Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 7, Issue, 12, pp.23972-23977, December, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

EVALUATION OF CURATIVE EFFECTS OF STEM CELLS AGAINST SOME INJURIES OF PHYSIOIMMUNOLOGICAL PARAMETERS RESULTING FROM RAT GAMMA IRRADIATION

Hamdy A. Ibrahim, *Kadeam A. Al-Shumisay, Mohamed F. Abouel-Nour, Tahany A. Mohamed

Department of Zoology, Faculty of Science, Mansoura University, 35516, Egypt

ARTICLE INFO

Article History:
Received 15th September, 2015
Received in revised form
29th October, 2015
Accepted 25th November, 2015
Published online 30th December, 2015

Keywords:
Gamma radiation,
Stem Cells,
ROS,
TNF*α*.

ABSTRACT

Radiation contamination can occur from natural radiation or from man-made sources, such as radiation for medical research or for nuclear weapons manufacture, and this one of the major problems facing the ratio biologists is how to infer the biological bad effects resulting from γ-radiation exposure. The aim of the work is to investigate the effects of γ-radiation exposure on the blood picture, liver function, kidney function and TNF-α of albino rats, and using mesenchymal stem cells (MSCs) to treatment these effects. The animals were divided into 5 groups: Control, γ-irradiation (6 grays), stem cells, γ-irradiation treated with stem cells post-irradiation and the 5th groups for preparation of mesenchymal stem cells for engrafting after one week and two weeks post-irradiation. The present study was undertaken to examine the effects of two dosages of MSCs on the survival of rats exposed to lethal doses of total body irradiation (TBI), and to explore the mechanisms by which MSCs in significantly improve gamma radiation effects.

***Citation*: Hamdy A. Ibrahim, Kadeam A. Al-Shumisay, Mohamed F. Abouel-Nour, Tahany A. Mohamed, 2015.** "Evaluation of curative effects of stem cells against some injuries of Physioimmunological parameters resulting from rat gamma irradiation", *International Journal of Current Research,* 7, (12), 23972-23977.

INTRODUCTION

Ionizing radiations induce oxidative stress on target tissues, mainly through the generation of reactive oxygen species (ROS) resulting in imbalance of the pro-oxidant and antioxidant in the cells, attack diverse cellular macromolecules such as DNA, lipids, and proteins, eventually inducing cell death. (Boerma and Hauer-Jensen, 2011) ROS such as superoxide ($O_2^{\bullet}$), hydroxyl radical ($OH^{\bullet}$) and hydrogen peroxide (H_2O_2) created in the aqueous medium of living cells during irradiation cause lipid peroxidation in cell membrane and damage to cellular activities leading to a number of physiological disorders situation and dysfunction of cells and tissues (Spitz *et al.,* 2004). So found several ways to treat the damage caused by ionizing radiation and these new ways are to apply the use of Stem Cells. Stem cells are undifferentiated biological cells. There are two broad types of stem cells: (1) Embryonic stem cells, which are isolated from the inner cell mass of blastocysts, (2) Adult stem cells, which are found in various tissues (Rob, 2013). Stem cell therapy is the use of stem cells to treat or prevent a disease or condition. Stem cell has many Properties: (1) Self-renewal: The ability to go through numerous cycles of cell division while maintaining the undifferentiated state (Shenghui *et al.,* 2009), (2) Potency: The capacity to differentiate into specialized cell types (Verfaillie, 2002). (3) Differentiation: The ability to differentiate is the potential to develop into other cell types. A totipotent stem cell (e.g. fertilized egg) can develop into all cell types including the embryonic membranes. A pluripotent stem cell can develop into cells from all three germinal layers (e.g cells from the inner cell mass). Other cells can be oligopotent, bipotent or unipotent depending on their ability to develop into few, two or one other cell type(s). (Sell 2004b). (4) Homing: Stem cells will probably migrate throughthe blood for you to additional organs in addition to niches, theprocess requires active navigation. Thisprogram termedhoming associated with SCs, that all be the expected step within stem cell transplantation (Lapidot *et al.,* 2005). (5) Plasticity: SC plasticity would be the ability in order to change its phenotypic characteristic (cell programming) inside response to external factors. The stem cells have the ability to cross lineage barriers and in order to adapt the own expression profile as well as artistic phenotypes of an cells that happen to be unique in order to other tissues. The transplanted adult stem cells show plasticity inside vivo. It offers integrated straight into a great mature host tissue in addition to assumed at least some regarding the attributes (Verfaillie, 2005). (6) Immunomodulation: the prominent feature regarding MSCs can be their ability in order to immunomodulate different immune cells, similar to T cells,

