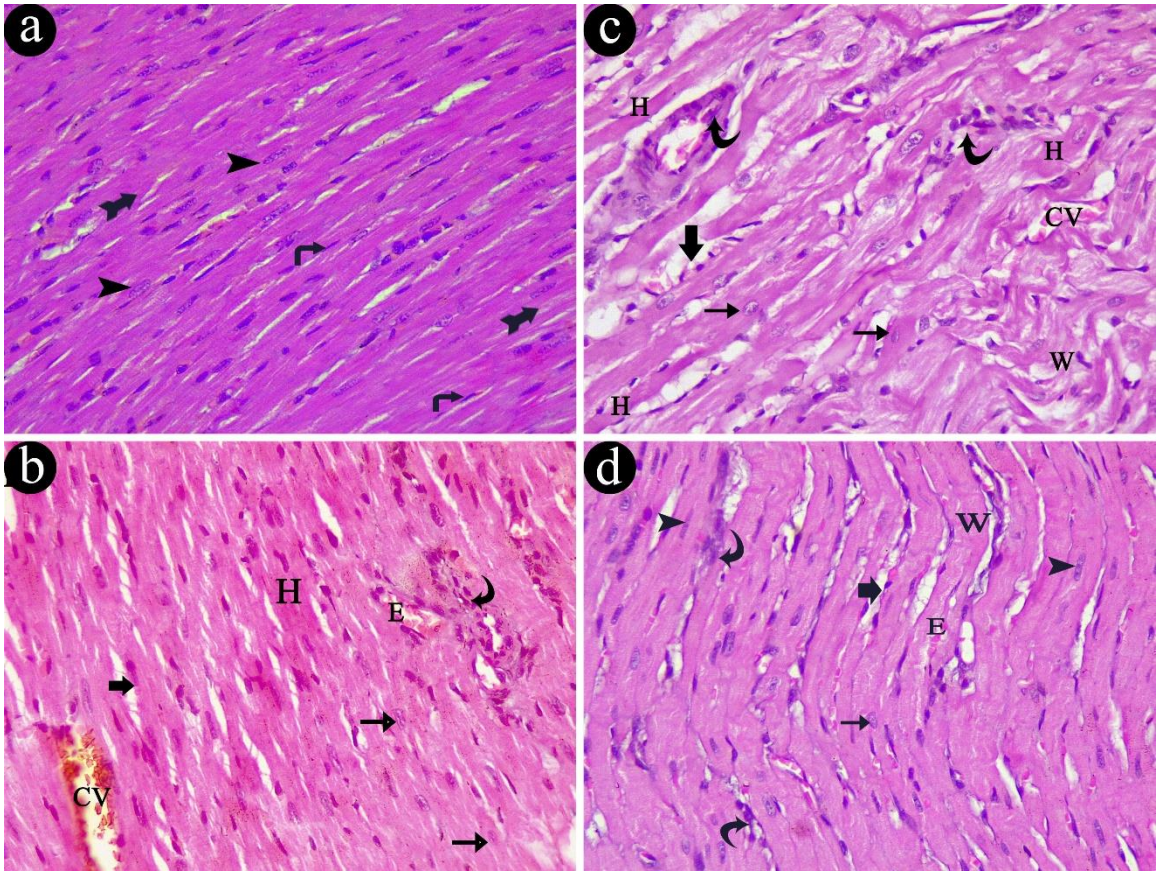

Figure 2: Photomicrograph of heart tissue stained with H&E. (a) control group I showing normally arranged branching and anastomosing cardiomyocytes (bifid arrow), normal large vesicular nuclei (arrowhead), normal fibroblast between cardiomyocytes are also seen (curved arrow) (b) after 24h of AMI induction, the experimental (AMI) group section showing hypereosinophilic cytoplasm (H) blood extravasation (E), small pyknotic nucleus (thin arrow), fibers separation (thick arrow), congested blood vessels (cv), and inflammatory cell infiltrates (curved arrow). (c) after 3 days of PBS injection in subgroup IIa (AMI untreated rats), showing marked destruction of cardiac architecture with muscle fibers waviness (W), marked fibers separation (thick arrow), hypereosinophilic cytoplasm (H), small pyknotic nucleus (thin arrow), congested blood vessels (CV), and marked inflammatory cell infiltrates (curved arrow). (d) after 3 days of cell infusion in subgroup IIb (AMI+MSCs) showing conservation of cardiac architecture hyper eosinophilic cytoplasm is not detected, minimal blood extravasation (E), few small pyknotic nucleus (Thin arrow) and milder fibers separation (thick

arrow), and milder inflammatory cell infiltrates (curved arrow) are seen, also many normal vesicular nuclei are seen (arrow head) (H&E X 400).

DISCUSSION

Animal models are being used to mimic and study human cardiac diseases which lead to heart failure such as myocardial infarction and ischemia-reperfusion. The acute myocardial infarction rat model is considered the best for studying the anatomical pathophysiology of the heart. The pathogenesis of AMI following blood supply cessation include 3 phases; inflammatory, proliferative, and healing phase **[17]**. Many central and peripheral pathways like oxidative, inflammatory, apoptotic pathways, overactive signals or chemokines cause exacerbated damage and dysfunction resulting in cell death and massive scar formation causing left ventricular dilation following myocardial infarction **[18].**

This research was constructed to investigate part of the inflammatory and oxidative changes that occur in AMI and the potential role of intravenous BM-MSCs transplantation as a new therapeutic implication after AMI induction.

