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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH


Kidney morphofunctional features after ascorbic acid administration in a model of acute radiation nephropathy

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Abstract. Relevance. The use of radiation therapy in the treatment of malignant neoplasms actualizes the study of ways to protect healthy tissues from radiation damage. Due to the small number of studies aimed at studying structural and functional changes of kidneys both at their direct irradiation with electrons and at radiotherapy of adjacent organs, it is necessary to carry out complex research. One of the promising directions of radiation nephropathy treatment is the use of antioxidant preparations, in particular ascorbic acid. **Aim.** Morphofunctional evaluation of the kidney after local electron irradiation and ascorbic acid administration. **Materials and Methods.** Wistar rats (n=90) were divided into groups: I — control (n=15); II — irradiation, 2 Gy dose (n=15); III — irradiation, 8 Gy dose (n=15); IV — irradiation, 2 Gy dose + ascorbic acid (intraperitoneal injection; dose 50 mg/kg) (n=15); V — irradiation, 8 Gy dose + ascorbic acid (intraperitoneal injection; dose 50 mg/kg) (n=15); VI — ascorbic acid (intraperitoneal injection; dose 50 mg/kg) (n=15). Kidney slides were stained with hematoxylin and eosin. In addition, blood biochemical examination was performed for creatinine, urea nitrogen, C-reactive protein, cystatin C to creatinine ratio

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was calculated, and kidney homogenate for malonic dialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH) concentration levels. *Results and Discussion.* It was found that pre-radiation administration of ascorbic acid (intraperitoneal injection; dose 50 mg/kg) in the model of acute radiation nephropathy induced by local irradiation with electrons at doses of 2 Gy and 8 Gy contributed to a pronounced reduction of pathomorphologic and biochemical changes. *Conclusion.* Local irradiation with electrons at doses of 2 Gy and 8 Gy leads to the development of radiation nephropathy. At the same time, pre-irradiation administration of ascorbic acid reduces the strength of radiation-induced kidney damage, as well as enhances the efficiency of antioxidant defense.

Keywords: radiation nephropathy, electron irradiation, kidney, ascorbic acid, oxidative stress

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Conflicts of interest statement. The authors declare no conflict of interest.

Ethics approval. All manipulations were performed in accordance with the “International Guidelines for Biomedical Research Using Animals” (EEC, Strasbourg, 1985) and the Declaration of Helsinki of the World Medical Association. The study was approved by the Local Ethics Committee of the National Medical Radiological Research Center (protocol No. 6 of 27/04/23).

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Introduction

In the treatment of malignant neoplasms, isolated or complex methods: radiotherapy, chemotherapy and surgery are the key choices. However, early, or late post-radiotherapy complications are possible with radiotherapy [1, 2]. Special attention is paid to the dose-dependent effects of charged particles: electrons and others [3].

Kidneys are the most important organ involved in the maintenance and regulation of fluid, acid-base, and electrolyte metabolism, as well as in the excretion of metabolites, regulation of blood pressure, synthesis of erythropoietin to stimulate red blood cell formation and activation of vitamin D, etc. [4].

Radiation damage to the kidneys leads to both acute and chronic morphofunctional changes in the glomerular apparatus and nephrons, which are accompanied by apoptosis or necrosis of endothelial cells, nephrocytes, etc., and, in late stages, to the development of fibrosis or atrophy. The accumulation of toxic metabolites caused by radiation nephropathy is complicated by chronic renal failure requiring replacement therapy, including dialysis or transplantation [5–7]. Therefore, high importance is attached to the development of effective methods of radiation complications protection [8].

A few studies have revealed that the use of antioxidants helps to reduce the level of post-radiation damage to various organs. One of such drugs is ascorbic acid [9–12].

Thus, due to the small number of studies aimed at studying structural and functional changes in the kidneys, both during their direct irradiation with electrons, and during radiotherapy of malignant neoplasms of neighboring organs, it is necessary to conduct a comprehensive study. It will help to form an idea about dose-dependent effect and pathogenesis of radiation damage of kidneys with determination of optimal mode of radiation therapy. To analyze the effects of radiation damage and recovery, first, of the glomerular apparatus, it is necessary to characterize the main pathomorphological changes, considering the range of toxic effects, to assess the state of the life cycle (proliferation and apoptosis), the degree of fibrosis and others. Separately, it should be emphasized the importance of developing methods of prevention of acute and chronic radiation nephropathy, for example, by the introduction of drugs with a protective effect.