Corresponding author: Kadeam A. Al-Shumisay
Department of Zoology, Faculty of Science, Mansoura University, 35516, Egypt

B cells, dendritic cells, NK cells and macrophages. (Pei-Min *et al.,* 2011)

MATERIALS AND METHODS

Radiation exposure

Animal irradiation was performed in the Egyptian Atomic Energy Authority (EAEA), Cairo, Egypt. Using 137 Cesium cell 40 giving a dose rate of 0.758 rad/second at the time of experiment. The animals of irradiated groups were subjected to whole body dose equal to 600 rad gamma radiations.

Isolation and preparation of MSCs

Bone marrow was harvested by flushing the tibiae and femurs of 12-16 week-old male rat with Dulbecco's modified Eagles medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% Antibiotic. The marrow plugs were cultured in 20 ml complete media and incubated at 370 C in 5% humidified CO2 incubator for 7-10 days as primary culture or upon formation of large colonies, Figure (1) (Abdel Aziz *et al.,* 2007).

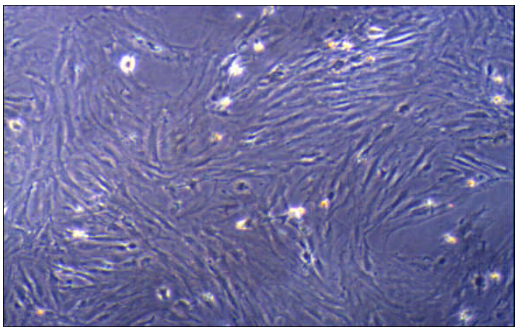

Figure (1): Mesenchymal stem cells, showing spindle shaped fibroblast like cells ten days after isolation (X 100)

Determination of Hematological Parameters

The red blood corpuscles (RBCs) and white blood cells (WBCs) counts were determined by the improved Neubauerhaemocytometer method. The haemoglobin (Hb) concentration was determined using the cyanomethaemoglobin method. Mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) were calculated and haematocrit measurement (HCT) (the microhaematocrit method) and Platelet (PLT) counting according to (Kateřina *et al.,* 2008 and Sanaullah *et al.,* 2012).

Lymphocyte count and Lymphocyte active was isolated according to (Maisel *et al.,* 1989) Absolute Neutrophil Count (ANC) according to(Al-Gwaiz and Babay, 2007)

Protein tests

Albumin content was estimated in serumaccording to the method by (Doumos *et al.,* 1971) and total Protein in Serum was estimated according to (Connon *et al.,* 1974).

Liver function tests

ALT and AST activity in serum was determined by a kinetic method according to (Breuer, 1996).Serum total bilirubin was determined by the method reported by (Balistreri and Shaw, 1987).

Kidney function tests

Creatinine concentration was estimated in serum according to the technique of Schirmeister, (1964) and uric acid was estimated according to the method of Barham and Trinder (1972).

Immunological investigations

Serum TNF-α was determined according to (Chen *et al.,* 1998).

Histological Investigations

The obtained tissue sections were collected on glass slides, deparaffinized, stained by hematoxylin& eosin stain for routine examination then examination was done through the light electric microscope according to (Banchroft *et al.,* 1996).

RESULTS

Physiological Studies

Table (1) and Figure (2) show RBCs count for different treated groups. It is obvious that exposure of rats to γ-radiation has seriously affected the tested parameters. The RBCs count, hematocrit content (HCT) and hemoglobin content (g/dl) were decreased significantly (P< 0.05) while the mean corpuscular hemoglobin (pg), mean corpuscular hemoglobin content (g/dl) and mean corpuscular volume (MCV) were increased. Treatments with stem cells post irradiation have significantly ameliorated the bad effects of radiation exposure.

