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Modulatory effects of Zn oxide nanoparticles on cardiotoxicity and hematological changes in irradiated rats

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► ***Original article***

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ABSTRACT

Background: Cardiotoxicity is one of the most serious complications of radiation. Nanoparticles, has gained increasing attention as therapeutic agents. This work aims to evaluate the beneficial effect of zinc oxide nanoparticles (ZnONPs) on the cardiotoxicity induced by ionizing radiation. ***Materials and Methods***: Twenty eight male rats were included in the study. Animals were categorized into four groups (n=7), group I: (control), group II: rats were irradiated with a single dose of ɣ radiation (6Gy), group III: rats injected with ZnONPs (10mg /Kg b.wt), intrapritoneally for two weeks (5days/week), group IV (treated): irradiated rats received ZnONPs intrapritoneally with the same dose for two weeks after 24hr of irradiation. ***Results***: ɣ-irradiation caused a significant elevation in the levels of creatine phosphokinase, creatine kinase, lactate dehydrogenase, troponin I, fibrinogen and C-reactive protein. Additionally, a noticeable increase in the lipid content including cholesterol, triglycerides and low density lipoprotein with concomitant decline in high density lipoprotein and finally, a marked decrease in hematological parameters as compared to the control group. These changes manifested good amelioration in the groups injected with ZnONPs. ***Conclusion***: Based on these findings, it can be argued that treatment with ZnONPs reduces the extent of radiation damage by providing significant hypolipidemic, anti-inflammatory and antioxidant effects in irradiated rats.

INTRODUCTION

Ionizing radiation (IR) can cause several harmful effects. A wide gamut of humans is exposed to radiations from different natural and manmade sources e.g. radiotherapy (RT), diagnostic processes, biomedical research, workforces in the radiation field and nuclear power sector [1].

With the increasing incidence of tumors, (RT) is widely used in controlling or eradicating solid tumors. RT causes some unfavorable complications [2]. The reactive oxygen species (ROS) production is one of the most important damaging effects of IR [3]. Oxidative stress is considered a key factor in several diseases and various pathological conditions in human and experimental animals and occurred as a result of the imbalance between excessive ROS generation and antioxidant defense system [4]. Radiation-induced heart disease (RIHD) is one of the most serious complications. Studies reported that the heart is resistant to radiation so the RIHD has not attracted much attention [5]. Researchers have gradually found that patients with cancer were succumbed to ischemic heart disease [6-8]. Hypertension, atherosclerosis, heart hypertrophy and myocardial infarction were considered the main causative factors for death in the world [9]. Therefore, early identification, prevention and prompt treatment are essential in the management of disease [10]. The nanotechnology is considered an attractive and innovative tool for the treatment of diseases, with better prognosis and reduce side effect [11]. Recently, the development of nanomaterials show promising prospect for medical field [12]. ZnONPs are used in different fields due to their special chemical and physical properties and are considered one of the most important metal oxide nanoparticles [13-14]. Moreover, ZnONPs have antibacterial [15], antidiabetic [16], antioxidant [17] and protective effects [18]. Therefore, the current study aims at evaluating the ameliorative effect of ZnONPs on the cardiotoxicity induced by gamma irradiation.

MATERIALS AND METHODS

Animals

Twenty eight adult male rats with average weight (180-200g) were used in this study. Before beginning the experiment, the rats were given a week to adapt to the laboratory conditions. They were maintained in metal cages under standard conditions; in a room

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with humidity of 45–64%, temperature of 24 - 28C and were given standard dry pellets and water ad libitum. All animal procedures were carried out by the public health guide in accordance with the Ethics for the Care and Use of Laboratory Animals guidelines. The experimental procedures were approved by the Research Ethics Committee at National Center for Radiation Research and Technology (NCRRT), and Ain Shams University, Egypt (REC-FS, Ino. 00033).

Radiation processing

Irradiation of rats was performed with gamma cell-40 (Cesium-137) *at (NCRRT), Atomic Energy Authority, Cairo, Egypt.* The animal, s whole body was exposed to (6 Gy) gamma rays [19]. The dose rate was 0.648 cGy/sec.

Chemicals

Zinc oxide nanoparticles (ZnONPs), CAS Number 1314-13-2. The diameters of the particle were <50 nm. They were obtained from Sigma Aldrich, part of Merck Company, USA. They were suspended in 0.9% NaCl. The Suspension was sonicated for 20 min. in a bath sonicator to avoid particles aggregations (Branson, 2510) and was vortexed for 1min before every injection. Rats were received ZnO NPs (10 mg/kg/b.wt), via intraperitoneal injection [20-21] for two weeks (5days/ week).

