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THE EFFECT OF BONE MARROW DERIVED MESENCHYMAL STEM CELLS IN AMELIORATING CYTARABINE-INDUCED INJURY IN THE SUBMANDIBULAR SALIVARY GLANDS OF ALBINO RATS (IN VIVO STUDY)

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ABSTRACT

Objectives: Cytarabine is one of the potent chemotherapeutic drugs, that has many cytotoxic side effects. Our study was conducted to evaluate the possible ability of systemically injected bone marrow mesenchymal stem cells (BMMSCs) to ameliorate the cytotoxicity caused by Cytarabine in the submandibular salivary glands of rats.

Methods: 30 albino male rats with weights 200-250gm were divided equally into three groups. Group I (control group). Group II (Cytarabine group) at a dose of (100 mg/kg) for five consecutive days. Group III (Cytarabine and BMMSCs): BMMSCs were administered intravenously via the tail vein one day after the last dose of Cytarabine drug at a dose ($1.5X10^6$ cells/body). After 6 days the rats were sacrificed and the submandibular salivary glands were dissected out. The glands were prepared for histological and immunohistochemical examination.

Results: Upon examination, Group II showed atrophied acini with cytoplasmic vacuolization. Dilatation of the striated ducts with stagnation of the secretory material in their lumen, the nuclei of the ductal cells showed pyknosis. Meanwhile, Group III showed a well-arranged acini and nearly normal ducts. Immunohistochemical results using anti-caspase-3 antibodies showed improvement in Group III over Group II, there was a significant difference between the optical densities of Group II and Group III.

Conclusion: Systemically injected BMMSCs have a therapeutic ability against the cytotoxicity caused by Cytarabine drug on the submandibular salivary glands.

KEYWORDS: Chemotherapy, Anti-caspase-3, Cytotoxicity.

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INTRODUCTION

The methods of treatment of malignant tumors involve chemotherapy, radiotherapy, or surgery. Chemotherapeutic medications work by disrupting the process of mitosis. As a result, they hinder the organelles of cells engaged in cell division or destroy DNA to stop mitosis. [1].

Cytarabine is an anti-metabolite chemotherapeutic agent which is a pyrimidine nucleoside-based drug. It is used in the treatment of white blood cell tumors, including chronic myelogenous leukemia, acute myeloid leukemia, and non-Hodgkin lymphoma. It is effective as an antiviral against Cytomegalovirus and Herpes Simplex virus. [2].

The drug has many side effects on many parts of the body. One of the most common disorders that could result from Cytarabine treatment is acute liver injury, often known as hepatotoxicity. The drug causes coagulation-induced necrosis of the hepatocytes, dilation in the hepatic sinusoids, fibrosis in the portal area, and blood vessel congestion [3].

Also, acute renal injury (nephrotoxicity) may occur after Cytarabine treatment. The medication disintegrates the epithelial cells lining the renal tubules, the glomeruli displayed atrophy of the glomerular tuft, and increased urinary spaces were detected [4].

The drug also has an adverse effect on salivary glands leading to a reduction of the salivary flow. Patients who take chemotherapeutic drugs suffer from Xerostomia [5].

In major salivary glands, Cytarabine has many cytotoxic effects which appear histologically in the form of reduction of the secretory acini size, vacuolization in the acinar cells, and pyknosis of their nuclei. Also, the striated ducts showed dilatation and stagnation of the secretory material. The granular convoluted duct showed signs of degeneration which were in the form of the loss of their granules [6]

The regenerative medicine field is about re-establishing normal tissues by replacing and regenerating cells. Stem cells have self-renewal capability so they have an important role in regenerative medicine [7].

These cells can be transformed into mature cells that have distinctive shapes and specific functions. It aims to repair damaged body tissues by replacing diseased cells with new healthy cells. Stem cells are found in Bone marrow, Adipose tissue, liver, and fetal tissues [8].

Ethical approval

The research protocol was approved by the Research Ethics Committee of the Faculty of Dentistry Minia University (RHDIRB2017122004) with protocol number (4-593/2022) at meeting number (87).

MATERIALS AND METHODS

Samples of 30 male albino rats with weights around 200-250 gm. The rats were obtained from the animal house, at Cairo University. The rats of each group were caged in separate cages in the animal house, they were fed on a balanced diet. They were kept under good ventilation and controlled room temperature.