The aim of the study was morphofunctional evaluation of the kidney after local electron irradiation and ascorbic acid administration.

Material and methods

Animals for in vivo study

Male Wistar rats (220.3±10.6 g; 9–10 weeks old; n=90) were kept in a vivarium under controlled temperature (22 °C) and light period (12L:12D) with free access to water and standard food. The rats were divided into six experimental groups:

- Group I (n=15) — control;
- Group II (n=15) — animals were subjected to a single local irradiation with electrons at dose of 2 Gy;
- Group III (n=15) — animals were subjected to a single local irradiation with electrons at dose of 8 Gy;
- Group IV (n=15) — before irradiation with electrons at dose of 2 Gy, animals were administered ascorbic acid (intraperitoneal injection; dose 50 mg/kg);
- Group V (n=15) — before irradiation with electrons at dose of 8 Gy, the animals were administered ascorbic acid (intraperitoneal injection; dose 50 mg/kg);
- Group VI (n=15) — animals were administered ascorbic acid (intraperitoneal injection; dose 50 mg/kg).

Animals of all groups were removed from the experiment by administering high doses of anesthetic (intraperitoneal injections of ketamine + xylazine) on the 7th day of the experiment (the start date of the experiment was considered the last day of irradiation). All manipulations were performed in accordance with the “International Guidelines for Biomedical Research Using Animals” (EEC, Strasbourg, 1985) and the Declaration of Helsinki of the World Medical Association. The study was approved by the Local Ethics Committee of the National Medical Radiological Research Center (protocol No. 6 of 27/04/23).

Biochemical assays

Blood levels of creatinine, urea nitrogen, C-reactive protein, and the ratio of cystatin C to creatinine were measured. Serum creatinine and urea nitrogen levels were determined using commercial kits (Pars Azemoo, Iran), and cystatin C levels were quantified by enzyme-linked immunosorbent assay using a commercial rat kit (Cusabio, China).

Oxidative stress markers

Kidney homogenate was obtained by homogenizing 1 g of tissue in 4.5 ml of cold potassium buffer (pH 7.4). The solution was then centrifuged at 13000 rpm for 10 min at 4 °C. The supernatant was then stored at — 80 °C. The levels of malonic dialdehyde (MDA) as a biomarker of lipid peroxidation, superoxide dismutase (SOD), and glutathione (GSH) in kidney homogenate were evaluated using ELISA kits (Lifespan Biosciences, USA).

Morphologic study

After extraction, the appearance of kidneys and the state of parenchyma on the section were evaluated (blood filling, inflammatory changes, atrophy, etc.), weighed (absolute — in grams and relative — in relation to body weight, in %). Kidney fragments were fixed in a solution of buffered formalin, after wiring (histological tissue wiring machine, “Leica Biosystems”, Germany) were cast into paraffin blocks, from which serial sections (3 µm thick) were prepared, dewaxed, dehydrated and stained with Mayer’s hematoxylin and eosin.

Considering that radiation nephropathy is manifested by lesions of tubules (thrombotic microangiopathy, collapse), nephron tubules and interstitial component, which lead to glomerulosclerosis and tubulointerstitial fibrosis by light microscopy (in 10 random fields of view at magnification x200) we evaluated vacuolization, dystrophy, atrophy of cortical tubules and nephron tubules; inflammation; necrosis.

Statistical analysis

All statistical analyses were performed using the computer program SPSS 12.0 for Windows (IBM Analytics, USA). All data are presented in the format of mean \pm standard deviation (M \pm SD). Kolmogorov-Smirnov test was used for each sample separately to test the hypothesis of normality of distribution of values. In case of normal distribution, Student's t-test was used. Differences between samples were considered statistically significant at a significance level of $p < 0.05$, established before the analysis.

Results and discussion

Body weight of animals of experimental groups decreased in relation to control ($p < 0.05$). The introduction of protectors in groups IV and V gave a statistically significant change in this index compared to groups II and III.