Table 1. RBCs Analysis for different treated groups

Parameters \ Treatment	Control	Irradiated	Stem cells	Irradiated + Stem cells
	no=6	no=6	no=6	no=6
RBC count($X10^6/mm^3$)	$8.15^a \pm 0.05$	$4.24^b \pm 0.23$	$8.73^a \pm 0.32$	$6.74^c \pm 0.23$
Mean corpuscular volume (fl)	$48.88^a \pm 0.46$	$73.58^b \pm 4.96$	$47.75^a \pm 1.69$	$54.24^c \pm 1.01$
Mean corpuscular hemoglobin(pg)	$18.48^a \pm 0.77$	$20.80^b \pm 1.03$	$18.17^a \pm 0.75$	$18.03^a \pm 0.22$
Hematocrit content (%)	$49.45^a \pm 0.36$	$33.38^b \pm 2.53$	$52.65^a \pm 2.14$	$44.37^c \pm 0.92$
Hemoglobin content(g/dl)	$13.78^a \pm 0.12$	$9.77^b \pm 0.66$	$14.32^a \pm 0.39$	$12.52^a \pm 0.17$
Mean corpuscular Hb content(g/dl)	$26.80^a \pm 0.92$	$29.50^b \pm 0.44$	$27.25^a \pm 0.58$	$28.55^a \pm 0.39$

Mean ± S.D. no = Number of rats in each group. Results with similar letters are insignificant, with different letters are significant P< 0.05.

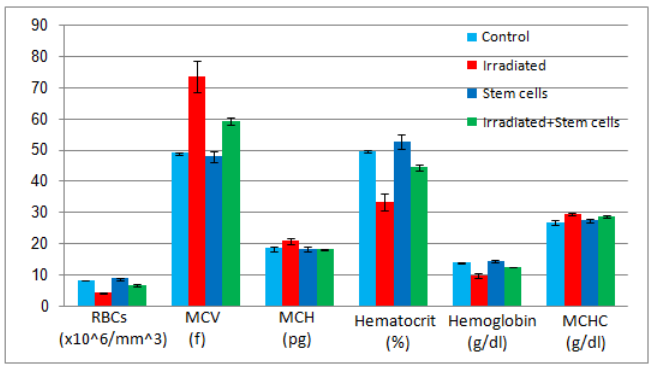

Figure 2. RBCs, MCV, MCH, MCHC, Hematocrit and Hemoglobin in blood of different treated rat groups

Table (2) and Figures (3 and 4) show the differential WBCs and platelets count for different treated rat groups. It is clear that the WBCs, lymphocytes and platelets count were significantly decreased, while the neutrophils count was significantly increased.

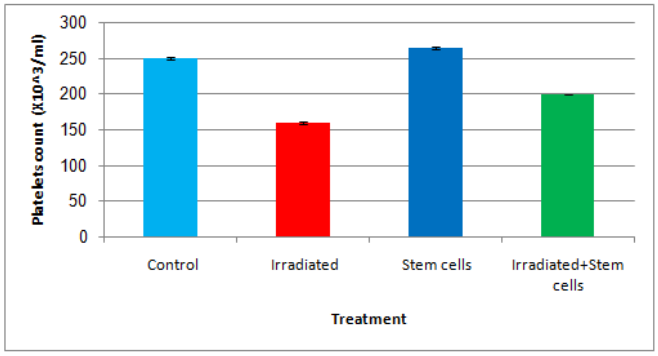

Figure 4. Showing platelets count ($X10^3/mm^3$) in different treated rat groups

Exposure of rats to γ- radiation didn't cause significant change in the serum total protein (g/dl), while significant increase was observed in the serum total globulins (g/dl), ALT (U/L), AST (U/L) and serum bilirubin (mg/dl). At the same time a significant decrease was reported for the total serum albumin.

Table 2. Rat blood WBCs and platelets count for different treated groups

Treatment Parameters	Control	Irradiated	Stem cells	Irradiated+ Stem cells
	no=6	no=6	no=6	no=6
Total WBCs($10^3/mm^3$)	$15.1^{a}\pm0.82$	$5.5^{b}\pm1.35$	$15.6^{a}\pm1.01$	$8.2^{c}\pm1.40$
Neutrophils($10^3/mm^3$)	$2.6^{a}\pm0.06$	$8.2^{b}\pm0.06$	$3.1^{a}\pm0.06$	$5.3^{c}\pm0.03$
Lymphocytes($10^3/mm^3$)	$6.10^{a}\pm0.09$	$1.86^{b}\pm0.52$	$7.12^{a}\pm1.10$	$4.79^{c}\pm0.52$
Platelets($10^3/mm^3$)	$250^{a}\pm1.50$	$160^{b}\pm1.70$	$265^{a}\pm2.03$	$200^{c}\pm0.24$

Results = Mean ± S.D. No = Number of animals in each experiment. Results with similar letters are insignificant. Results with different letters are significant (P< 0.05).