- Cytarabine drug was obtained from Zydus Celexa (A division of Cedilla Healthcare Co, Ltd), India.
- Bone marrow mesenchymal stem cells (BMMSCs) were isolated from the femur bones of albino rats, the cells were labeled with PKH67 green fluorescent dye obtained from Sigma Aldrich, Saint Louis, USA.
- Polyclonal rabbit anti-caspase-3 antibody (active/cleaved) (1:1000 PBS, Novus Biologicals, Minnesota, USA).

Anti-caspase-3 was used as caspase-3 is one of the mediators of programmed cell death. Detection

of active caspase-3 in cells and tissue identifying the presence of apoptosis [9].

Experimental design

- Group I: 10 rats (Control group) received intraperitoneal injection of 0.5 ml of phosphate-buffered saline (PBS) for five consecutive days.
- Group II: 10 rats (Cytarabine group) were given a daily intraperitoneal dose injection of Cytarabine at a dose of 100 mg/kg body weight for five consecutive days (6).
- Group III: 10 rats (Cytarabine and BMMSCs group) were given Cytarabine at the same previously mentioned dose. The day after the last dose of Cytarabine, the rats received BMMSCs with a single dose of 1.5 × 106 cells / body suspended in 0.5 ml of PBS intravenously at the tail vein [10].

After 6 days from administration of the BMMSCs, the animals were sacrificed under chloral hydrate anesthesia. The submandibular salivary glands were dissected out of each group for histological and immunohistochemical studies.

The submandibular salivary glands were fixed in buffered formalin solution, then they were dehydrated, after that they were embedded in paraffin wax, and sections of 5-6 μm thickness were obtained. Then they were deparaffinized and stained by:

1- Hematoxylin and Eosin stain: for general histological examination.

2- Immunohistochemical staining using the polyclonal rabbit anti-caspase-3 antibody.

Morphometric Statistical Analysis

Morphometric analysis for caspase-3 was measured using ImageJ computer system version 1.54f 29. Ten fields of each group were examined for optical densities by a Leica DMLB light microscope connected to a digital camera (Leica Microsystems, Germany), at x200 magnification.

Data entry and analysis were done using IBM-compatible computer software SPSS version 24. A comparison of quantitative data was conducted using the One-way ANOVA/Kruskal-Wallis test after normality testing using the Shapiro-Wilk test.

RESULTS

Hematoxylin and Eosin results

Group I

Examination of this group showed that the submandibular gland's parenchyma had a normal histological structure. The secretory portions were composed of serous cells composed of pyramidal cells with deeply basophilic-stained nuclei at the basal third of the serous cells. The striated ducts were composed of low columnar cells with centrally placed rounded nuclei. Basal striations were seen in the basal part of the ductal cells. The granular convoluted ducts had columnar cells with apical acidophilic granules and basophilic nuclei (fig.1A).

Group II

Upon examination of this group, the gland lost its normal architecture. The serous acini showed a reduction in size and cytoplasmic vacuolization, and an increase in the interstitial spaces was clearly found. The striated ductal cells showed a reduction in their height, the duct's lumens showed dilatation, and their nuclei showed pyknosis. There was stagnation with the secretory material. The granular convoluted ducts lost their normal architecture. Their cells had indistinct borders and contained vacuolization. Their lumens were ill-defined. The excretory ducts showed stagnation with the secretory material. The inter-acinar blood vessels showed dilatation and congestion with red blood cells (fig.1B).

Group III

Examination of this group revealed an improvement in the acinar and ductal cell arrangement. There was a reduction in the interstitial spaces

between the acini. The majority of the acini restored their normal size and arrangement. The striated ducts and the granular convoluted ducts regained their normal architecture (fig.1C).

III- Anti-Caspase 3 Immunohistochemistry results

Group I (Control Group):

Immunohistochemical examination showed that the secretory cells of serous acini presented negative cytoplasmic and nuclear immunoreactions to anti-caspase-3. The ductal cells showed negative cytoplasmic and nuclear immunoreactions (fig.2B).

Experimental groups

Group II

Immunohistochemical examination of this group revealed the serous acinar cells with a weak positive cytoplasmic and negative nuclear immunoreaction for caspase-3. The striated and granular convoluted ductal cells presented intense positive cytoplasmic immunoreactions to caspase-3. Some ductal cells showed negative nuclear immunoreactions, and some others showed positive nuclear immunoreactions to caspase-3 (fig.2B).

