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ORIGINAL ARTICLE

Histopathological Comparison of The Effects of Amifostine and L-Carnitine on Radiation-induced Acute Bladder Toxicity in Rats

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OBJECTIVE

Modern radiotherapy (RT) techniques aim to preserve normal tissues as much as possible, though some normal tissue may inevitably be included in the target volume. The study aimed to evaluate the potential protective role of amifostine and L-carnitine against radiation-induced bladder toxicity and compare their effects.

METHODS

Experiments were conducted on 30 male Wistar Albino rats, divided into four groups: Control, AMI + RT, LC + RT, and RT alone. All groups received a 20 Gy dose of radiation, and histopathological evaluations were performed.

RESULTS

Statistically significant differences were found in epithelial desquamation, stromal edema, and vessel wall thickness in irradiated rats. Amifostine significantly decreased epithelial desquamation and vessel wall thickness changes but had no effect on stromal edema. L-carnitine had no statistically significant protective effect on epithelial desquamation, vessel wall thickness, and stromal edema.

CONCLUSION

This study is the first to demonstrate amifostine's protective effect against radiation-induced bladder toxicity in a preclinical setting and to compare it with L-carnitine. Findings suggest that amifostine is more effective than L-carnitine in protecting against radiation-induced bladder damage.

Keywords: Amifostine; bladder; carnitine; radiotherapy; rat.

INTRODUCTION

Radiotherapy (RT) plays an important role in the treatment of pelvic tumors. Up to 30% of all cancers originate from the pelvis or have a significant pelvic component. Tumors of the pelvic region are more common in men. According to 2024 statistics, 43% of new patients in men (bladder, rectum, colon, and prostate) and over 14% in women (uterus, ovary, rectum, and vagina/vulva, etc.) were diagnosed with tumors originating from the pelvic

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region in the United States.[1] The aim of radiotherapy is to deliver the desired dose homogeneously and completely to the target volume while providing maximum protection to the surrounding normal tissues. In radiotherapy planning, normal tissues are protected by excluding them from the radiation field as much as possible.

RT-induced changes in normal tissues depend on many factors, such as beam type, RT parameters (dose, fractionation, total duration, irradiation technique, etc.), irradiated normal tissue volume, tissue and cell characteristics, and whether radiosensitizing and radioprotective agents or chemotherapeutic drugs are used together with RT. Modern RT techniques (three-dimensional conformal RT, intensity-modulated RT, etc.) allow preservation of normal tissues as much as possible. In the treatment of many tumors, it is inevitable that a certain amount of normal tissue is included in the target volume. Drugs that aim to protect normal tissues within the radiotherapy field from radiation effects without reducing tumor control are defined as "radioprotective agents".[2]

The best-known group of radioprotectors are sulfhydryl (SH) compounds. The protective effect of sulfhydryl compounds is provided by the ability of the SH groups they contain to capture free radicals. Amifostine is a prodrug that is phosphorylated by alkaline phosphatase of vascular endothelial cells and converted into its active metabolite, free thiol. Free thiol acts by binding free radicals produced by radiation.[3] Studies have shown that amifostine is effective in the prevention of normal tissue damage due to RT and chemotherapy (CT) and reduces the dose-limiting toxic effects of treatment.[4] The radioprotective effects of amifostine on the bladder are mostly based on information obtained from clinical studies. To the best of our knowledge, no preclinical research has been conducted on this topic yet.

Carnitine is a natural substance that acts as a carrier in the beta oxidation of fatty acids, transport to the mitochondrial membrane, and removal of toxic metabolites such as acyl-CoA and acylcarnitine from the mitochondria. Carnitine and its short-chain esters, propionyl-L-carnitine and acyl-L-carnitine, are both endogenously synthesized in the human body and found in the diet.[5] Carnitine is an essential factor of some enzymes required for the transformation of long-chain fatty acids and acts as a scavenger of free radicals. Carnitine may play a modulatory role against ionizing radiation-induced free radicals in cells with its antioxidant and free radical scavenging properties.[6] Although carnitine has been shown to have a radioprotective impact on a variety of tissues, its protective effect on the bladder has not yet been investigated.

