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RESEARCH ARTICLE

Possible Therapeutic Effect of Anisodamine on Heart Complications Induced by Irradiation

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Abstract

Radiation-induced heart disease is becoming an increasing concern for patients and clinicians alike as the use of radiation therapy for the treatment of certain malignancies increases. Anisodamine (ANI) is a naturally occurring atropine derivative, first isolated in China it has capability of improving the microcirculatory flow, ANI has been reported to work as an anti-shock medicine to treat burn shock, septic shock, So the object of this study is to investigate the beneficial therapeutic effects of anisodamine on the complications occurred to heart after exposure to ionizing radiation.

Forty female Wistar rats, weighing 150 ±21 g were randomly divided into four groups: group I (normal control group), group II (control group administrated ANI 2mg/kg), group III: (irradiated group with 5 Gy γ irradiation single dose) and group IV (irradiated group with 5 Gy γ irradiation single dose and treated with ANI 2mg/kg) drugs were given i.p. to the experimental groups daily for 15 days after irradiation and saline was given i.p. to the control group. The results of the present study showed benefit effects of the anticholinergic anisodamine, administration of ANI remarkably reduced the plasma concentrations of cholesterol, triglycerides (TG), and increased high density lipoproteins (HDL) as compared with group of rats exposed to γ irradiation. It also reduced malondialdehyde (MDA) content, myeloperoxidase (MPO) activity, and enhanced superoxide dismutase (SOD) activity in heart tissues of treated group as compared with irradiated group, and significantly decreased ($p< 0.05$) the concentration of tumor necrosis factor alpha (TNF-α) and intercellular adhesion molecule 1 (ICAM) in heart tissues of the treated group with ANI as compared with irradiated group. Also the results revealed up-regulation in monocyte chemotactic protein-1 (MCP-1) and copeptine genes in group of rats exposed to ionizing radiation, anisodamine alleviated the inflammatory damage by significantly reducing the expressions of these genes as indicated in the treated group.

Histopathological observation showed haemorrhages in the pericardium as well as in between the myocardial bundles in focal manner in group of rats irradiated with acute dose gamma irradiation, and ANI treatment markedly improved haemorrhages in the pericardium but there were hyalinization and granular degeneration in the myocardium.

These results indicated that ANI has the benefit effects on heart damage resulting from exposure to gamma irradiation.

Introduction

Radiation therapy is a powerful tool for improving the survival rate of those diagnosed with certain forms of cancer. (**Seattle, 2013**)

Cardiovascular disease and cancer are the two leading causes of morbidity and mortality worldwide. Over the last half century, radiation therapy (RT) has evolved to become one of the cornerstones of treatment for various types of cancers. It is estimated that more than 50% of patients with cancer are treated with radiotherapy. Along with the development of novel chemotherapeutic agents, radiation therapy (RT) has revolutionized the prognosis of patients with various cancers (**Fuster and Voûte 2005**).

Disease of the heart and pericardium may occur after malignant tumors of the chest have been treated by ionizing radiation (**Luis et al, 1970**).

Cancer patients undergoing radiation therapy need to have baseline studies of cardiac function and routine screening for heart disease, according to recommendations from the European Society of Cardiology and the American Society of Echocardiography published July 16 in the European Heart Journal–Cardiovascular Imaging. (**ALexander otto, 2013**)

Anisodamine is a naturally occurring atropine derivative that has been isolated, synthesized in China from the root of Anisodus tanguticus. Like atropine and scopolamine, anisodamine is a non-specific cholinergic antagonist exhibiting the usual spectrum of pharmacological effects of this drug class. It appears to be less potent and less toxic than atropine and displays less CNS toxicity than scopolamine (**Poupko et al, 2007**).

Experimental evidence implicates anisodamine as an anti-oxidant that may protect against free radical-induced cellular damage. Its cardiovascular properties include depression of cardiac conduction and the ability to protect against arrhythmia induced by various agents. It is a relatively weak alpha (1) adrenergic antagonist which may explain its vasodilating activity. Its anti-thrombotic activity may be a result of inhibition of thromboxane synthesis (**Ruan et al., 2001; Hu and Sheng, 2002**).

Numerous therapeutic uses of anisodamine have been proposed including treatment of septic shock, various circulatory disorders, organophosphorus (OP) poisoning, migraine, gastric ulcers, gastrointestinal colic, acute glomerular nephritis, eclampsia, respiratory diseases, rheumatoid arthritis, obstructive jaundice, opiate addiction, snake bite and radiation damage protection (**Ruan et al., 2001; Hu and Sheng, 2002**).

