Research Square

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Does L-carnitine have a protectiveeffect on the development of radiationinducedkidney damage in infancy?Scintigraphic and histopathologicevaluation

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Abstract

Background

Radiation-induced nephropathy (RIN) is an impairment of function caused by ionizing radiation which develops after6-12 months as acute or after years as chronic period.

Methods

This paper aims to clarify, whether L-carnitine has a protective effect in the prevention of RIN in an infant rat model.

Results

Two-week-old forty male Wistar albino rats were divided into four groups such as control (C), L-carnitine alone (LC), irradiation alone (RT), and L-Carnitine before irradiation (L-carnitine + RT), injected with LC (300 mg/kg) i.p., 30 minutes before the irradiation. The rats in the RT and L-Carnitine + RT groups were irradiated individually with a single dose of 8 Gy. All animals underwent both Tc99m DTPA dynamic renal imaging and Tc99m DMSA static renal imaging at the end of three months follow-up period. Proximal tubular degeneration, tubular atrophy, interstitial fibrosis, and glomerular degeneration were assessed histopathologically. While the kidney damage caused by irradiation was shown in line with both scintigraphy and histopathology findings, it was shown that L-carnitine did not have any negative effects on the kidney. Also, we could not demonstrate the protective effect of L-carnitine on radiation-induced kidney damage, both scintigraphically and histopathologically.

Conclusion

Although kidney damage due to irradiation was created in infantile rats successfully, the protective effect of L-carnitine could not be demonstrated in our study.

Introduction

The use of ionizing radiation for locoregional tumor control in pediatric patients demands a good balance between documented efficacy and potential long-term toxicity. Although radiation therapy is very effective for controlling cancer by preventing tumor growth, because of the negative effects of irradiation on healthy tissue, the doses are limited, potentially leading to suboptimal tumor control. Additionally, multimodal treatment approaches used in combination with radiotherapy increase radiation-induced toxicity and cause a decrease in the maximum tolerable radiation dose [1-6]. Radiation-induced toxicity, especially that resulting in somatic and functional effects, is more pronounced in children than in adults (6). The kidneys are probably the most radiosensitive abdominal organs with a proposed tolerance dose of 20 Gy, and one of the most significant determinants of radiation-induced nephropathy (RIN) is age [7,8]. Irradiation to the abdomen is an integral part of treatment in most frequent extracranial pediatric tumors, such as Wilm's tumor, neuroblastoma, non-Hodgkin's lymphoma, and Hodgkin's disease.

Additionally, total body irradiation is an alternative to cyclophosphamide for the preparation of leukemia patients for bone marrow transplantation. Whether radiation therapy should be administered without kidney protection is still a matter of debate due to a relapse that can occur in the kidney bed [2,4,5]. For this purpose, although shielding of the kidneys at different levels and different fractionation regimens other than conventional fractionation were used in the past to prevent RIN formation, the reported results are not promising [2,7]. Solely physical methods are not enough to protect the kidneys from the late effects of irradiation. Therefore, several medical interventions, such as radioprotective agents, should be implemented to reduce RIN formation [8-14]. Previous studies demonstrated the protective effect of L-carnitine against nephrotoxicity-related gentamicin, doxorubicin, cisplatin, and cyclosporine-A [15-18].

In this study, we aimed to investigate the protective effects of L-carnitine against RIN in infant rats by using functional imaging and histopathological evaluation.

Materials And Methods

Animals

Forty infant Wistar albino rats were housed with their mothers until they reached four weeks old; then, they were housed in rat cages with free access to a standard rodent diet and tap water under a 12:12-hr artificial light cycle, with a mean temperature of 21 ± 2 °C and a mean humidity of 55 ± 2%. All animals were randomized to four groups and treated as follows:

Group 1 (n = 10): Control, normal saline alone, injected with saline (10 ml/kg) i.p.

Group 2 (n = 10): L-Carnitine alone, injected with L-Carnitine (300 mg/kg) i.p.

Group 3 (n = 10): Irradiation alone (RT), injected with saline (10 ml/kg) i.p. 30 minutes before irradiation.