The purpose of this study was to assess L-carnitine's potential protective role against acute bladder toxicity caused by radiation and, if it exists, to compare it to the amifostine effect.

MATERIALS AND METHODS

Animals

All animal experiments were conducted in accordance with the guidelines of the Institutional Animal Ethics Committee. In this study, 30 male Wistar Albino rats with an average weight of 170–200 g, aged 3 months, were used. All rats were housed in polypropylene cages (containing sterile paddy husk, procured locally, as bedding throughout the experiment) of 8 rats each in an environment with 50–60% humidity, 22±1°C temperature, and a 12-hour night and 12-hour daylight period until the end of the experiment. All animals had free access to sterile water and food.

Experimental Design

The 30 male rats were randomly divided into four groups:

1. Control group (n=6): Rats pretreated with 1 ml of 0.9% NaCl solution with a single-dose injection intraperitoneally (i.p.) without radiation.
2. AMI + RT group (n=8): Rats pretreated with 1 ml of AMI (200 mg/kg) (Ethyol; MedImmune Pharma B.V., Nijmegen, the Netherlands) with a single-dose injection i.p., 30 minutes prior to irradiation, and then irradiated individually with a single dose of 20 Gy radiation.
3. LC + RT group (n=8): Rats pretreated with 1 ml of LC (300 mg/kg) (Santa Pharma Co., Istanbul, Türkiye) with a single-dose injection i.p., 30 minutes prior to irradiation, and then irradiated individually with a single dose of 20 Gy radiation.
4. RT group (n=8): Rats pretreated with 1 ml of 0.9% NaCl solution i.p., 30 minutes prior to irradiation, and then irradiated individually with a single dose of 20 Gy radiation.

All experimental procedures were performed on anesthetized rats. During irradiation, anesthesia was maintained with a mixture of 100 mg/kg i.p. ketamine (Ketalar; Pfizer Ilaçlari, Istanbul, Türkiye) and 3.9 mg/kg i.p. xylazine (Rompun; Bayer Türk Kimya Sanayi, Istanbul, Türkiye).

Bladder Irradiation

The rats in the AMI + RT, LC + RT, and RT groups were irradiated individually with a single dose of 20 Gy. The rats were anesthetized and then fixed onto a 20×30 cm blue Styrofoam treatment couch (Med-Tec, Orange City,

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IA, USA) in a supine position. Correct positioning of irradiation fields was controlled for each rat using a therapy simulator (Mecaserto-Simics, Paris, France). Irradiation was delivered by a cobalt-60 teletherapy unit (Cirus; cis-Bio Int., Gif Sur Yvette, France) at a source–surface distance of 65 cm. A single dose of 20 Gy radiation was given at a depth of 1.5 cm (half thickness) with a dose rate of 129.13 cGy/min to the 4×3 cm pelvic area including the bladder. Special dosimetry was used for the irregular fields. The dose homogeneity across the field was ±5%. After the irradiation, the animals were closely observed until recovery from anesthesia. The animals in the control group received equal-field sham irradiation.

Euthanasia

The rats were euthanized 5 days after the radiation therapy. Prior to euthanasia, the rats received anesthesia using a combination of ketamine and xylazine. Euthanasia was performed by decapitation. The bladder was removed and placed in 10% formaldehyde for histopathologic examination.

Histopathological Evaluation

After 24 hours of formaldehyde fixation, the tissues were sliced with 1 transverse incision in the middle and placed in tissue tracking. After tissue tracking, paraffin embedding was performed, and 4-micron thick sections were taken. The sections were stained with hematoxylin-eosin stain and examined under a light microscope. Vascular wall thicknesses were measured with a Zeiss Axioplan 2 imaging light microscope (KS 300 Imaging System). Epithelial desquamation, epithelial regeneration, stromal edema, stromal fibrosis, stromal inflammation, increased vascularization, and vessel wall thickness were also evaluated as present or absent. All histopathological evaluations were made by a pathologist who was blinded to the study group allocations.