Table 3. Liver function tests on serum of different treated rat groups

Treatment Parameters	Control	Irradiated	Stem cells	Irradiated+ Stem cells
	no=6	no=6	no=6	no=6
Total protein (g/dl)	$4.81^{a}\pm0.09$	$4.42^{a}\pm0.18$	$5.87^{a}\pm0.14$	$5.24^{a}\pm0.26$
Total Albumin (g/dl)	$3.90^{a}\pm0.06$	$2.18^{b}\pm0.23$	$4.70^{a}\pm0.13$	$3.30^{a}\pm0.13$
Total globulin (g/dl)	$0.91^{a}\pm0.06$	$2.24^{b}\pm0.09$	$1.17^{a}\pm0.05$	$1.94^{a}\pm0.17$
ALT (U/L)	$23^{a}\pm2.61$	$47^{b}\pm7.97$	$27.33^{a}\pm4.63$	$28.67^{a,c}\pm4.50$
AST (U/L)	$121.33^{a}\pm1.51$	$152.50^{b}\pm8.38$	$118.50^{a}\pm6.02$	$128.17^{a}\pm3.19$
Bilirubin (mg/dl)	$0.37^{a}\pm0.02$	$0.97^{b}\pm0.06$	$0.44^{a}\pm0.05$	$0.69^{c}\pm0.06$

Results = Mean ± S.D. No = Number of animals in each experiment. Results with similar letters are insignificant. Results with different letters are significant (P< 0.05).

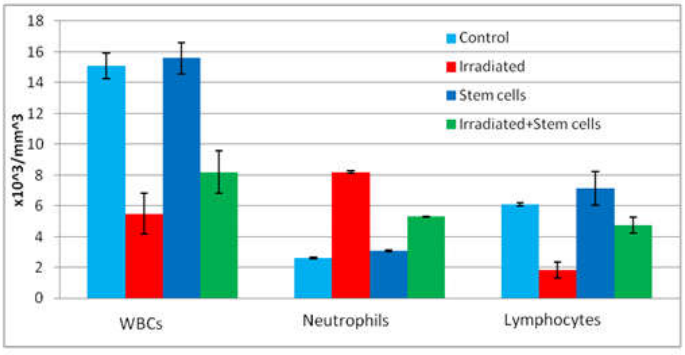

Figure 3. WBCs, Neutrophils, Lymphocytes in different treated rat groups

Table (3) and Figures (5, 6 and 7) show the liver function tests in serum of different treated groups.

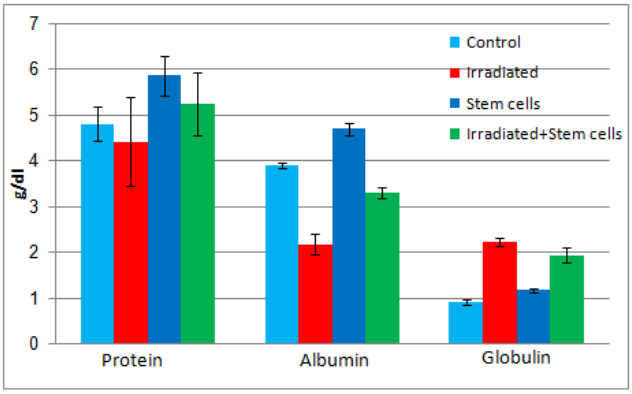

Figure 5. Concentration of total Protein, total Albumin and total Globulin in serum of different treated rat groups

Treatment with stem cells after irradiation had significantly improved these parameters.