Experimental design

Animals

Twenty-eight rats were randomly allocated to four groups (n=7): Group I (control): Rats received saline (1ml/rat) by intraperitoneal injection. Group II (irradiated group): Rats were irradiated with one dose of gamma radiation (6Gy) & left for two weeks. Group III: Rats received zinc oxide nanoparticles (ZnONPs) dispersed in 0.9% saline (10mg /Kg b.wt) via intraperitoneal injection for two weeks (5days/ week). Group IV (Treated group): Rats received zinc oxide nanoparticles (ZnONPs) dispersed in 0.9% saline (10mg /Kg b.wt) via intraperitoneal injection for two weeks (5 days/week) after 24 h of irradiation.

Sampling

After the last experimental day, the animals were anesthetized. Blood samples were collected in 3-tubes, one part into heparinized tubes for hematological parameters determination. The 2nd part on sodium citrate for fibrinogen determination and the 3rd part of blood was centrifuged for 10 minutes and the sera were stored at -20 for biochemical investigations.

Enzyme-linked immunosorbent assay (ELISA) for determination of serum creatine kinase (CK), lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), Troponin I (cTnI), and plasma fibrinogen have been carried out using commercially kits purchased from DRG International Inc., USA.

C reactive protein (CRP) was measured by Immunoturbidimetry Assay using kit purchased from Roche Diagnostics Gmbs, Mannheim, (Germany).

The levels of cholesterol (TC), triglycerides (TG), and high density lipoprotein (HDL) were estimated enzymatically on spectrophotometer (Milton Roy Spectronic 1201) using commercial kits purchased from Biodiagnostic Co. Cairo, Egypt, while the low density lipoprotein levels (LDL) were calculated according to *Friedwald et al*. [22].

Heparinized blood samples were immediately used for the hematological parameters. Red blood cells (RBCs), Hemoglobin (Hb), Hematocrit (HCT), White blood cells (WBCs) and platelets were determined using Sysmex (KX-21) cell counter, with a kit manufactured by (Diamond, Philadelphia, USA).

Statistical analysis

Statistical comparison of data was performed using SPSS program version10.0. The results were analyzed using one-way analysis of variance (ANOVA). Duncan's test was used for testing the intergrouping homogeneitys. Data were presented as mean±SE. Statistical significance was considered at $P \leq 0.05$.

RESULTS

The current study revealed that ɤ irradiation induced elevations ($p<0.05$) in the levels of cardiac enzymes (CK, CK-MB and LDH) compared to the control group, while their levels were reduced significantly after treatment by ZnONPs (10mg/kg/b.wt) as compared to the irradiated group (table 1).

Table 1. Effect of ZnONPs on the levels of CK, CK-MB and LDH in the irradiated rats.

Parameters / Groups	CK (U/L)	CKMB (U/L)	LDH (U/L)
Control	1365.4^{c}±25.8	370.5^{c}±10.56	1439.42^{c}±14.97
Irradiated (6Gy)	3395.1^{a}±76.0	786.4^{a}±15.6	3067.86^{a}±99.81
ZnONPs (10mg/Kg b.w.)	1300.57^{c}± 7.38	367.42^{c}±9.24	1415.71^{c}±15.1
Treatment (R+ZnONPs)	2496.3^{b}±1.12	538.14^{b}±13.43	1914.57^{b}±14.3

CK: Creatine kinase: CK-MB: Creatine kinase-MB; LDH: Lactate dehydrogenase. Values are expressed as mean ± SE significant at ($p<0.05$). Means marked with the same superscript letters are not significant, whereas, means with the different superscript letters are significant.

Significant increases ($p<0.05$) in the levels of CRP, cTnI and fibrinogen were markedly demonstrated in the irradiated group in comparison to the control group. Conversely, the group treated with ZnONPs after ɤ irradiation showed a marked decrease ($p<0.05$) in their levels (table 2).

The lipid pattern of sera from rats in the present study exhibited a considerable rise ($p<0.05$) in total cholesterol, LDL-C and triglycerides level with a

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substantial reduction in HDL-C levels ($p<0.05$), post gamma irradiation as compared to the control group. Meanwhile, the intraperitoneal injection of ZnONPs resulted in obvious decrease ($p<0.05$) in the levels of TC, LDL, and TG, as well as a significant rise in the level of HDL as compared to the irradiated group (table 3).