Several mechanisms have been proposed to explain its beneficial effect though most mechanisms are based upon the assumption that anisodamine ultimately acts by an improvement of blood flow in the microcirculation. Preliminary studies suggest another important therapeutic use of anisodamine is for the treatment of OP poisoning. (**Poupko et al, 2007**)

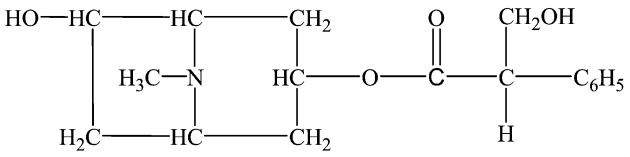
Material and methods:-

Experimental design

Forty female Wistar rats, weighing 150 ±21 g were obtained from the animal house at the Institute of Ophthalmology, Cairo University. they were randomly divided into equal four groups: group I (normal control group) the animals were given saline intraperitoneally (i.p.) group II (control group administrated ANI 2mg/kg), group III (irradiated group with 5 Gy γ irradiation single dose) and group IV (irradiated group with 5 Gy γ irradiation single dose and treated with ANI 2mg/kg) drugs were given i.p. to the experimental groups daily for 15 days after irradiation and saline was given i.p. to the control group, the doses of ANI were determined according to **Zhang et al, 1990**. The animals were randomized and housed under ambient room- temperature and relative humidity conditions, a commercial diet and water were provided add libitum. All animal experiments were performed following the 'Principles of laboratory animal care' (NIH publication no. 85-23, revised 1985), as well as specific local institutional laws for protection of animals under the supervision of authorized investigators. Animals of the irradiated groups were irradiated using ^{60}Co source in Middle Eastern Regional Radioisotopes Center for Arab Countries, Dokki, Giza, Egypt.

Anisodamine:

Anisodamine was purchased from Sigma -Aldrich. The chemical structure of anisodamine is shown in Fig. 1. Chemical name [(3S,6S)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-yl] (2S)-3-hydroxy-2-phenylpropanoate



Anisodamine

Fig. 1. Chemical structure of anisodamine.

Blood and tissue Sampling:

At the end of the experiment animals were anaesthetized with diethyl ether. The blood samples and heart tissues were collected. Blood samples were collected in dry clean centrifuge tubes and then centrifuged at 3000 rpm for 15 min at 4 °C. Serum samples were collected, stored in clean plastic Eppindorff tubes till analysis. Tissue samples were divided into two parts for molecular, biochemical and histopathological investigations.

Biochemical Analysis:.

Serum total cholesterol was assayed as described by **Siedel et al., (1983),** while the protocols of **Gordon and Gordon (1977)** and **Jacobs and Van Denmark (1960)** were adopted for the determination of HDL-cholesterol and triglycerides (TAG) respectively. Malondealdehyde (MDA) concentration was evaluated according to **Wills (1987),** superoxide dismutase (SOD) activity in tissue according to **Misra and Fridovich (1972).**

Determination of myloperoxidase (MPO) activity in heart tissue homogenate

Assaying of MPO activity was described by **Mizutani et al., (2003).** MPO activity was assayed by measuring the change in optical density at 450 nm using tetramethylbenzidine, as substrate (1.5 mmol/L) and H_2O_2 (0.5 mmol/L). Results were expressed as MPO relative units/100 mg tissue. One unit of MPO activity was defined as the quantity of enzyme degrading one mmol peroxide at 25°C. The activity of purified known human neutrophil MPO was used as the standard (Sigma Chemical Co, Egypt).

Measurement of TNF alpha and ICAM

TNF alpha and ICAM were measured by using ELISA (quantikine R&D system USA) according to the manufacturer`s instructions **Maskos et al., (1998) & Jun et al., (2001).**

Detection of Copeptin and MCP-1 gene expression using real time PCR (RT–PCR)

RNA extraction

Total RNA was isolated from htissue homogenates using RNeasy Purification Reagent (Qiagen, Valencia, CA) according to manufacturers instruction . The purity (A260/A280 ratio) and the concentration of RNA were obtained using spectrophotometry (GeneQuant 1300, Uppsala, Sweden).

cDNA synthesis

First-strand cDNA was synthesized from 4 µg of total RNA using an Oligo(dT)12-18 primer and Superscript™ II RNase Reverse Transcriptase, This mixture was incubated at 42°C for 1 h, the kit was supplied by SuperScript Choice System (Life Technologies, Breda, the Netherlands).

Real-time quantitative polymerase chain reaction (PCR)

Real-time PCR (RT-PCR) amplification was carried out using 10 µL amplification mixtures containing Power SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA USA), equivalent to 8 ng of reverse-transcribed RNA and 300 nM primers, the sequences of PCR primer pairs used for each gene are shown in Table 1. Reactions were run on an ABI PRISM 7900 HT detection system (Applied Biosystems) PCR reactions consisting of 95°C for 10 min (1 cycle), 94°C for 15 s, and 60°C for 1 min (40 cycles), Data were analyzed with the ABI Prism sequence detection system software and quantified using the v1·7 Sequence Detection Software from PE Biosystems (Foster City, CA). Relative expression of studied genes was calculated using the comparative threshold cycle method. All values were normalized to the copeptin and MCP-1 genes according to **Kenneth et al., (2001).**