AMI induction by adrenaline injection used in this work is the least invasive method to induce ischemic changes within the myocardium which had been confirmed by the increasing level of cardiac enzymes; CKMB and Troponin (both enzymes considered diagnostic criteria for AMI after 24 hr of MI induction and this was in consistence with **Mythili & Malathi, [19].** Also many previous studies used Catecholamines (epinephrine, nor epinephrine and Isoproterenol to induce MI [20], while others used surgical ligation of coronary arteries **[21]** which needs an expert and could be lethal to the animals.

Cardiac enzymes Assessment especially troponin level is considered the most sensitive, accurate method for AMI diagnosis [22], which also was confirmed by histopathological changes observed in the experimental rats 24 h. after AMI induction that showed the signs of ongoing coagulative necrosis as waviness of fibers, separating fibers, vascular congestion, blood extravasation, inflammatory cell infiltrates, pyknotic nuclei and hypereosinophilic cytoplasm that represent loss of cardiomyocytes striation and necrosis, while the tissue samples from the control group showed normal cardiac architecture and the interstitium showed no inflammatory cell infiltration or any other abnormalities, this come in consistence with **[23].**

BM-MSCs used in this study are most popular in application by many researchers due their low immunogenicity, easy extraction, isolation, expansion, proliferation, safety, effective transplantation, their capability for multidirectional differentiation, and they don't have ethical issue as they can be autologously transplanted **[24].** In the current experiment, BM-MSCs were infused intravenously 24_{hr} after MI induction which was preferred by many researchers as they showed that BM-MSCS homing if given intravenously is optimal within 24_{hr} of MI induction **[25].**

Three days after BM-MSCs infusion; the present study reported that AMI markedly elevated TNF-α which is a potent inflammatory trigger and has a significant role in AMI pathogenesis and deterioration of cardiac function and cardiac remodeling. Also, AMI markedly decreased the anti-inflammatory interleukin 10 (IL-10). On the contrary; BM-MSCs in group IIb reduced the local myocardial inflammation by marked suppression of TNF-α level and elevation of IL-10 which comes in coincidence with previous studies as **Guo et al [26]** who confirmed the anti-inflammatory action of BM-MSCs by decreasing TNF-α, IL-1β, and IL-6 and elevating IL-10. So BM-MSCs transplantation proved to modulate the immuno-inflammatory response in AMI and improved cardiac function. BM-MSCs were able to alternate the characteristic inflammatory response generated following AMI.