Group III

Immunohistochemical examination of this group showed that the serous acinar cells presented negative cytoplasmic and nuclear immunoreactions to anti-caspase-3. The striated and granular convoluted ducts showed moderate positive cytoplasmic and negative nuclear immunoreactions to anti-caspase-3 (fig.2C).

Statistical analysis results

Statistical analysis of the optical densities of the three groups, when immune-stained by anti-caspase-3. There was a significant difference between groups ($p = 0.001$). When group II was compared to group III, there was a significant difference with a p-value = 0.011. Also, when group III was compared to group I, there was a non-significant difference with a p-value = 0.583.

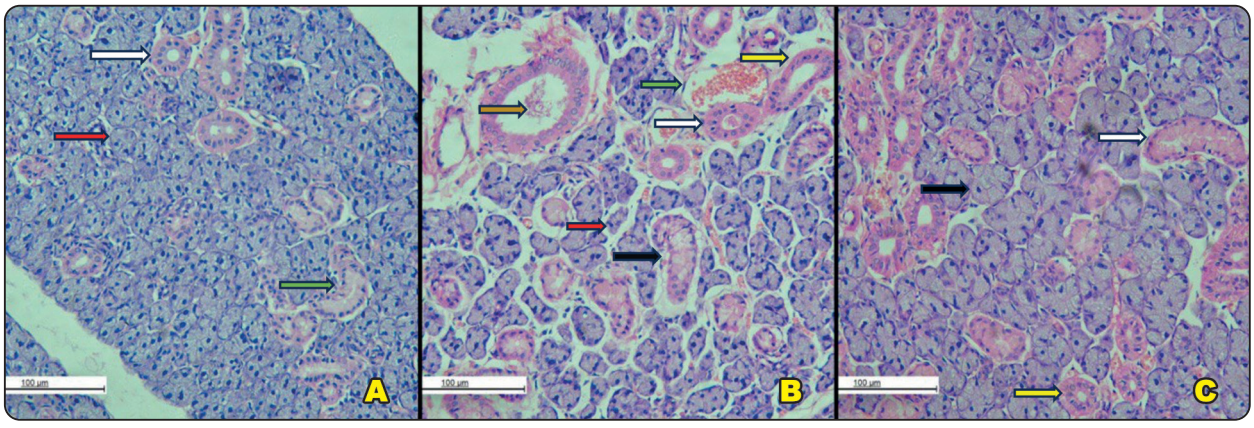

Fig (1): Photomicrograph of rats' submandibular salivary glands showing: (A) Group I: Normal serous acini (red arrow). Normal striated duct (white arrow). Normal granular convoluted duct (green arrow). (B) Group II showing: Atrophied serous acini with an increase in the inter-acinar spaces (red arrow). Dilated striated duct (yellow arrow). Striated duct has Stagnation of the secretory material in the striated duct and pyknotic nuclei (white arrow). The granular convoluted duct lost its architecture (black arrow). Stagnated secretory material in the execratory duct. Dilated blood vessel and engorged with red blood cells (green arrow). (C) Group III showing: Serous acini regained their normal arrangement and limited inter-acinar spaces (black arrow). Normal striated duct (yellow arrow). Granular convoluted duct with nearly normal architecture (H&E, X200).