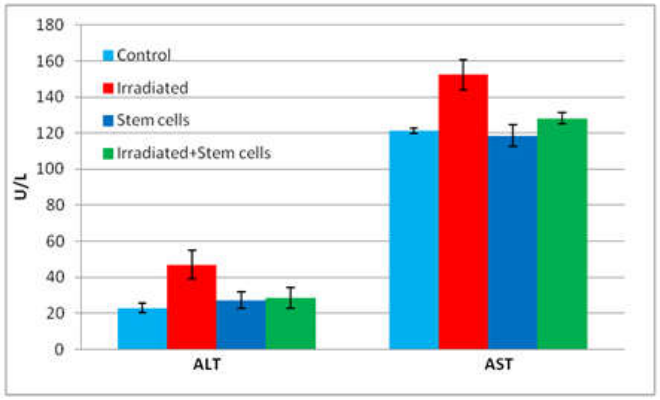

Figure 6. Concentration of ALT and AST in serum of different treated groups

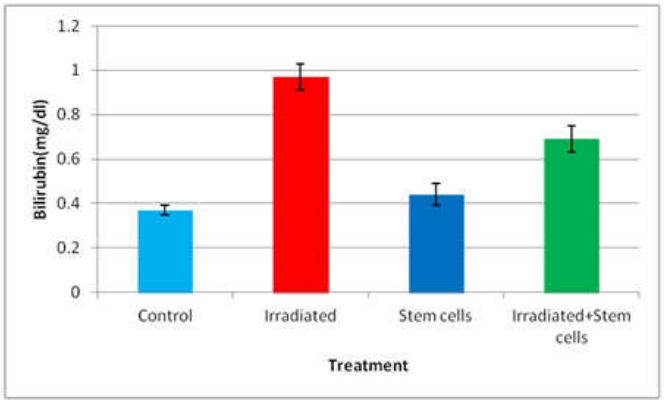

Figure 7. Concentration of bilirubin (mg/dl) in serum of different treated groups

Table 4. Kidney function tests and tumor necrosis factor (TNF-α) in serum of different treated groups

Treatment Parameters	Control	Irradiated	Stem cells	Irradiated+ Stem cells
	no=6	no=6	no=6	no=6
Creatinine(mg/dl)	0.47^{a}±0.05	0.67^{b}±0.08	0.37^{a}±0.05	0.5^{a}±0.03
Uric acid(mg/dl)	1.97^{a}±0.07	4.91^{b}±0.62	1.57^{a}±0.19	2.81^{c}±0.40
TNF alpha(U/L)	4.67^{a}±2.22	27.93^{b}±3.35	5.29^{a}±1.73	16.72^{c}±0.87

Results = Mean ± S.D. No = Number of animals in each experiment. Results with similar letters are insignificant. Results with different letters are significant (P< 0.05).

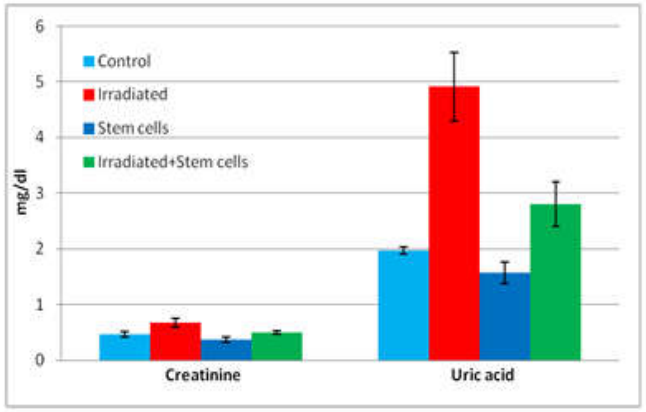

Figure 8. Concentration of creatinine and Uric acid in blood serum of different treated rat groups

Table (4) and Figures (8 and 9) show the function of the kidney of different treated groups represented by serum creatinine and uric acid levels.

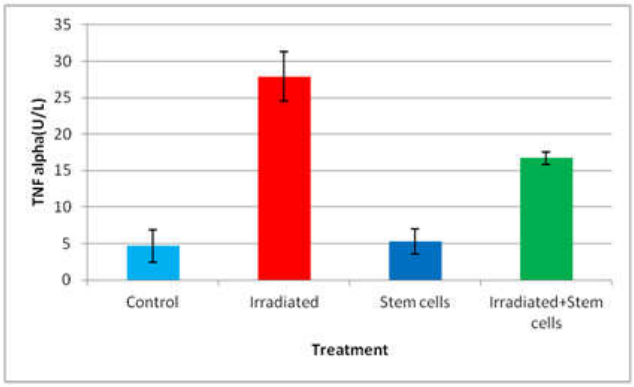

Figure 9. Concentration of TNF-alpha (U/L) in blood serum of different treated rat groups

It was clear from the data reported that exposure of the rats to γ- radiation had significantly increased the concentration of serum creatinine (mg/dl) and uric acid (mg/dl). Also shown in table (4) the results of serum tumor necrosis factor (TNF-α) as affected by γ- radiation. It was obvious that irradiation had significantly increased the level of (TNF-α). Treatment of the rats with stem cells post-irradiation improved the dangerous changes in this parameter.