The kidney weight after electron irradiation decreased in relation to the control groups ($p < 0.05$). As a result

of ascorbic acid administration, statistically significant changes in organ weight were observed in groups IV and V compared to groups II and III. In Group VI no statistically significant changes in these parameters were observed compared to the control group (Table 1).

A significant increase was found in the study of serum creatinine level in groups II and III, in comparison with the control group ($p < 0.05$). In group IV and V insignificant changes were observed in comparison with the control ($p < 0.05$). In group VI no statistically significant changes in these parameters were observed compared to the control group (Table 2).

The level of urea nitrogen in serum in all groups exposed to radiation increased significantly compared to the control group ($p < 0.05$). In groups IV and V, the amount of urea nitrogen in blood decreased compared to the groups exposed to electrons (Table 2).

The study revealed a significant increase in the level of C-reactive protein in the blood of groups II and III compared to the control ($p < 0.05$). However, with pre-radiation administration of ascorbic acid the increase in CRP level was insignificant. No statistically significant changes in these parameters were observed in Group VI compared to the control group ($p < 0.05$) (Table 2).

The ratio of cystatin C to creatinine in serum significantly increased after irradiation at a dose of 8 Gy (group III) compared to the control group ($p < 0.05$). In the other groups no statistically significant changes in these parameters were found ($p < 0.05$) (Table 2).

Table 1

Animal weight and kidney weight of control and experimental groups

Group	n	Weight of animal, g	Weight of kidney, g
Control	15	220,3 \pm 10,6	2,16 \pm 0,03
Irradiation 2 Gy	15	196,4 \pm 4,7a	1,76 \pm 0,01a
Irradiation 8 Gy	15	181,2 \pm 6,1a	1,62 \pm 0,02a
Irradiation 2 Gy + AA	15	206,4 \pm 2,1b	1,83 \pm 0,02b
Irradiation 8 Gy + AA	15	193,4 \pm 3,4b	1,71 \pm 0,03b
AA	15	226,1 \pm 5,7	2,26 \pm 0,02

Note: Data are presented as mean \pm standard deviation (M \pm SD). The Kruskal – Wallis test was used to test the statistical significance of differences between groups. Statistically significant differences compared to the control group are labeled in the Table as Irradiation (a) and Irradiation + AA (b); $p < 0.05$.

Table 2**Levels of creatinine, C-reactive protein, urea nitrogen, cystatin C to creatinine ratio in control and experimental groups**

Group	Creatinine, mg/dL	C-reactive protein, mg/l	Urea nitrogen level, mg/dL	Cyst. C/ creatinin, ng / ml / mg / dl
Control	0,516 ± 0,005	2,11 ± 0,031	16,24 ± 0,27	6,0 ± 0,14
Irradiation 2 Gy	0,563 ± 0,015a	2,81 ± 0,029a	18,56 ± 0,38a	6,15 ± 0,07a
Irradiation 8 Gy	0,641 ± 0,024a	3,54 ± 0,21a	22,1 ± 0,13a	7,18 ± 0,1a
Irradiation 2 Gy + AA	0,524 ± 0,002b	2,63 ± 0,12b	17,18 ± 0,31b	6,20 ± 0,05b
Irradiation 8 Gy + AA	0,537 ± 0,003b	3,17 ± 0,095b	19,75 ± 0,12b	6,74 ± 0,18b
AA	0,519 ± 0,001	2,22 ± 0,134	15,88 ± 0,26	6,03 ± 0,12

Note: Data are presented as mean ± standard deviation (M±SD). The Kruskal – Wallis test was used to test the statistical significance of differences between groups. Statistically significant differences compared to the control group are labeled in the Table as Irradiation (a) and Irradiation + AA (b); $p < 0.05$.

In the kidney tissue homogenate after a single irradiation with electrons at doses of 2 Gy and 8 Gy, an increase in the level of malonic dialdehyde (MDA) by 3.1 times and 7.3 times was found, respectively. In addition, in group III, a 31.4 % decrease in superoxide dismutase (SOD) and a 28 % decrease in glutathione (GSH) level were observed compared to the control group ($p < 0.01$). In groups IV and V, insignificant changes in MDA, SOD and GSH values were observed compared to control values. In group VI, no significant changes in SOD and GSH levels were found, but MDA level was insignificantly lower (by 7.1 %) than in the control group ($p < 0.05$) (Table 3).