Table 1. Primer sequences used for RT-PCR

primer	sequence
MCP-1	Forward :5' TCT GGC ACC ACA CCT TCT ACA ATG 3' Reverse: 5' AGC ACA GCC TGG ATA GCA ACG 3' according to gene bank accession number NM_031530.1
copeptin	Forward :5' TATTAAAGTCAGAGAGAACGTAA3' Reverse: 5' GTGCAGCTGTTAAAGTTTGAGAGATGTATT3' according to gene bank accession number NP_000482.1
GAPDH	forward: 5′- CTCCCATTCTTCCACCTTTG-3′ reverse: 5′- CTTGCTCTCAGTATCCTTGC-3′ according to gene bank accession number XR_145951.1

Histological Examination

Autopsy samples were taken from the heart of rats in different groups and fixed in 10% formol saline for twenty four hours. Washing was done in tap water then serial dilutions of alcohol (methyl, ethyl and absolute ethyl) were used for dehydration. Specimens were cleared in xylene and embedded in paraffin at 56 degree in hot air oven for twenty four hours. Paraffin bees wax tissue blocks were prepared for sectioning at 4 microns thickness by slidge microtome. The obtained tissue sections were collected on glass slides, deparaffinized, stained by hematoxylin &eosin stain for routine examination through the light electric microscope (**Banchroft et al., 1996).**

Statistical analysis

All the results were statistically analyzed according to **Steel and Torrie (1980)** using SPSS statistical software package (v.17). The results were presented as mean ±SE. The differences between mean values were determined by analysis of variance (ANOVA test), followed by Waller-Duncan k- ratio **(Waller and Duncan 1969).** All statements of significance were based on probability of $P \leq 0.05$. Statistical significance of the relationships between variables was calculated by correlation analysis.

Results

The results of the present study showed that the acute dose of γ- irradiation induced a significant increase ($p< 0.05$) in each of cholesterol and triglycerides levels while significant decrease ($p< 0.05$) in HDL level in irradiated group as compared with normal control group as shown in figs (2A , 2B & 2C) The elevation of cholesterol and TG levels in plasma were significantly ($p< 0.05$) improved in group of rats irradiated and treated with anisodamine .It also remarkably increase the level of HDL to close to normal in the treated group .

The SOD activities, MDA contents and MPO activities of heart tissues were investigated, the results of SOD activities in heart tissues as shown in Figure (3A) indicating significant decrease in irradiated rats group as compared with normal control group (0.20 ± 0.012 U/mgvs 0.64 ± 0.11U/mg) and this activities return to increase significantly ($p< 0.05$) in group of rats exposed to gamma radiation and treated with anisodamine to become (0.55 ± 0.03 U/mg).

The results of MDA contents in heart tissues increased to (10.10 ±0.26 nmol/mg) in irradiated rats group as compared with (1.53±0.14 nmol/mg) in normal control group while this contents significantly decreased ($p< 0.05$) in group of rats exposed to gamma radiation and treated with anisodamine to be (3.30 ±0.30 nmol/mg) as shown in Figure (3B). As for MPO activities the results also showed significant increase ($p< 0.05$) in the activity in irradiated rats group as compared with normal control group as shown in Figure (3C) and this activity in the enzyme return to decrease in group of rats exposed to gamma radiation and treated with anisodamine as shown the Figure.

As shown in figures (4A &4B) which revealed significant elevation ($p< 0.05$) in the concentrations of TNF and ICAM in irradiated rats group as compared with normal control group. It was noticed that the elevation in the concentration of both parameters significantly ($p< 0.05$) decreased in group of rats exposed to gamma radiation and treated with anisodamine as compared with irradiated rats group. As well as, irradiated rats group showed significant elevation ($p< 0.05$) in MCP1 and copeptine concentration in heart tissues as compared with normal control group,

this elevation significantly ($p < 0.05$) decreased in group of rats exposed to gamma radiation and treated with anisodamine as compared with irradiated rats group (figs 4C &4D).