Histopathological studies

Liver histology

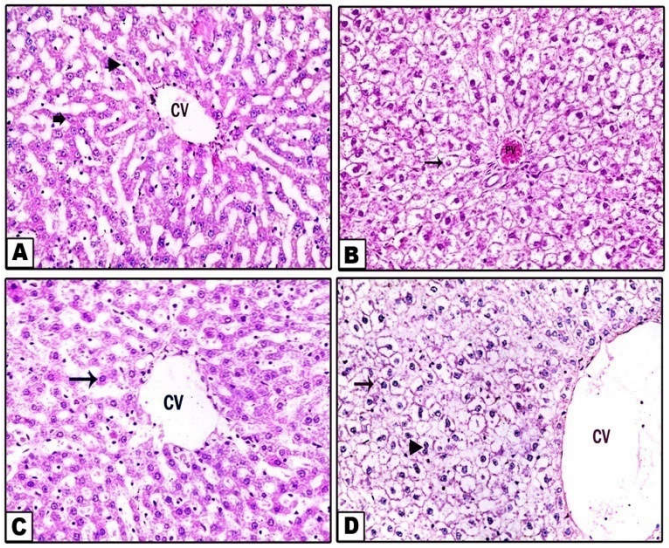

Figure 10. Liver T.S. from rat (A) control showing normal hepatocytes (arrow) in normal radial arrangement around central vein (CV), besides kupffer cells (arrow head) in hepatic sinusoids.(B) γ-radiation showing hydropic degeneration and necrosis of hepatocytes (arrow), with congestion of portal vein (PV).(C)Treated with stem cells showing normal hepatocytes (arrow) in normal radial arrangement around central vein (CV).(D) γ-radiation and treated by stem cells showing hydropic degeneration of hepatocytes (arrow), with normal radial arrangement around central vein (CV) and increase number of dublicytes (arrow head)

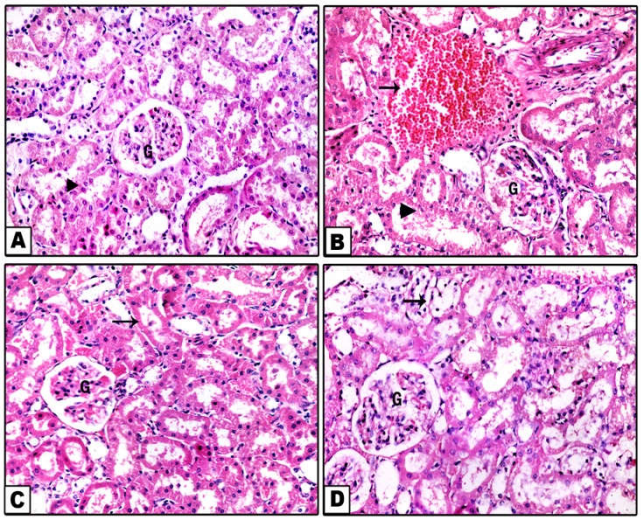

Figure 11. Kidney T.S. from rat (A) control showing renal glomeruli (G) and normal renal tubules with normal lining renal tubular epithelium (arrow head).(B) γ-radiation showing hemorrhage in interstitial tissue replacing renal parenchyma (arrow), with dissolution of renal glomeruli (G), beside degeneration and necrosis of renal tubular epithelium (arrow head).(C)Treated with stem cells showing renal glomeruli (G) and normal renal tubules with normal lining renal tubular epithelium (arrow).(D) γ-radiation and treated by stem cells showing normal renal glomeruli (G), with mild degeneration of renal tubular epithelium (arrow)

DISCUSSION

The results proved that γ-irradiation of rat has caused a significant decrease in RBCs count, MCV, Ht content and Hb content while the MCH and MCHC content were increased. The WBCs count and the platelets were drastically decreased due to γ-irradiation. These results are acceptable as γ-radiation affects the cell membrane permeability particularly the lipid layer as a result of the oxidation performed by ROS coming from ionization of the water and biological molecules. It is known that Ionizing radiations induce oxidative stress on target tissues, mainly through the generation of reactive oxygen species (ROS) resulting in imbalance of the pro-oxidant and antioxidant in the cells, attack diverse cellular macromolecules such as DNA, lipids, and proteins, eventually inducing cell death (Boerma and Hauer-Jensen, 2011)