Table 2. Effect of ZnONPs on serum CRP, cTnI and plasma fibrinogen in the irradiated rats.

Parameters / Groups	CRP (mg/l)	cTnI (ng/ml)	Fibrinogen (g/L)
Control	2.09^{c}±0.11	1.58^{c} ±0.05	4.53^{c}± 0.16
Irradiated group (6Gy)	6.39^{a}± 0.09	7.04^{a}±0.17	8.81^{a}± 0.13
ZnONPs (10mg/Kg/b.wt.)	1.91^{c}± 0.08	1.47^{c} ± 0.03	4.35^{c}±0.12
Treatment R+ZnONPs	4.45^{b}± 0.1	4.96^{b} ±0.18	6.64^{b}±0.16

CRP: C reactive protein; cTn1 Troponin1; Fibrinogen. Values are expressed as mean ± SE significant at ($p<0.05$). Means marked with the same superscript letters are not significant, whereas, means with the different superscript letters are significant.

Table 3. Effect of ZnONPS on the lipid profile in irradiated rats.

Parameters / Groups	TC (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	TG (mg/dl)
Control	1o5.14^{c}± 3.13	41.85^{a}± 2.8	35.11^{c}± 1.18	140.71^{c}± 1.7
Irradiated (6Gy)	140.85^{a}± 2.6	32. 71^{b}± 2.2	67.31^{a}± 2.19	203.42^{c}± 4.9
ZnONPs(10mg/ Kg/b.wt.)	102.0^{c}± 2.76	40.02^{a}± 1.75	34.4^{c}± 1.28	137.85^{a}± 2.5
Treatment R+ZnONPs	123.42^{b}± 3.19	37^{ab}±1.9	53.48^{b}± 1.41	164.71^{b}± 3.67

TC: Total cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglycerides. Values are expressed as mean ± SE significant at ($p<0.05$). Means marked with the same superscript letters are not significant, whereas, means with the different superscript letters are significant.

The results showed a significant reduction ($p<0.05$) in the hematological parameters (RBCs, Hb, HCT%, WBCs and platelets) post gamma irradiation (6 Gy). After ZnONPs treatment, their levels increased significantly ($p<0.05$) as compared to the irradiated group (table 4).

Table 4. Effect of ZnoNP on some hematological parameters in irradiated rats.

Parameters / Groups	RBCs n×106	Hb (g/dl)	HCT (%)	Platelets nx10¯3	WBC n×10¯3
Control	6.96^{a}± 0.18	12.92^{a}± 0.24	38.7^{a}± 0.72	509.95^{a}± 11.5	8.58^{a}± 017
Irradiated (6Gy)	4.51^{d}± 0.08	10.21^{c}± 0.15	30.64^{c}± 0.47	302.0^{c}± 11.8	4.81^{c}± 0.16
ZnONPs (10mg/Kg b.wt.)	6.44^{b}± 0.17	12.4^{a}± 0.18	37.2^{a}± 0.55	491.71^{a}± 14.81	8.32^{a}± 0.19
Treatment R+ZnONPs	5.87^{c}± 1.08	11.48^{b}± 0.15	34.3^{b}± 0.50	404.71^{b}± 14.6	6.65^{b}± 0.16

RBCs: Red blood cells; Hb: Hemoglobin; HCT: Hematocrit; WBCs: White blood cells. Values are expressed as mean ± SE significant at ($p<0.05$). Means marked with the same superscript letters are not significant, whereas, means with the different superscript letters are significant.

Ionizing radiation (IR) exposure causes several adverse effects on humans. Excessive outpot of ROS following radiation might led to oxidative stress which is a key factor in several diseases and several pathological conditions [23]. Radiation-induced cardiovascular diseases are the second most common cause of mortality worldwide. Thus, treatment of CVD is increasingly needed. Nanoparticles are reasonable candidates for delivering bioactive agents to reduce cardiotoxicity [24]. Zinc oxide nanoparticles are a promising platform and have shown positive effects especially in the medical field. Hence, the goal of this study was conducted to evaluate the possible therapeutic effect of ZnONPs on cardiotoxicity induced by exposure to gamma irradiation. The cardiotoxicity induced by exposure to γ irradiation was clearly demonstrated by the increase in the levels of CK, CKMB & LDH (table 1).