At light microscopy of kidney slices of the control group (intact animals) normal histoarchitectonics was observed (Fig.).

In kidneys after a single local irradiation with electrons at doses of 2 Gy and 8 Gy the number of vascular tubules was reduced, Bowman's capsule was dilated, signs of dystrophic changes in the epithelium of nephron tubules with the appearance of intense pycnotic nuclei in the proximal part, dissociation of macula densa cells, as well as perivascular and paraglomerular edema, abundance of blood vessels were observed. The deepest kidney damage was observed in group III, where damaged tubules accounted for up to 1/5 of the kidney.

At pre-radiation administration of ascorbic acid in groups IV and V, the degree of pathomorphologic changes was reduced. No significant differences in renal structures were found between the groups of ascorbic acid mono-injection and the control group.

Table 3**Levels of malonic dialdehyde (MDA), superoxide dismutase (SOD) and glutathione (GSH) in kidney homogenate of control and experimental groups**

Group	MDA	SOD	GSH
Control	11,2 ± 0,3	63,9 ± 4,6	11,2 ± 0,6
Irradiation 2 Gy	34,6 ± 2,7a	53,4 ± 3,1a	9,4 ± 0,5a
Irradiation 8 Gy	79,5 ± 4,2a	42,1 ± 2,2a	8,1 ± 0,3a
Irradiation 2 Gy + AA	26,8 ± 3,1b	57,5 ± 1,7b	10,4 ± 0,7b
Irradiation 8 Gy + AA	38,8 ± 2,1b	48,8 ± 3,6b	9,1 ± 0,3b
AA	10,4 ± 0,4	59,8 ± 2,8	12,8 ± 0,8

Note: Data are presented as mean ± standard deviation (M±SD). The Kruskal – Wallis test was used to test the statistical significance of differences between groups. Statistically significant differences compared to the control group are labeled in the Table as Irradiation (a) and Irradiation + AA (b); $p < 0.05$.