BM-MSCs also provoke anti-inflammatory signaling initiated with inhibitory subsets of monocytes and lymphocytes as well as anti-inflammatory macrophages, are well-suited to control the inflammatory process in the infarcted myocardium **[27].** The progression of inflammatory signals in the infarcted myocardium also depends on reactive oxygen species formation by ischemia **[28].** By stimulating all stages of inflammatory cell recruitment, ROS enhance leukocyte penetration into the repairing infarct **[29].** Increased oxidative stress leads to oxidation and destruction of energy-producing macromolecules such as proteins, lipids, DNA and enzymes resulting damage of the cells, energetic deficit and cell death acceleration through apoptosis and necrosis **[30].**

AMI in this study resulted in the previous cascade which was represented by marked elevation in MDA, and depletion of the intracellular anti-oxidant SOD, while the group treated by BM-MSCs showed marked reduction in MDA level and marked elevation in SOD level, and this can be attributed to the immunomodulatory, anti-infilmmatory, and anti-

oxidant paracine activity of BM-MSCs. **Stavely & Nurgali [31]** reported the ability of BM-MSCs to directly scavenging the free radicals, increasing endogenous antioxidant defenses. Also, BM-MSCs can secrete all isoforms of SOD in many disease as hepatic ischemia reperfusion injury, arthritis and hepatotoxicity **[32].**

The antioxidant enzymes counteract the effect of reactive species. Superoxide dismutase (SOD) and catalase are the most effective enzymatic antioxidants. The dismutation of superoxide anion to H2O2 is catalyzed by superoxide dismutase. Peroxidases like glutathione peroxidase or catalase then convert H_2O_2 to H_2O and O_2. When ROS production increase or there is diminished antioxidant defenses; antioxidant/pro-oxidant imbalance occur leading to oxidative damage **[33]**.

The histopathological examination of the cardiac tissue 3 days after BM-MSCs administration showed that AMI induced histopathological changes of acute inflammation and necrosis as increases the fibers waviness, increases interstitial edema, congestion, blood extravasation, and more pyknotic nuclei. While marked improvement of the cardiac tissue and marked reduction in the inflammatory cell infiltrate with preservation of the cardiac architecture were observed in the treated group IIa (AMI+MSCs) in contrast to the AMI. BM-MSCs role as cytoprotective was confirmed by **[34]** who showed that BM-MSCs administration had the ability to modulate both the inflammatory phase with reduction of inflammatory cells recruitment and the reparative phase leading eventually to preserve cardiac architecture after 30 days in rat model of ischemic cardiomyopathy.

The beneficial effect of BM-MSCs in our study is attributed to their paracrine action rather than differentiation into cardiomyocytes due to short duration of the experiment and this was in agree with **Du et al [35]**. Also, BM-MSCs transplantation after MI dramatically improve angiogenesis, boost apoptotic resistance, and perform anti-fibrotic effects thus increasing the repair of myocardium after infarction, according to research **[36].** BM-MSCs protect the myocardium, from inflammatory reactions and immune responses by ameliorating the remodeling process **[37].**

Also**, Aggarwal & Pittenger [38]** confirmed the cytoprotective effect of BM-MSCs on cardiomyocyte. BM-MSCs had been used in cardiovascular disease and showing promising outcomes due to their immunomodulatory, anti-inflammatory and antioxidant properties in vitro and in vivo.

Conclusions

From results of the present work, we concluded that AMI results in oxidative stress and initiates inflammatory cascade causing cardiac cell death, Intravenous administration of BM-MSCs is a valid promising therapeutic potential and can modulate these pathways via reverting them towards a normal physiological tone.

Conflict of Interest: None

Financial Disclosures: None

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