The results stated by Yan˜ez *et al.* (2006) said that MSCs protect the haematopoietic cells from apoptosis and enhance the cell-cycle transition after irradiation and explained that this may be that MSCs have radio protective effects by secreting cytokines. MSCs reduced apoptosis, enhanced cell-cycle transition, improved the microenvironment, and accelerated haematopoietic stem cell proliferation and differentiation, and may be an effective treatment strategy for acute radiation sickness (ARS). The obtained results explained that the functions of the rat liver were serially affected by γ-irradiation. The level of serum total albumin was decreased, while the total globulin, ALT and AST levels and bilirubin increased significantly. Explained that the increase in serum aminotransferase activities by radiation may be due to the damage of cellular membranes of hepatocytes, which in turn leads to an increase in the permeability of cell membranes and facilitates the passage of cytoplasmic enzymes outside the cells leading to the increase in the aminotransferase activities in blood serum.

Also, ionizing radiation enhanced lipid peroxidation in cell membrane which contains fatty acids and excessive production of free radicals; this in turn increases the cytoplasmic membrane permeability to organic substances and causes leakage of cystosolic enzymes such as AST, ALT (Weiss and Lander, 2003). Therefore, the therapeutic effects of MSCs may depend largely on the capacity of MSCs to regulate inflammation and tissue homeostasis via an array of immunosuppressive factors, cytokines, growth factors and differentiation factors, (Ma *et al.,* 2014). In the present study, the obtained results explained that the functions of the rat kidney were serially affected by γ- irradiation. The level of uric acid and creatinine were significantly elevated, indicating renal impairment. The serum creatinine and uric acid significantly increased by exposure of the rat to γ- radiation.

This means that kidney function was not proper and was injured by irradiation and fail to secrete the excess of uric acid and creatinine to outside in the urine. Kafafy *et al.* (2005a) revealed that irradiation of rats caused significant drop in serum total protein, elevation in serum uric acid, urea and creatinine. Also, it is reported in previous published researches that γ- radiation exposure caused destruction of the skeletal muscles causing increase in the serum creatinine in serum. Elevation of serum creatinine is an indication of muscle damage (Holger *et al.,* 2005). For MSC therapy to work, it is crucial that MSCs reach the site of injury. Different studies indicated that systemically delivered MSC can indeed home to the kidney after renal injury (Ittrich *et al.,* 2007).

Conclusion

The obtained results revealed that rat γ-irradiation caused bad effects on the blood picture, liver and kidney functions, as well as the immune system represented by TNF-α. Treatment of the irradiated rat by MSCs engrafting improved the tested parameters towards the stats of normal case. Nevertheless, the wide application of the stem cells engrafting still needs more investigations to be assured.

REFERENCES

Abdel Aziz, M.T., Atta, H.M., Mahfouz, S., Fouad, H., Roshdy, N.K., Ahmed, H.H., Rashed, L.A., Sabry, D., Hassouna, A.A. and Hasan, N.M. 2007. Therapeutic potential of bone marrow-derived mesenchymal stem cells on experimental liver fibrosis. *Clin. Biochem.,* 40 (12): 893-899.

Al-Gwaiz, L.A., and Babay, H.H. 2007. "The diagnostic value of absolute neutrophil count, band count and morphologic changes of neutrophils in predicting bacterial infections". *Med Princ. Pract*., 16 (5): 344–7.

Balistreri, W.F. and Shaw L.M. 1987. Liver function. In: Tietz NW, ed. Fundamentals of Clinical Chemistry. 3rd ed. Philadelphia, PA: WB Saunders Co, p. 729-761.

Banchroft, J.D., Steven, A. and Turner, D.R. 1996. Theory and practice of histological techniques. Livingstone, New York, London, San Francisco, Tokyo. P. 766-767.

Barham, D. and Trinder, P. 1972. Enzymatic determination of uric acid. Analyst. 97:p.142-145.

Boerma, M. and Hauer-Jensen, M. 2011. Preclinical research into basic mechanisms of radiation- induced heart disease.Cardiol. *Res. Pract.* P.1-8.

Breuer, J. 1996. Report on the Symposium "Drug effects in Clinical Chemistry Methods". *Eur J ClinChem ClinBiochem.,* 34: p.385–386.