Statistical Analysis

A normal distribution test was performed for the measurable data, and Kruskal-Wallis analysis of variance was used for intergroup comparisons. The Mann-Whitney U test was used for pairwise comparisons. Differences in vessel wall thickness between groups were evaluated by an ANOVA test. If the p-value was less than 0.05, it was judged as "significant." The STATISTICA AXA 7.1 statistical program was used for this analysis.

RESULTS

Among the evaluated parameters, epithelial desquamation (p=0.001), stromal edema (p=0.003), and vessel wall thickness (p=0.003) showed statistically significant differences between the groups.

Table 1 Epithelial desquamation seen in the groups

Epithelial desquamation	Cont (n=6)	RT (n=8)	LC+RT (n=8)	AMI+RT (n=8)
Yes	1	6	6	1
No	5	2	2	7
p value		0.001	0.001	0.003

p<0.05 for epithelial desquamation. Cont: Control; RT: Radiotherapy; LC: L-carnitine; AMI: Amifostine

Table 2 Stromal edema seen in the groups

Stromal edema	Cont (n=6)	RT (n=8)	LC+RT (n=8)	AMI+RT (n=8)
Yes	–	7	6	5
No	6	1	2	3
p value		0.001	0.002	0.008

p<0.05 for stromal edema. Cont: Control; RT: Radiotherapy; LC: L-carnitine AMI: Amifostine

Epithelial desquamation was observed in 14 out of 30 animals across all experimental groups. Within the RT group and the LC+RT group, epithelial desquamation occurred in 6 out of 8 animals. Only 1 out of 6 animals in the control group exhibited epithelial desquamation. Statistical analysis revealed no significant difference in epithelial desquamation between the LC+RT and RT groups (p>0.05). However, both the RT group (p=0.001) and the LC+RT group (p=0.001) showed statistically significant exacerbation of epithelial desquamation compared to the control group (Table 1). Furthermore, epithelial desquamation was observed in 1 out of 8 animals in the AMI+RT group, with no significant difference compared to the control group. Notably, the addition of amifostine to radiotherapy resulted in a significant reduction in epithelial desquamation compared to radiotherapy alone (p=0.003).

Stromal edema was observed in 18 out of 30 animals included in the study. Within the RT group, stromal edema was present in 7 out of 8 animals, while none of the 6 animals in the CONT group exhibited this condition. Consistent with expectations, the incidence of stromal edema was significantly higher in the RT group compared to the CONT group (p<0.0001) (Table 2). Additionally, stromal edema was observed in 5 out of 8 animals in the AMI+RT group and 6 out of 8 animals in the LC+RT group. Notably, both the AMI+RT (p=0.008) and LC+RT (p=0.002) groups

Table 3 Vascular wall thickness in the groups

Vessel wall thickness	Cont (n=6)	RT (n=8)	LC+RT (n=8)	AMI+RT (n=8)
1	20.31	27.4	16.95	17.55
2	14.91	19.72	23.02	23.3
3	17.56	19.37	13.41	17.62
4	11.23	26.76	26.9	10.05
5	20.31	26.9	12.55	19.27
6	10.05	16.78	22.88	16.55
7		17.18	17.99	16.95
8		21.32	19.53	17.63
Mean	15.72	21.92	19,15	17,36
p value		0.0001	0.005	0.009

p<0.05 for vessel wall thickness. Cont: Control; RT: Radiotherapy; LC: L-carnitine; AMI: Amifostine

demonstrated statistically significant elevations in stromal edema compared to the CONT group. Importantly, no significant difference in stromal edema was observed between the AMI+RT and LC+RT groups when compared to the RT group.