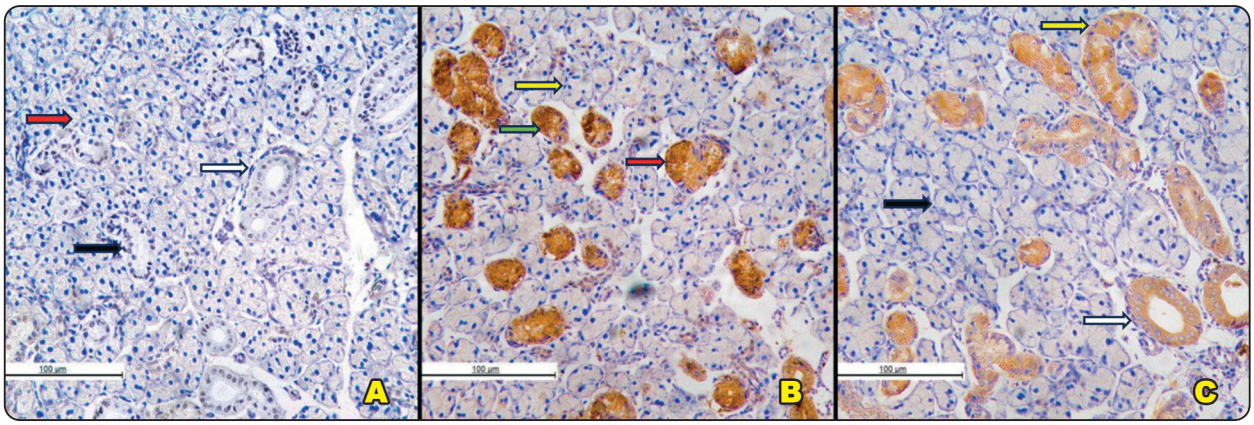

Fig (2): Immunostained photomicrographs of rat's submandibular salivary glands showing: (A) Group I: Serous acini showed negative immunoreaction (red arrow). Striated ductal cells showed negative immunoreaction (white arrow). Granular convoluted ductal cells showed negative immunoreactions (black arrow). (B) Group II: Acinar cells showed weak positive cytoplasmic and negative nuclear immunoreactions (yellow arrow). Striated ductal cells showed intense positive immunoreactions (green arrow). Granular convoluted ductal cells showed intense positive immunoreactions (red arrow). (C) Group III: Serous acinar cells showed negative immunoreactions (black arrow). Striated ductal cells showed moderate positive immunoreactions (white arrow). Granular convoluted ductal cells showed moderate immunoreactions (caspase-3, X200).

	Group I (n = 10)	Group II (n = 10)	Group III (n = 10)	P-value
❖ **Mean ± SD**	0.09 ± 0.01	0.27 ± 0.02	0.14 ± 0.01	**0.001**
P-value		**Group II vs. Group III = 0.011**	**Group I vs. Group III=0.583**	

DISCUSSION

Cytarabine is used in chemotherapy regimens for high-growth fraction tumors. It's used mainly in the treatment of white blood cell malignancies. It has many adverse effects on many organs of the body, as it affects the tumor and the normal cells [3].

The results of the Cytarabine group were vacuolization in the serous acini, atrophy, and shrinkage in the acini sizes, an increase in the inter-acinar spaces, the striated ducts and granular convoluted ducts showed loss of their normal cell arrangement, and also there was a stagnated secretory material in the striated ducts. The blood vessels showed dilatation and congestion with red blood cells.

These results coincide with the results of previous studies that showed the effects of Cytarabine, 5-fluorouracil, and Cisplatin drugs on the submandibular salivary glands of rats [6],[11],[12].

The results regarding cytoplasmic vacuolization of the acinar cells may be attributed to the chemotherapeutic drugs that induce the release of free radicals, and damage the intracellular components. This damage results in the formation of small vacuoles which fuse to form large vacuoles [13].

The results regarding the atrophy in the acini, and the loss of the cellular arrangement of the ductal cells were explained by that the chemotherapeutic drugs cause the production of reactive oxidative stress (ROS) resulting in oxidative damage in the

mitochondrial DNA, leading to DNA fragmentation, also the ROS causes an increase in the amount of lipid peroxidation and calcium ions (Ca2+) entering the cell [14].

Moreover, chemotherapy can cause oxidative stress in salivary gland tissues by disrupting the balance of antioxidant enzymes made to counteract the high levels of free radical generation and maintain homeostasis [15].

Furthermore, one of the primary signs of oxidative damage is lipid peroxidation. It's an autolytic pathway that leads to the removal of a hydrogen atom from the side chain of the membrane's polyunsaturated fatty acids. This abstraction causes oxidative damage to the cell membrane [13].

Our findings regarding spacing between the serous acini and the ducts could be explained by edema. Edema happens when an excessive amount of fluid builds up in the tissues in the interstitial spaces inside the collagen mucopolysaccharide matrix causing interstitial edema [16].

The secretory material was stagnated inside the lumen of the ducts. This may be connected to the mitochondrial oxidative cytotoxicity that was induced by the administration of the chemotherapeutic drug, which decreases the activity of the ductal cells and causes this stagnation[17]. Another suggestion was that chemotherapy negatively affects the myoepithelial cells that embrace the ducts causing failure in expelling the secretory material, thus leading to its stagnation [12].

Regarding blood vessel dilatation and engorgement with red blood cells after Cytarabine treatment, chemotherapeutic drugs cause oxidative stress and the production of free radicals. This causes lipid peroxidation, which is a process where free radicals attack the lipids in the cell membranes causing cell destruction. Therefore, the blood vessels are dilated to increase the blood flow to the damaged tissues [18].