Group 4 (n = 10): L-Carnitine before irradiation (L-Carnitine + RT), injected with LC (300 mg/kg) i.p. 30 minutes before irradiation.

All experimental procedures were performed on anesthetized rats. Anesthesia was maintained with ketamine and xylazine (35 mg/kg body weight (BW) and 3 mg/kg BW intramuscular injection for infant rats and 50 mg/kg BW and 5 mg/kg BW intramuscular injection for adults) during irradiation and scintigraphic evaluation.

Rats were followed up for three months after the experimental procedures. During the follow-up period, all rats received veterinary care. Before euthanasia, the rats received anesthesia using a combination of ketamine and xylazine. Euthanasia was performed by decapitation, and a histopathologic assessment of the kidney was performed. All animal experiments were conducted according to the guidelines from the Institutional Animal Ethics Committee (TUHDYEK 2012/13).

Irradiation

The rats in the RT and L-Carnitine + RT groups were irradiated individually with a single dose of 8 Gy (6 MV photon) at a depth of 2.25 cm through an anterior 2.5 × 2 cm single portal (with a 1.5 cm bolus) covering the left kidney in its entirety. A linear accelerator treatment unit (Varian 2100 C/D, Varian Inc., Palo Alto, CA) was used at a source skin distance of 100 cm. The dose rate was 600 MU/min. The rats were anesthetized and then fixed on a 20×30 cm blue Styrofoam treatment couch (Med-Tec, Orange City, IA) in a prone position. The position of the kidney was determined in an X-ray scope image by measuring the distance between the tip of the nose and the middle of the kidney hilus. The distance information was used to position the center of the irradiation field to the middle of the kidney hilus in the anesthetized rat. Correct positioning of the fields was confirmed for each individual rat using a therapy simulator (Mecaserto-Simics, Paris, France). Special dosimetry was performed for the irregular radiotherapy fields. The dose homogeneity across the radiotherapy field was ± 3%.

Imaging Study

All animals underwent both Tc99m DTPA dynamic renal imaging and Tc99m DMSA static renal imaging three months after radiotherapy.

For Tc99m DMSA imaging, a commercially available DMSA kit (Renocis, France) was prepared according to the manufacturer's recommendations. 99mTc-DMSA was administered intravenously through the 24F cannula in the tail vein at a regular dose of 37-50 MBq (in 0.2 ml). Posteroanterior views of the abdomen of the rats were taken in the supine position (at least 300 counts/view) using a single-head gamma camera (Philips, Eindhoven, the Netherlands) with a low-energy, high-resolution pinhole and parallel collimators in a 256 × 256 matrix format at 3 hours after the injection of Tc-99m DMSA. The relative uptake of the kidneys was quantitatively calculated by drawing regions of interest for kidney and background areas on the computed anterior and posterior images. 99mTc-DMSA uptakes (mean value/pixel) of renal tissue and background tissue were calculated from images with the drawn region of interest. The total renal function percentage for the left kidney (LF %) was calculated using the following formulas:

Eq. 1: LF%= Left kidney uptake/(Left kidney uptake + Right kidney uptake) ×100.

For 99mTc-DTPA imaging, a commercially available DTPA kit (CIS, France) was prepared according to the manufacturer's recommendations. Dynamic scans were acquired for 20 minutes on a single-head gamma camera (Philips, Eindhoven, the Netherlands) with low-energy, high resolution, and parallel collimators in a 64×64 matrix format after the injection of 99mTc-DTPA. Regions of interest (ROIs) were placed around each kidney. Curves of the 30-second frame rate were generated from both ROIs over the 20-minute study. The time to peak count (Tmax) and time from peak count to a half count (T1/2) was calculated from the curve data.

Histopathological analysis

The left kidneys were dissected and decapsulated after imaging and then prefixed in formaldehyde for 24 h for further histopathological evaluation. The kidneys were divided into halves with a central transverse section. After formalin fixation, they were processed into paraffin wax tissue blocks, and thin tissue sections (4 nm) were produced using a microtome. All sections were then stained with hematoxylin and

eosin (H&E) and evaluated under a light microscope. A certified pathologist who was blinded to the experimental protocol assessed the tissue sections.