Vascular wall thickness was markedly increased in animals that received radiation therapy (RT) alone compared to the CONT group (p<0.0001) (Table 3). In the RT group, the highest recorded wall thickness was 27.4 µm, the lowest was 16.78 µm, with a mean of 21.92 µm. Similarly, in the LC+RT group, the highest wall thickness was 23.02 µm, the lowest was 12.55 µm, with a mean of 19.15 µm. In the AMI+RT group, the highest wall thickness measured was 23.3 µm, the lowest was 10.05 µm, with a mean of 17.36 µm. Conversely, in the CONT group, the highest wall thickness was 20.31 µm, the lowest was 10.05 µm, with a mean of 15.72 µm.

The co-administration of amifostine with RT resulted in a statistically significant reduction in vessel wall thickness (p=0.009). However, no similar effect was observed with carnitine in combination with RT. Notably, the CAR+RT group exhibited a significantly increased vessel wall thickness compared to the CONT group (p=0.005). Nevertheless, no significant difference in vessel wall thickness was detected between the AMI+RT and CONT groups. Examples of histopathological findings are given in Figures 1–4.

DISCUSSION

The use of advanced RT techniques has led to significant improvements in cancer treatment. By using modern treatment techniques, the goal is to achieve maximum tumor control and minimum normal tissue

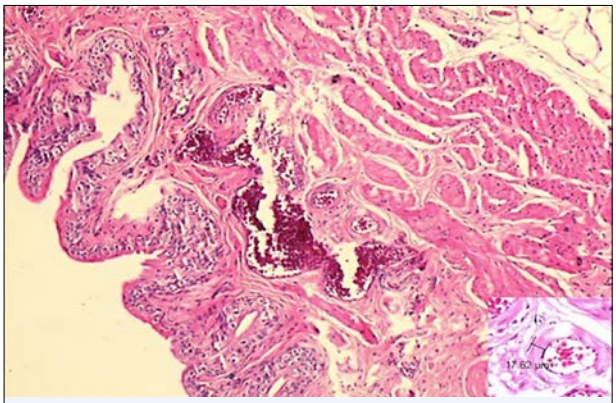

Fig. 1. Amifostine+radiotherapy group. In addition to regeneration in the surface epithelium, scattered and mildly inflammatory cells, edema, and connective tissue increase are observed in the stroma. The thickest vessel wall thickness that can be observed is 17.62 µm (Hematoxylin- eosin, X50).

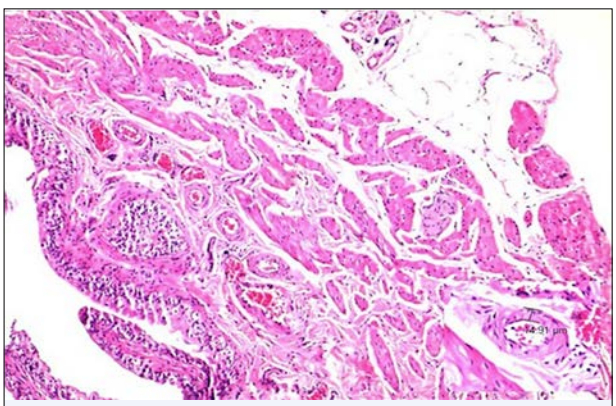

Fig. 2. Control group. The surface epithelium appears normal, with mild edema and fibrosis in the stroma. The thickest vessel wall thickness that can be observed is 14.91 (Hematoxylin- eosin, X50).

toxicity. However, despite all technological advances, it is not possible to eliminate both acute and late side effects related to RT. Therefore, the role of radioprotectors used during irradiation becomes more important to minimize normal tissue toxicity.