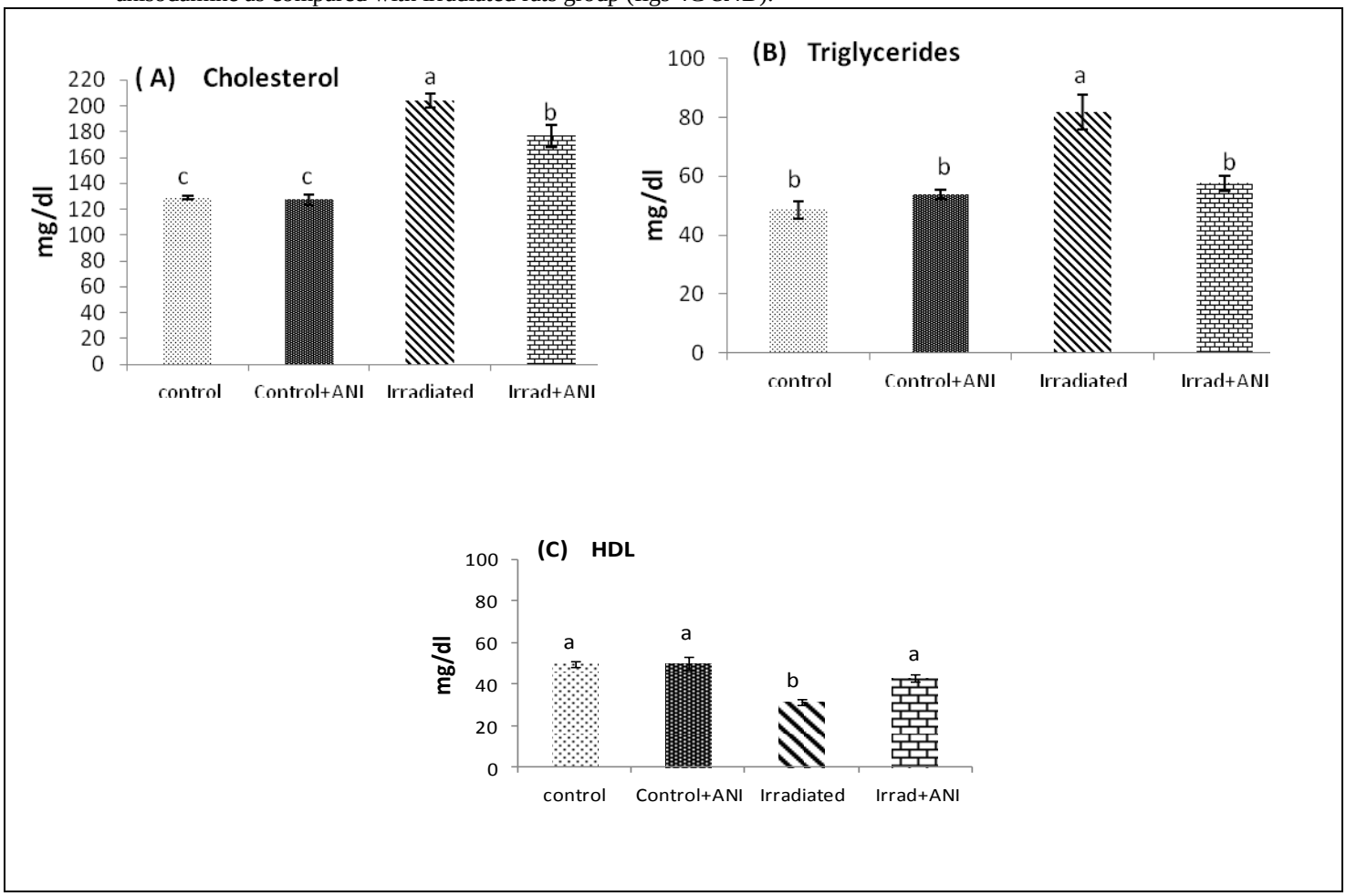


Figure 2. (A) The levels of cholesterol, (B) triglycerides and (C) high density lipoprotein in plasma of the four experimental groups. Data presented means ±SE. $P<0.05$.