In the present study, we evaluated the therapeutic effect of the systemic administration of the BMMSCs on the adverse effects of Cytarabine drug on the submandibular salivary glands.

We decided on intravenous injection of the BMMSCs. It is feasible, the least invasive method, and has systemic effects that help to treat a variety of diseases brought on by chemotherapeutic drugs.

In our study, the rats were sacrificed after six days of the BMMSCs injection day. This period was chosen according to a previous comparative study that compared the therapeutic effect of systemically injected BMMSCs on the side effects of 5-Fluorouracil (chemotherapeutic drug) on the parotid glands after six and ten days. The statistical analysis showed a non-significant difference between the two groups with a p-value>*0.05* (p-value=0.280)[11].

The results of group III specimens showed improvement in the serous acini and their normal arrangement was regained. There was a reduction in the interstitial spacing. The striated and granular convoluted ductal cells retained their normal arrangement. No stagnation of the secretory material in the ducts was observed. These results were in the same line as previous studies that evaluated the therapeutic role of BMMSCs on the side effects of irradiation on the submandibular salivary glands [19].

Furthermore, our results agreed with the effect of BMMSCS on the negative effects of Cisplatin (chemotherapeutic drug) in the parotid glands. The BMMSCs group showed an improvement in the gland as they had well-organized acini with regular nuclei, and the ducts appeared normal [20].

In addition, our results were in accordance with a previous study that evaluated the treating ability of the adipose stem cells on the cytotoxicity caused by Cisplatin in the submandibular salivary glands of rats. After stem cell injection, the majority of the serous acini and the ducts restored their normal arrangement and appearance [12].

Many proposed theories explain how the BMMSCs improve the damage of tissue. The first theory is that the BMMSCs can differentiate into specialized mature cells. The stem cells' plasticity occurs by genetic reprogramming. This reprogramming happens by responding to extracellular signals then intracellular tissue-specific transcription factors are activated [21].

The second proposed mechanism is that the BMMSCs fuse with the cells found originally in the tissues. Extracellular signals are not needed for fusion since the merged cells already contain the transcription factors that are needed for fusion [22].

The third and most recent proposed mechanism is that the BMMSCs release growth factors, chemokines, and cytokines. BMMSCs may produce a local paracrine effect on endogenous cells by secreting substances that promote proliferation, anti-apoptosis, and anti-inflammatory responses such as interleukin 6,10 (IL-6, IL-10), transforming growth factor beta (TGFβ), and vascular endothelial growth factor (VEGF) [23].

IL-6 is a cytokine that controls inflammation, apoptosis, and immunological responses. IL-10 is a cytokine that accelerates the healing process and modifies the host immunological responses [24].

TGFβ controls wound healing, carcinogenesis, angiogenesis, and immunological responses. VEGF is a paracrine mediator that induces angiogenesis by encouraging endothelial cell survival, and proliferation [25].

Our immunohistochemical results regarding caspase-3 expression showed a significant increase in the mean label index of caspase-3 optical density in group II that received Cytarabine drug compared to the control group, and the index was significantly decreased in group III.

These results agreed with a previous study that evaluated the effect of the 5-Fluorouracil drug on the tongues of rabbits. This group was assessed with caspase-3 immunostaining, it was found that the 5-Fluorouracil increased caspase-3 expression. However, when the group that received BMMSCs after the 5-Fluorouracil was examined, there were fewer positive areas [26].

Also, our results agree with a previous study that evaluated the effect of the adipose-derived stem cells on the Cisplatin-induced injury of the submandibular salivary glands of rats. The Cisplatin group showed an increase in the area fraction. When the group that received adipose-derived stem cells after administration of Cisplatin was examined, there was a gradual decrease in the area fraction of apoptotic cells [12].

These findings indicate that there was an increase in apoptotic activity after treatment with the Cytarabine drug. This was explained as the chemotherapeutic drugs result in oxidative damage in the mitochondrial DNA. As a result of mitochondria becoming selectively permeable after death, cytochrome c is released and caspase-9 is activated, which leads to the activation of caspase-3 and caspase-7 [27].

CONCLUSION

It can be concluded from this study that the systemically administered BMMSCs can have a therapeutic effect against the adverse effects of the Cytarabine chemotherapeutic drug on the submandibular salivary glands.

RECOMMENDATIONS

Further studies should be done on the regenerative effect of BMMSCs on the salivary glands by increasing the time interval between the administration and examination of the tissues. Also, higher doses of BMMSCs should be studied for better therapeutic effect.

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