In our study, epithelial desquamation, epithelial regeneration, stromal edema, stromal fibrosis, stromal inflammation, increased vascularization, and vessel wall thickness were evaluated as histopathologic changes caused acutely by 20 Gy RT applied in a single fraction. Among the above histopathologic changes, statistically significant differences were found in epithelial desquamation, stromal edema, and vessel wall thickness. Amifostine significantly decreased epithelial

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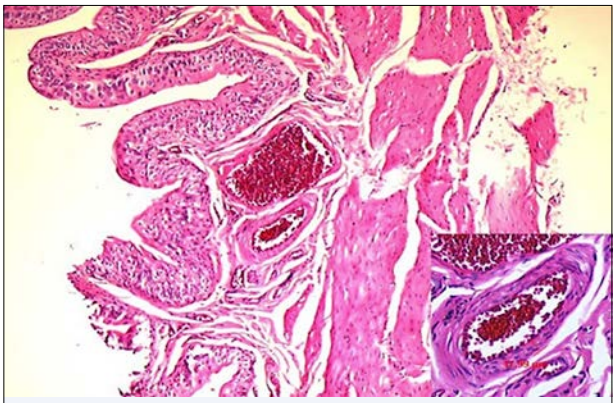

Fig. 3. Carnitine+radiotherapy group. In addition to desquamation and regeneration in the surface epithelium, scattered and mildly inflammatory cells, edema, and connective tissue increase are observed in the stroma. The thickest vessel wall thickness that can be observed is 17.99 μm (Hematoxylin- eosin, X50).

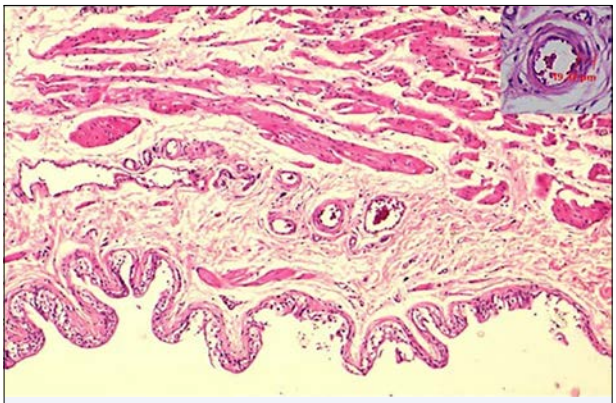

Fig. 4. Radiotherapy group. In addition to desquamation of the surface epithelium, there is marked edema and connective tissue increase in the stroma. The thickest vessel wall thickness that can be observed is 19.37 μm (Hematoxylin- eosin, X50).

desquamation and vessel wall thickness changes but had no effect on stromal edema. Carnitine administered before radiotherapy had no statistically significant protective effect on epithelial desquamation, vessel wall thickness, or stromal edema.

In most preclinical studies, doses between 10–30 Gy were used. In studies using rats, lower doses were preferred compared to studies using mice. The most preferred doses are 10 Gy and above.[7–9] In a study by Jaal and Dörr, early and late side effects of radiation were evaluated in mouse bladder. In the study, changes in the number of bladder superficial urothelial cells were measured after a 20 Gy dose was applied in a single fraction. According to the LQ model and α/β ratio of 5 Gy, the selected dose corresponds to approximately 70 Gy from a fraction of 2 Gy as a rough biological equivalent dose.[9] In our study, rats were irradiated with a single dose of 20 Gy, similar to the literature.

In preclinical studies, acute and late side effects of radiotherapy on bladder tissue were frequently evaluated by functional methods. One functional method used is the measurement of intravesical pressure, which is a marker of organ capacity, by cystometry. Another frequently used method is measuring the frequency of urination. In a study by Stewart et al.[10] evaluating radiation-induced acute and late damage in the mouse bladder by urinary frequency and cystometry, a transient wave of damage was observed in mice 1–3 weeks after 10–30 Gy single-dose bladder irradiation. During this period, urinary frequency increased twice or more in the RT group compared to the control group, depending on the dose. Again, during this period, compared to the control group, 20–40% of the mice receiving 20 Gy doses showed a decrease in bladder volume below approximately 50%. Early damage terminated in approximately one week. Lundbeck et al.[11] evaluated bladder function using the cystometric method within 30 days after irradiating the mouse bladder with a single dose of 5–30 Gy and found that bladder wall compliance decreased dose-dependently during this period. However, they observed that the resulting damage recovered in the second month.