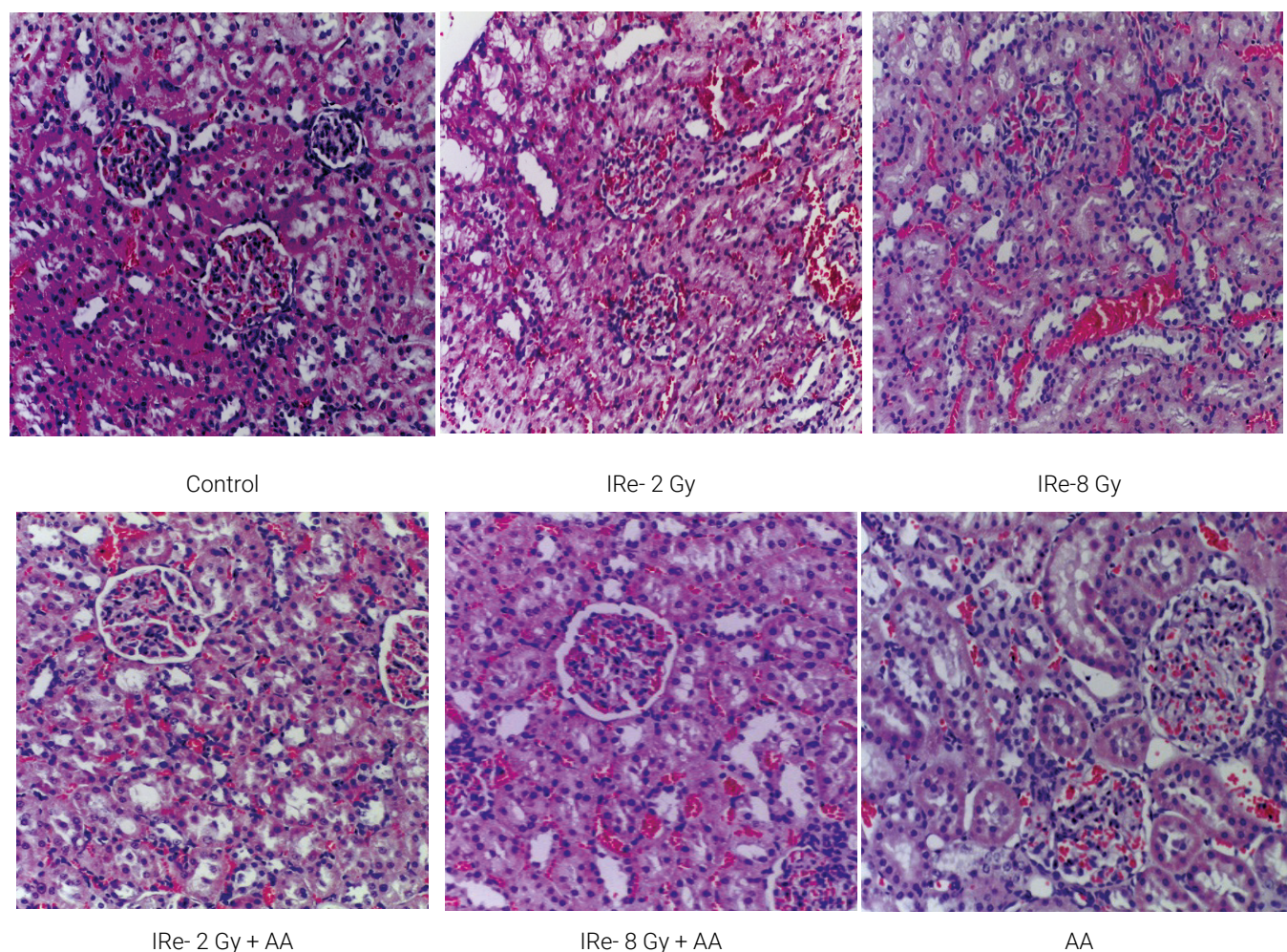


Fig. Kidneys of control and experimental groups. Hematoxylin and eosin staining, magnification. $\times 200$. In kidneys after irradiation at doses 2 Gy and 8 Gy, a decrease in the number of tubules, dystrophic changes in the epithelium of nephron tubules, and abundance of blood vessels were found, especially at dose 8 Gy. At doses 2 Gy + AA and 8 Gy + AA groups the degree of pathomorphologic changes was reduced

Notes: IRe- 2 Gy – experimental group irradiated with electrons at a single focal dose of 2 Gray; IRe- 8 Gy – experimental group irradiated with electrons at a single focal dose of 8 Gray; IRe- 2 Gy + AA and IRe- 8 Gy + AA – experimental groups irradiated with electrons at a single focal dose of 2 and 8 Gray); AA – ascorbic acid.

The present work is devoted to the structural and functional study of the protective effect of ascorbic acid on kidney structures in a model of acute radiation nephropathy induced by single electron irradiation at doses of 2 Gy and 8 Gy.

Radiotherapy, in particular electron irradiation, is one of the effective methods of treatment of malignant tumors of the kidney and retroperitoneum [13, 14]. However, its use is accompanied by the risk of radiation-induced organ damage development,

including two subsequent phases — inflammation and fibrosis [15, 16]. Therefore, the most important task of modern radiation therapy is to improve the safety of radiation exposure and minimize the associated side effects.

To date, there is limited data on the issue of electron irradiation. Most studies in specialized literature are devoted to other types of radiation. For example, after X-, gamma-exposure deep degenerative changes of nephron tubules and tubules are observed, etc. [17, 18].

The observed development of acute vascular reactions after local irradiation with electrons may indicate dysfunction due to damage of the renal tubular apparatus, which are most pronounced after exposure to a dose of 8 Gy. However, the revealed pathomorphologic changes were less pronounced compared to other types of irradiations.

To assess the severity of oxidative stress as well as the independence of antioxidant defense, GSH, MDA and SOD markers were analyzed. Exposure to electrons initiates the formation of reactive oxygen species as well as lipid peroxidation. These biochemical changes are accompanied by an increase in the level of malonic dialdehyde, which reflects the degree of lipid peroxidation, a decrease in the level of superoxide dismutase (one of the key participants of the protective antioxidant system of the body), and changes in the level of glutathione [19–21].