Cannon, D.C., Olitzky, I. and Inkpen, J.A. Proteins. In: Henry, R.J., Cannon, D.C. and Winkelman, J.W. 1974.Clinical Chemistry Principles and Techniques.2nd Edition. Harper and Row, Publishers, Hagerstown, M.D: pp. 411–421.

Chen, A.F., O'Brien, T. and Katusic, Z.S. 1998. Transfer and expression of recombinant nitric oxide synthase genes in the cardiovascular system. *Trends Pharmacol Sci.,* 19: 276−286.

Doumas, B., Wastson, W. and biggs, H. 1971. Albumin standards and the measurements of serum albumin with bromocrsol green. *Clin. chem*., 31:p.87-96.

Holger, L., Melanie, S., Vivienne, W. and Uwe, S. 2005. The Creatine Kinase System in Human Skin Creatine against Oxidative and UV Damage In Vitro and In Vivo. *Journal of investigative Dermatology.* 124: p. 443–452.

Ittrich, H., Lange, C. and Togel, F. 2007. In vivo magnetic resonance imaging of iron oxide-labeled, arterially-injected mesenchymal stem cells in kidneys of rats with acute ischemic kidney injury. *J. Magn. Reson. Imaging,* 25:1179-1191.

Kafafy, Y. A., Roushdy, H., Abdel-Haliem, M., Mossad, M., Ashry, O. and Salam, S. 2005a. Protective role of green tea administration against radiation-induced changes in pregnant rats. *Egypt. J. Rad. Sci. Appli.* 18(2): P. 367-384.

KateřinaKaňková, Julie Bienertová-Vašků, LydieIzakovičová-Hollá. and Anna Vašků. 2008. Pathophysiology practicals for General Medicine and Dental Medicine courses. Masaryk University Faculty of Medicine. 46 pp. 1801-6103.

Lapidot, T. , Dar A. and Kollet, O. 2005. How do stem cells find their way home? Blood, 106(6), P.1901-1910.

Ma, S., Xie, N., Li, W., Yuan, B., Shi, Y. and Wang, Y. 2014.Immunobiology of mesenchymal stem cells. Cell Death Differ. 21, p.216–225.

Maisel, A.S., Fowler, P., Rearden, A., Motulsky, H.J. and Michel, M.C. 1989. New method for isolation of human lymphocyte subsets reveals differential regulation of h-adrenergic receptors by terbutaline treatment. *Clin. Pharmacol. Ther.* 46, p. 29– 39.

Pei-Min Chen, Men-Luh Yen, Ko-Jiunn Liu, Huey-Kang Sytwu and B-Linju Yen. 2011. Immunomodulatory properties of human adult and fetal multipotentmesenchymal stem cells. *J. Biomed .Sci.* 18: 49.p. 18-49.

Rob Burgess. 2013. Introduction to stem cells, in book (Stem cells Handbook) Second Edition Editor Stewart Sell, M.D. Sell, S. (ed), Stem Cells Handbook. New York. P.1-27.

Sanaullah Khan, Aamir Khan. and Faisal SalehKhattak. 2012. An Accurate and Cost Effective Approach to Blood Cell Count. *International Journal of Computer Applications,* 50(1).p.18-24.

Schirmeister, J. 1964. Determination of creatinine in serum. DSH. Med. Wschr. 89: (13): p. 156-159.

Sell, S. 2004b.Stem cells. What are they? Where do they come from? Why are they here? When do they go wrong? Where are they going? In Sell S (Ed) Stem Cell Handbook. Humana Press, Totowa. NY. P 1-18.

Shenghui, H., Nakada, D. and Morrison, S. J. 2009.Mechanisms of stem cell self-renewal. Annual Review of cell and Developmental, 25, p.377-406.

Verfaillie, C. M. 2002. Adult stem cells: assessing the case for pluripotency. *Trends in cell biology*, 12(11), p.502-508.

Verfaillie, C. M. 2005. Stem cell plasticity. Hematology, 10(Supplement 1), p.293-296.

Weiss, J. F. and Lander, M. R. 2003. Protection against ionizing radiation by antioxidant nutrients and phytochemicals. Toxicol. 189(1-2): p.1-20.

Yan˜ez, R., Lamana, M.L., Garcia-Castro, J., Colmenero, I., Ramirez M. and Bueren, J.A. 2006. Adipose tissue-derived mesenchymal stem cells have in vivo immunosuppressive properties applicable for the control of graft-versus-host disease. Stem Cells; 24 : p. 2582-91.

****