In the literature, there are animal studies investigating the acute and late side effects of radiotherapy on the bladder, examining histopathological changes as well as functional studies. Several animal models, employing both mouse and rat, have been developed with the aim of investigating the pathological modifications that occur in the bladder after irradiation, but a "standard" universally recognized radiation cystitis model is still lacking. To standardize the evaluation of histologic patterns, which are meant to be surrogates of the functional status of the bladder, morphological scores have been used. To date, hematoxylin and eosin (H&E) indisputably remain the most informative staining employed, allowing the recognition of macroscopic signs of both early acute and late histological changes.[12]

In a study investigating early and late morphological changes in the rat bladder with a single dose of 20 Gy, the urothelium, bladder wall, and nerve cells were evaluated.[8] One month post-irradiation, the urothelium appeared normal except for more-than-usual numbers of lysosomes in the basal layer. By 1 month,

some basal cells were necrotic, and macrophages had invaded the epithelium. The smooth muscle of the bladder wall proved surprisingly sensitive to radiation damage. One week after irradiation, the marginal pinocytotic vesicles were very conspicuous, and by 1 month many cells were edematous. Morphological changes were detected in nerve cells by electron microscopy in the first month. In another study by Jaal and Dörr, a 7% loss of superficial umbrella cells was found in the RT group with a single 20 Gy dose two to three days after irradiation compared to the control group.[9] Similarly, Schreiber et al.[13] found a loss of urothelial cells eight days after 20 Gy RT to the bladder in rats. In the study conducted by Sener et al.,[14] whole-body irradiation was performed in rats with a single dose of 8 Gy, and the protective effect of melatonin was investigated. Epithelial desquamation or the vacuolation of epithelial cells was observed in the urinary bladders of the subjects in this study 12 and 72 hours after irradiation. The presence of interstitial edema suggested prominent tissue injury. In our study, with a single dose of 20 Gy RT to the pelvic region, acute side effects of RT such as epithelial desquamation and stromal edema were observed on the fifth day.

Vascular changes due to radiotherapy are also among the side effects reported in preclinical studies. In the study in which Costa et al.[15] investigated the effects of nutritional supplementation with L-arginine, 10 Gy was given to the pelvic regions of rats in a single fraction. The researchers found that the density of blood vessels and the thickness of the arterial wall decreased on the fifteenth day with this single dose. On the contrary, in our study, on the fifth day, radiation-induced vessel wall thickness was found significantly higher compared to the control group. This difference between the two studies is due to the fact that the days on which acute effects were investigated were different (day 5 vs. day 15). However, the decrease in vessel density and arterial wall thickness is one of the side effects that will be seen in the late period rather than the acute period. The researchers explain this unexpected finding as, "Because the part of the arterial wall that was included in our measurements was basically the tunica media, it can be inferred that this reduction in thickness was due mainly to atrophy or loss of smooth muscle cells, either as a direct effect of ionizing radiation or through activation of apoptosis cascades."

Amifostine, a classic example of a radioprotective agent, scavenges ROS and protects cells from radiation damage. Amifostine has been used to reduce acute and chronic toxicities, as shown in several studies.[16] Its radioprotective effect on bladder tissue has also been shown in some studies.[17,18] Interestingly, these studies are in the form of phase II or phase III clinical studies rather than preclinical studies. Athanassiou et al.[17] conducted a phase III study in which they investigated the protective effect of amifostine in patients receiving fractionated radiotherapy for pelvic carcinoma. In this study, significantly less acute grade 2–3 bladder toxicity was detected in the group given amifostine. Similarly, in the study of Koukourakis et al.,[18] a significant reduction in rectal mucositis and acute perineal skin and bladder toxicity was noted in the amifostine arm in 40 patients with pelvic malignancies undergoing RT. To the best of our knowledge, there is no preclinical study investigating the radioprotective effect of amifostine on bladder tissue in the literature. Our study is the first to investigate the radioprotective effect on acute side effects and to show that it is histopathologically protective.