The increasing might be due to the excessive production of free radicals, which causes an increase in the permeability of cytoplasmic membrane causing leakage of cardiac enzymes such as CK & LDH [25-26]. On the other side, ZnONPs treatment after exposure to gamma rays can ameliorate the levels of these enzymes. This could be due to ZnONPs' capacity to reduce inflammation and oxidative stress in heart tissue by inhibiting the release of cardiac enzymes from cells [27]. Thus, ZnONPs at a low dose act as radiomitigator agent [26].

CRP is a sensitive indicator of inflammation initiated by radiation [28]. Exposure of rats to ϫ irradiation (6Gy) caused a marked elevation in the CRP level (table 2). This could be clarified by the relationship between stimulation of inflammatory pathways and the oxidative status. An excessive oxidative damage occurs by releasing reactive oxygen species by inflammatory cells [26]. Furthermore, ZnONPs treatment moderated the raised level of CRP in irradiated rats. This might be attributed to the ability of Zn to decrease the inflammation post exposure to radiation [29]. Thus, Zn is considered an atheroprotective agent by decreasing the level of CRP and inflammatory cytokines [30].

The present study showed increase concentration level of troponin 1 (cTn1) post radiation (table 2). This finding is in accordance with Gharib [31], who found that the increment of (cTn1) after radiation due to heart damage. The cardiotoxicity induced by radiation might be attributed to the formation of superoxide anions and hydroxyl radicals, which induce peroxidation of cell membrane [32]. Conversely, ZnONPs have the ability to improve the level of troponin1.

Fibrinogen is considered a key modulator of tissue injury and inflammation, as well as in fibrosis development and that plays an important role in blood clotting [33-34]. This study, revealed that a marked elevation in the level of plasma fibrinogen in

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rats post irradiation (table 2). This finding, agree with that of Zhen-*Lin et al.* [35].

The hyperlipidemia and oxidative stress increases the risk of heart diseases, similarly the chronic overproduction of ROS leads to increasing oxidation of LDL-C causing arteriosclerosis which increases the risk of stroke and heart failure [36].

The hyperlipidemia induced by gamma irradiation caused a significant increase in all lipid contents except HDL-C which was decreased (table 3). This might be due to the effect of γ-radiation on the metabolic capacity of the liver and intestine which synthesize lipoproteins [37].

The observed hypercholesterolemia might be attributed to an extracellular release of cholesterol through the cell membranes after gamma radiation [38]. Additionally, the exposure to ɤ-irradiation can alter the metabolism of HDL & LDL by various inflammatory cytokines [39]. *ZnONPs* treatment showed an obvious improvement in the lipid contents. These findings may be due to the antioxidant character of ZnONPs.

The health status of the experimental animals can be determined by measurement of blood parameters [40]. It helps in assessing and recognizing the hazardous effects induced by radiation. In this study, gamma irradiation (6 Gy) caused a marked decrease in the number of RBCs, WBCs, and PLTs with a remarkable fall in Hb (table 4). Similar findings were obtained by *Osman & Hamza* [41]. The high radio sensitivity of hematopoietic tissue may be responsible for these declines [42]. The decrement of RBCs may be related to the cessation of erythrocytic production in the bone marrow, increase of permeabitity in the hemolytic process as well as erythrocytic membrane stability which was the main cause of the decrease in red blood cells after radiation [43-46].

Furthermore, the decrease in the Hb content after radiation exposure may be due to the formation of free radicals which affect the erythrocyte membrane leading to the leakage of hemoglobin out of the cells [47].

The decrease in the hematocrit value after exposure to gamma radiation (table 4) can be explained by the disturbances in blood forming organs [48]. Furthermore, a decrease in WBCs after radiation could be attributed to lipid peroxidation and cell membrane damage [49].

These hematological parameters were improved in irradiated rats with ZnONPs treatments. This could be attributed to the fact that Zn serves as a cofactor of many enzymes and has antioxidant effects [50]. Zinc is an essential trace elements that provide protection against free radicals produced in the cell as a result of any cause. ZnO NPs have exhibited promising biomedical applications based on its antidiabetic, anticancer, anti-inflammatory and antibacterial [51].

CONCLUSION

The present study shed the light on the probable therapeutic role of ZnONPs as an anti-inflammatory, antioxidant, and hypolipidemic agent against γ-radiation-induced cardiotoxicity and hematological alterations in rats.

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