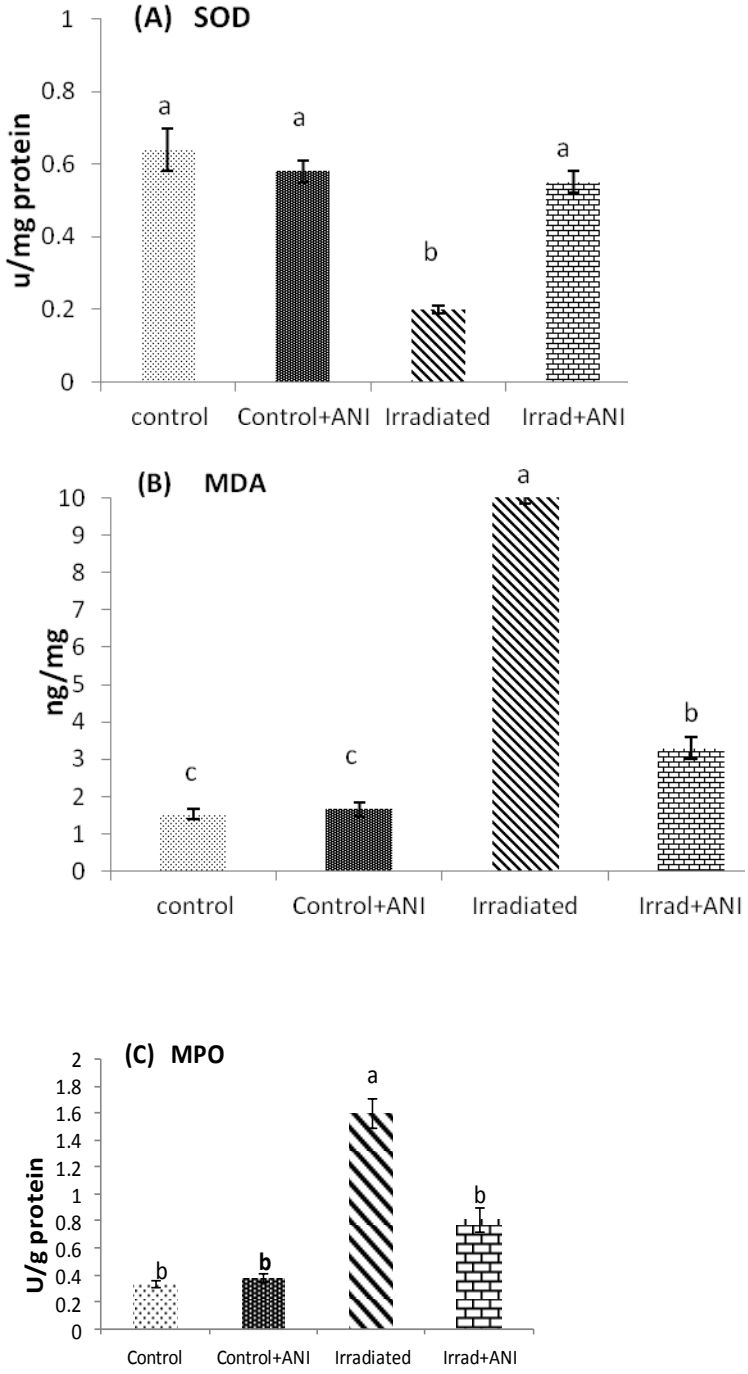


Figure3.(A)The SOD activities, (B) MDA content and (C) MPO activities in heart tissues of the four experimental groups. Data presented means ±SE. P<0.05.

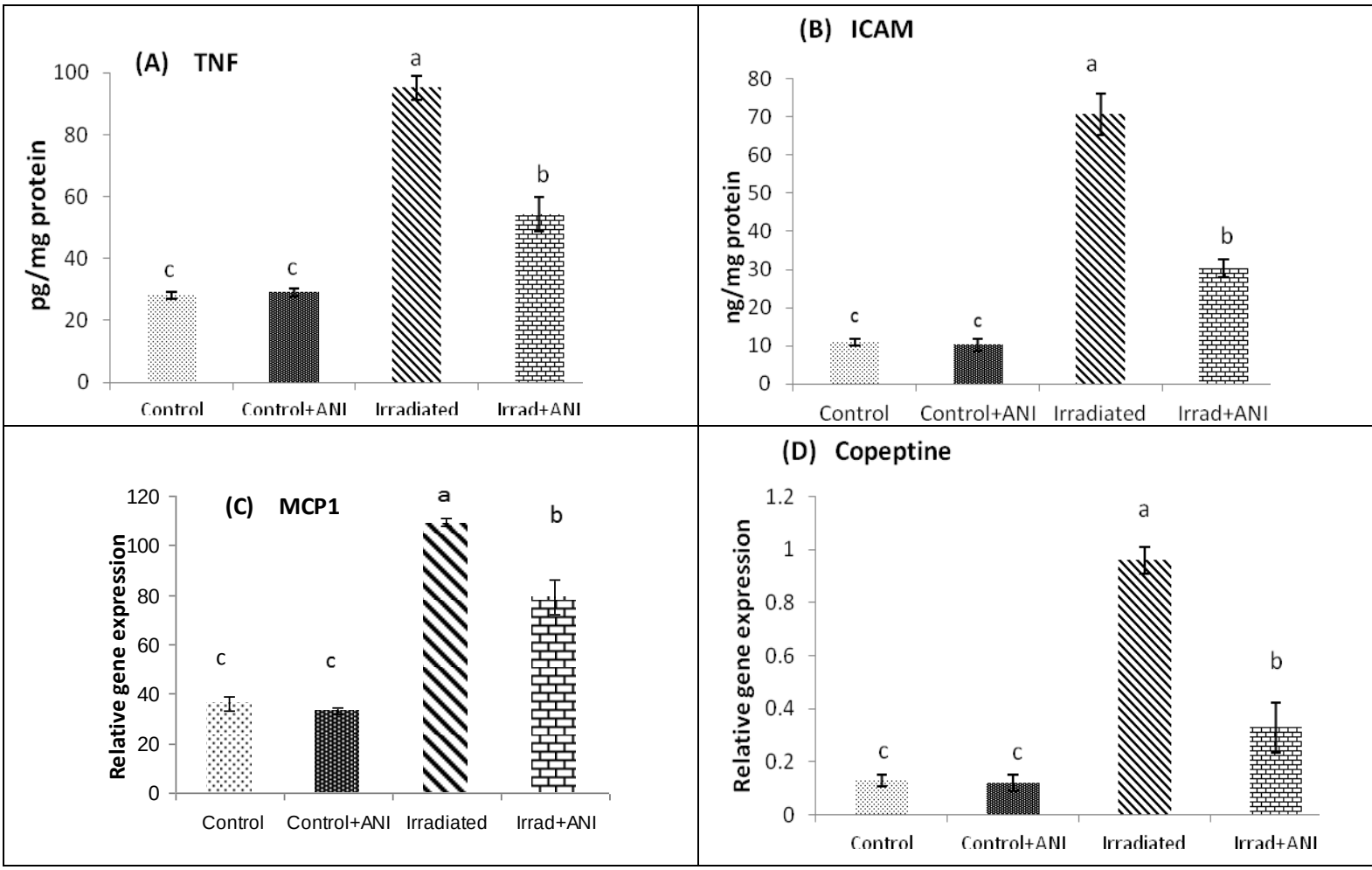
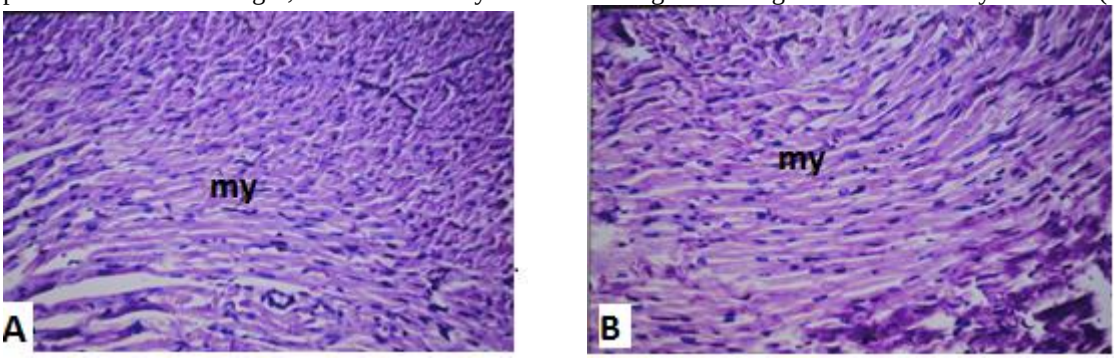