Thus, one of the elements of kidney damage after electron irradiation is oxidative stress caused by the exponential release of large amounts of free oxygen radicals, nitrogen radicals, and lipid peroxidation products. Due to the lack of sufficiently effective methods to protect genetic material from the direct effects of radiation, the fight against oxidative stress turns out to be the key direction of action of protective agents. This concept became a determining factor in the choice of ascorbic acid as a protector.

Ascorbic acid can block the key biochemical components of oxidative stress, preventing the formation of toxic radicals. Protective properties contribute to the protection not only of nephron tubule epithelial cells, but also of endothelial cells of the vascular tubule. In groups IV and V, where ascorbic acid was administered before electron irradiation (at doses 2 Gy and 8 Gy, respectively), a decrease in the degree of pathomorphological changes characteristic of radiation damage to the kidneys was found.

Analysis of malonic dialdehyde (MDA), superoxide dismutase (SOD) and glutathione (GSH) levels in kidney homogenate demonstrates a potential protective effect of ascorbic acid to reduce radiation-induced nephropathy.

Thus, based on morphofunctional and biochemical analysis of kidneys after irradiation with electrons

at doses of 2 Gy and 8 Gy and pre-irradiation administration of ascorbic acid we can speak about its possible protective effect, for confirmation of which it is necessary to conduct further studies.

Conclusion

Local irradiation with electrons at doses of 2 Gy and 8 Gy leads to the development of radiation nephropathy. At the same time, administration of ascorbic acid reduces the strength of radiation-induced kidney damage, as well as enhances the effectiveness of antioxidant defense.

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Морфофункциональные особенности почки после введения аскорбиновой кислоты в модели острой лучевой нефропатии

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Аннотация. *Актуальность.* Использование лучевой терапии при лечении злокачественных новообразований (ЗНО) актуализирует изучение способов защиты здоровых тканей от радиационного повреждения. Ввиду малого количества исследований, направленных на изучение структурно-функциональных изменений почек, как при их непосредственном облучении электронами, так и при радиотерапии ЗНО соседних органов необходимо проведение комплексного исследования. Одним из перспективных направлений лечения радиационной нефропатии является использование препаратов-антиоксидантов, в частности аскорбиновой кислоты. Цель: морфофункциональная оценка почки после локального облучения электронами и введения аскорбиновой кислоты. Материалы и методы. Крысы Wistar (n=90) были разделены на группы: I – контрольная (n=15); II – облучение, РОД 2 Гр (n=15); III – облучение, РОД 8 Гр (n=15); IV – облучение, РОД 2 Гр + аскорбиновая кислота (интраперитонеальная инъекция; доза 50 мг/кг) (n=15); V – облучение, РОД 8 Гр + аскорбиновая кислота (интраперитонеальная инъекция; доза 50 мг/кг) (n=15); VI – аскорбиновая кислота (интраперитонеальная инъекция; доза 50 мг/кг) (n=15). Микропрепараты почек окрашивали гематоксилином и эозином. Кроме того, проводили биохимическое исследование крови на уровень креатинина, азота мочевины, С-реактивного белка, рассчитывали отношение цистатина С к креатинину, а также гомогената почки на уровень концентрации малонового

диальдегида (MDA), супероксиддисмутазы (SOD), а также глутатиона (GSH). Результаты и обсуждение. Исследование показало, что предлучевое введение аскорбиновой кислоты (интраперитонеальная инъекция; доза 50 мг/кг) в модели острой лучевой нефропатии, индуцированной локальным облучением электронами в РОД 2 Гр и РОД 8 Гр, способствовало выраженному снижению патоморфологических и биохимических изменений. Выводы. Локальное облучение электронами в РОД 2 Гр и РОД 8 Гр приводит к развитию радиационной нефропатии. В то же время предлучевое введение аскорбиновой кислоты снижает силу радиационно-индуцированного повреждения почек, а также усиливает эффективность антиоксидантной защиты.

Ключевые слова: лучевая нефропатия, облучение электронами, почки, аскорбиновая кислота, оксидативный стресс

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