LC is a significant additional radioprotective agent. It can be obtained through food, or the skeletal muscle, heart, liver, kidney, and brain can synthesize it internally. It can also be taken as a dietary supplement. It's a safe and reasonably well-tolerated compound as well. In addition to its ability to regulate the metabolism of carbohydrates, LC is a necessary cofactor in the oxidation of long-chain fatty acids and preserves the integrity of cell membranes.[19] Several important enzymes involved in the metabolism of lipids and proteins are also impacted. Furthermore, LC is a material that can scavenge free radicals and function as an antioxidant.[20] Moreover, it increased endogenous antioxidant defense mechanisms, which might have protected the animals from radiation-induced organ toxicity.

According to Altas et al.,[21] LC can help guinea pigs with radiation-induced cochlear damage. In another study, Kocer et al.[22] demonstrated that LC also functions as a protective agent against irradiation-induced lens damage in rats. Other animal studies have also documented the radioprotective qualities of LC in postponing the onset and lessening the severity of radiation-induced damage to the kidney, bone, testicles, ovaries, and oral mucosa.[4,23] However, there have been no studies investigating its radioprotective effect on the bladder so far.

In our study, we investigated both whether L-carnitine has a protective effect and, if so, its efficacy compared to amifostine. We could not determine the protection conferred by L-carnitine. This could be attributed to several factors. Firstly, L-carnitine has a low bioavailability (14–18%), and it cannot be stored in the

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body, which, coupled with its short half-life (30–60 minutes), necessitates frequent dosing to achieve therapeutic efficacy.[24] However, its radioprotective effect was observed at a single dose in multiple investigations.[16,23,25] A plausible rationale would be that, as L-carnitine is predominantly excreted by the kidneys and extensively reabsorbed by the renal tubules, there may not have been much transfer of the compound from the kidneys to the bladder during our investigation.

While our study has yielded valuable insights into the subject matter, it is essential to acknowledge its inherent limitations and caveats. Firstly, in this study, we investigated the protective effects of amifostine and L-carnitine against radiation-induced toxicity in bladder tissue only by histopathological methods. In addition to histopathological methods, functional and biochemical assessments could have been performed to provide a more comprehensive evaluation of tissue damage. Another limitation of our study might be that L-carnitine was administered as a single dose. Further research is needed to explore the effects of repeated administration of L-carnitine on radiation-induced bladder toxicity.

In conclusion, this study is the first to demonstrate the protective effect of amifostine against radiation-induced bladder toxicity in a preclinical setting and to compare its efficacy with that of L-carnitine. Furthermore, our findings suggest that, unlike amifostine, L-carnitine, administered as a single dose, may not confer similar protection against radiation-induced bladder damage. Further research is warranted to explore the potential benefits of amifostine in mitigating radiation-induced bladder injury and to investigate alternative strategies for enhancing bladder radioprotection.

Ethics Committee Approval: The study was approved by the Trakya University Animal Experiments Local Ethics Committee (no: 2010/04.10, date: 07/06/2010).

Authorship contributions: Concept – V.Y.Ç., H.M.Ç., D.N., T.A.; Design – V.Y.Ç., H.M.Ç., D.N., O.İ.; Supervision – V.Y.Ç., H.M.Ç., O.İ., Ö.Y., T.A.; Data collection and/or processing – D.N., T.A., E.A., Ö.Y.; Data analysis and/or interpretation – V.Y.Ç., H.M.Ç., O.İ.; Literature search – V.Y.Ç., H.M.Ç., D.N., E.A.; Writing – V.Y.Ç., H.M.Ç., D.N., T.A.; Critical review – H.M.Ç., V.Y.Ç.

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