Figure 4. The concentration of (A) TNF, (B) ICAM , (C) MCP1and (D) copeptine in heart tissues of the four experimental groups. Data presented means ±SE. P<0.05.

Histopathological Findings:

There was no hitopathological alteration and the normal histological structure of the myocardium was recorded in the normal control group and control group administrated anisodamine as shown in Fig. (5A&5B). But in group of rats irradiated with acute dose gamma irradiation Haemorrhages were detected in the pericardium as well as in between the myocardial bundles in focal manner (Fig.5C&5D) there was hyalinization in the wall of dilated myocardial blood vessels, the myocardium showed vacuolar degeneration and hyalinization. On the contrary, the group of rats exposed to gamma radiation and treated with anisodamine showed significant protective effects on pericardium haemorrhages, but there were hyalinization and granular degeneration in the myocardium (Fig.5E).



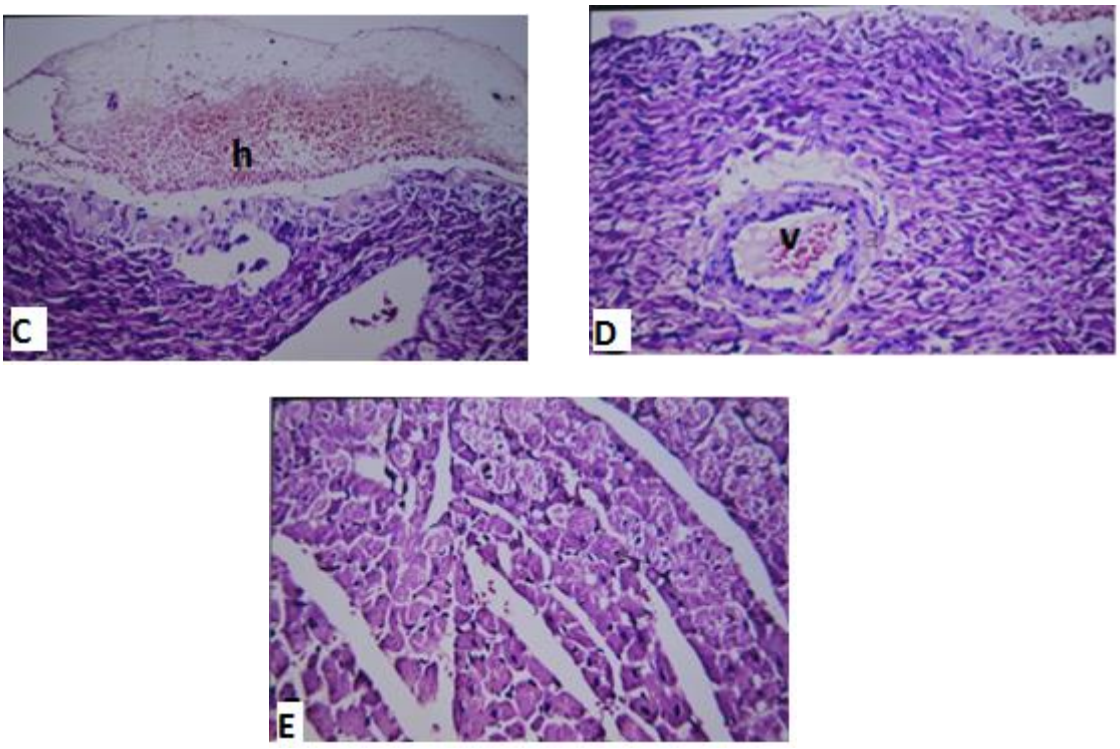


Figure 5. Histopathological examination of heart tissues A: the normal control group. B: the control group administrated anisodamine. C&D: irradiated group with 5 Gy γ irradiation single dose. E: irradiated group and treated with anisodamine.

Discussion:

Radiation-induced heart disease is becoming an increasing concern for patients and clinicians alike as the use of radiation therapy for the treatment of certain malignancies increases, and patient mortality secondary to neoplasms of the thorax, in particular Hodgkin's lymphoma and breast cancer, decreases. The spectrum of pathology affecting the heart spans from acute to chronic and can affect almost all facets of the heart, including but not restricted to the pericardial sac, coronary arteries, myocardium, and heart valves. (**Filopei and Frishman 2012**).

Anisodamine has been used as a vasoactive drug in China for decades to improve microcirculation, especially during septic shock (**Xiu, 1980; Xiu et al., 1982**). The microcirculatory effects of anisodamine have been demonstrated to be associated with its ability to inhibit the aggregation of platelet and synthesis of thromboxane, malondialdehyde and 6-keto-prostaglandin F1a (Xiu et al., 1982). In addition to its beneficial effects on microcirculation, anisodamine has also been used to protect against arrhythmias, myocardial ischemic reperfusion injury and cardiopulmonary bypass surgery-induced hypertension **(Hu et al., 1986; Wang et al., 1988).** To date, the mechanisms of action behind anisodamine-induced cardiovascular effects have been largely attributed to its antagonism against cholinoceptors and adrenoceptors (**Verma and Yue, 1986**).

The experimental results of this study demonstrated that serum cholesterol and triglycerides levels in rats exposed to γ -irradiation were significantly increased ($p< 0.05$) compared to the control group. However in the group treated with anisodamine 15 days post-irradiation, both cholesterol and triglyceride values recorded a significant decrease ($p< 0.05$) compared to the irradiated group. The significant elevation of total cholesterol in serum of irradiated animals was explained by **Bok, et al.,(1999)** who mentioned that irradiation increases activation of HMG-CoA reductase enzyme, the key regulatory enzyme in the reaction of the cholesterol synthesis process. **El-Khafif, et al.,(2003)** reported that increased level of serum cholesterol fractions was probably due to its release from tissues, destruction of cell membrane and increase rate of cholesterol biosynthesis in the liver and other tissues. The increase in plasma triglycerides in rats exposed to γ -irradiation may be attributed to inhibition of the activity of lipoprotein lipase. These results are consistent with the observation of **Sedlakova, et al.,(1986)** who mentioned that lipoprotein lipase activity decreases post irradiation exposure in adipose tissues giving rise to hypertriglyceridemia.

Significant increase in the levels of serum lipid profile are demonstrated post radiation exposure of rats. These changes are in agreement with previous studies by **Feurgard et al., (1999)** and **Agrawal et al., (2001)** who indicated that ionizing-radiation-induced oxidative stress which might alter hepatic lipid metabolism and serum lipoproteins. It seems that there is an association between radiation-induced oxidative stress and elevated levels of lipid fractions and LDL **(Onody et al., 2003)**. This association is similarly observed in other conditions characterized by increased oxidative stress (**Baynes, 1991; El-Missiry et al., 2004**). Therefore, it is suggested that oxidative stress might be an important determinant of altered lipid metabolism due to radiation exposure.

The present study also revealed that malondialdehyde (MDA) content in the myocardium significantly decreased ($p< 0.05$) and SOD activity significantly increased ($p< 0.05$) after the treatment with ANI for15 days post irradiation, this results are in agreement with **YAO Xiu. et al., 1992**. Also MPO activities attenuated after treatment with anisodamine, the results are in harmony with **Dong-Ting et al., 2012**. MPO is an enzyme mainly located in the primary granules of neutrophils; the tissue MPO levels may indicate neutrophils infiltration (**Tuğtepe et al., 2007**). MDA, a lipid peroxidation end product, is widely worked as a marker of oxidative stress (**Gaweł et al., 2004**). According to our findings, ANI treatments significantly suppressed the activity of MPO and the MDA contents in heart tissue, which illustrated that the treatment with ANI could inhibit the infiltration of neutrophils and attenuate oxidative stress. SOD is an enzyme that exists in cells removing oxyradicals, whose activity variation may represent the degree of tissue injury **(Macarthur et al., 2000).** The present study also revealed that SOD activities in the treated group were remarkably lower than the group exposed to gamma irradiation. These findings implied that the feature of anticholinergics are to reduce MDA contents and enhance SOD abilities, which prevented heart tissue from cellular membrane destroy and attacked by oxygen free radicals **(Dong-Ting et al., 2012).**

The present study revealed significant increase in the levels of TNFα and MCP1 (and induces up-regulation of MCP1 gene) in heart tissues in group of rats exposed to γ –irradiation this is in agreement with **Sharath and collogues (2014)** who reported ionizing radiation (IR) increases tissue levels of TNF. TNF signaling regulates numerous cytokines and chemokines that are known to mediate radiation-induced non-targeted effects (NTEs). Irradiation of the liver induces up-regulation of the genes of the main proinflammatory chemokines, probably through the action of locally synthesized proinflammatory cytokines. (**Federico Moriconi et al., 2008**).

The present study found the tissue concentrations of TNF-α and MCP1 in group of rats treated with anticholinergics anisodamine were significantly lowered, the data demonstrated that ANI acted positively to inflammatory response. The protection against inflammation induced by ANI can probably be ascribed to the reduced generation of MCP1and TNF-α generated by macrophages this is in agreement with **Dong-Ting et al., 2012**.

Indirect association of inflammation with radiation-induced vascular damage comes from studies showing elevated levels of the proinflammatory cytokines IL-6, CRP, TNF-α, and INF-γ and also increased levels of the anti-inflammatory cytokine IL-10 (**Hayashi et al., 2005**).

In experimental atherosclerosis model it has been shown that following multiple small radiation doses the chemoattractant (MCP-1) concentration increases proportionally to cumulative dose; this increase in MCP-1 is largely driven by radiation-induced monocyte death (**Little et al., 2009**). In an animal model, following a single dose of radiation to the heart, from 3 months onwards changes in coronary arteries of the irradiated hearts included endothelial cell loss, a loss of smooth muscle cells, and fibrosis in media and adventitia (**Boerma et al, 2004**). Chemokines are the main modulators of the inflammatory and reparatory events may have a key role in heart repair after MI. MCP-1 (monocyte chemotactic protein-1) plays a critical role in the development of cardiovascular diseases (**Hlatky et al, 2009**).

Inflammation process involves multiple inflammatory mediators, neutrophils recruitment, and macrophages infiltration. Macrophages produce pro-inflammatory cytokines that can stimulate the activity of other leukocytes. Analysis of infiltrating macrophages demonstrated that these leukocytes were the major producer of the cytokines IL-1, IL-6, and TNF-α (**Bajwa et al., 2009**). TNF-α has been proven to play a "master-regulator" role in orchestrating the cytokine cascade in many inflammatory diseases (**Parameswaran and Patial, 2010**). IL-1 and IL-6 have been reported as good indicators of activation of cytokine cascade in various conditions (**Oda et al., 2005**). These pro-inflammatory cytokines were essential during the early phase of IR, inflammation, and endotoxemia (**Ishii et al., 2010; Lloyd et al., 2003**). Therefore, it is important to inhibit the release of IL-1, IL-6, and TNF-α for lessening inflammatory responses.

Copeptin is the stable C-terminal part of pro arginine-vasopressin (AVP). It is released with AVP after hemodynamic or osmotic stimuli and is also an endocrine stress hormone. It is released into the circulation early after MI onset, and may aid in rapid diagnosis (**Buckley et al., 2009**). The results revealed over expression in copeptine gene in heart tissue in group of rats exposed to ionizing radiation and this agreed with **Antoni (1993)** who

reported chronic psychosocial stress is frequently accompanied by increased plasma levels of arginine vasopressin (AVP), which is an amplifier of the hypothalamic pituitary-adrenal (HPA) axis along with corticotropin-releasing hormone (CRH).

ICAM-1 (intercellular adhesion molecule-1) may play a role in signal transduction associated primarily with proinflammatory pathways. In particular, ICAM-1 signaling seems to produce a recruitment of inflammatory immune cells such as macrophages and granulocytes **(Buckley et al., 2009).**

ICAM-1 is found abundantly in endothelial, epithelial, and mesangial cells and fibroblasts. It is up-regulated in vitro and in vivo by cytokines such as TNF-α and IL-1 (**Burne et al., 2001**). **Park et al. (2008)** reported that IL-1 and TNF-α could regulate the expression of leukocyte-binding adhesion molecules in endothelial cells derived from human glomerulus. Our study showed that ICAM-1 level decreased significantly in the groups treated with anticholinergic anisodamine as compared with the group of rats exposed to ionizing radiation.

These data suggested that ICAM-1 played a significant role during the neutrophil dependent injury phase after gamma irradiation. As a result, suppressing adhesion molecule may have potential to against radiation induced inflammation. Anisodamine possess these characteristics such as anti-inflammation, antioxidation, improving the function of the endothelium **(Zhenxiang et al., 2012).**

Histopathological observation showed haemorrhages in the pericardium as well as in between the myocardial bundles in focal manner in group of rats irradiated with acute high dose gamma irradiation, and ANI treatment markedly improved haemorrhages in the pericardium but there were hyalinization and granular degeneration in the myocardium. The protective effects of anisodamine may also be associated with activating super oxide dismutase (SOD) in the tissues, decreasing the level of malondialdehyde (MDA), inhibiting expression of endothelin and inhibiting apoptosis of cells **(Nakagawa et al., 2005).**

Recently, some studies have shown that anisodamine could enhance spontaneous vasomotion of microvessels, increase the velocity of blood flow, and reduce the permeability of microvasculature, which is beneficial for improving microcirculation (**Wang Yan-bo, et al., 2012).**

Conclusion

In conclusion, this study demonstrates a direct response of anisodamine on heart damage induced by exposure to radiation and has potential therapeutic effect in improving this damage through activating SOD and attenuating MDA and MPO so resist oxygen free radicals, also probably through inhibiting the production of inflammatory cytokines TNF-α, and suppress the expression of MCP-1, copeptine and ICAM-1 in heart tissue. Future studies should focus on the action of anisodamine to understand the cellular effects and pharmacological profiles of this herbal compound.

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