To evaluate RIN, we evaluated proximal tubular degeneration, proximal tubular atrophy, interstitial fibrosis, and glomerular damage microscopically. Cytoplasmic eosinophilia, apical blebbing, loss of intercellular adhesions, cytoplasmic vacuolization, karyorrhexis, and karyolysis were defined as proximal tubular degeneration. Capillary loop collapse and dilatation of Bowman's capsule were defined as glomerular damage. Proximal tubular degeneration, proximal tubular atrophy, interstitial fibrosis, and glomerular damage were scored as follows: 0 (no abnormality), 1 (weak lesions affecting <25% of the kidney samples), 2 (moderate lesions affecting 25-50% of the kidney samples), and 3 (marked lesions affecting >50% of the kidney samples).

Statistical analysis

Scintigraphy data are presented as the mean (±) standard deviation (SD), and histopathological data are presented as the median (min-max). Differences in the scored parameters among the four groups were analyzed with ANOVA. Intergroup comparisons were tested by post hoc Bonferroni tests. These differences were considered significant when the probability was less than 0.05.

The results are expressed as the median (interquartile range). The normality distribution of the variables was tested by a one-sample Kolmogorov–Smirnov test. The Kruskal–Wallis test was used to assess the statistical significance of comparisons, and then the Dunn test was used for multiple comparisons when significant results were obtained. Statistics were performed with Statistica version 7.1 (Statsoft Inc., Tulsa, OK, USA). Statistical differences were considered significant when the p-value was smaller than 0.05 with two-sided probability.

Results

Scintigraphy results

The DMSA and DTPA findings are given in Table 1. In the results of the comparison of the DMSA and DTPA findings among the groups with the one-way ANOVA test, a difference was found between the groups only in terms of DMSA findings. While there was no difference between the control and L carnitine groups, worsening of DMSA findings was detected in the RT group, and no difference was found when L carnitine was added to RT. An example of 99mTc-DMSA is shown in Fig. 1.

Table 1
99mTc-DMSA and 99mTc-DTPA results of groups

		n	Minimum	Maximum	Mean	Std. Deviation	ANOVA	Bonferroni		
							Sig.	**L Carnitine (LC)**	**Radiotherapy (RT)**	**Radiotherapy + L Carnitine (RT + LC)**
Left DMSA %	**Control (C)**	10	42	54	47.400	3.470	**0.000**	1.000	**0.001**	**0.000**
	L Carnitine (LC)	8	42	52	47.625	3.248			**0.002**	**0.001**
	Radiotherapy (RT)	5	25	42	33.600	6.655				1.000
	Radiotherapy + L Carnitine (RT + LC)	9	24	51	34.555	8.805				
Left DTPA Max	**Control (C)**	8	1	9	3.375	2.774	0.567	1.000	1.000	1.000
	L Carnitine (LC)	8	2	4	3.250	0.707			1.000	1.000
	Radiotherapy (RT)	5	2	3	2.200	0.447				1.000
	Radiotherapy + L Carnitine (RT + LC)	6	2	5	3.500	1.049				
Left DTPA T1/2	**Control (C)**	7	8	20	13.710	4.572	0.291	0.884	1.000	1.000
	L Carnitine (LC)	7	8	13	10.860	1.574			1.000	0.447
	Radiotherapy (RT)	5	9	17	12.400	3.209				1.000
	Radiotherapy + L Carnitine (RT + LC)	6	9	19	14.500	4.087				

Histopathological results

The histopathological findings are summarized in Table 2. Statistically significant differences were detected for tubular degeneration, tubular atrophy, interstitial fibrosis, and glomerular damage when comparing groups using the Kruskal–Wallis test. All histopathological findings worsened with radiotherapy, and a positive effect of L-carnitine was not detected statistically. Examples of histopathological examinations of the RT and RT + L-carnitine groups are shown in Figs. 2 and 3.

Table 2
Histopathologic results of groups

	Control (C)	L-Carnitine (LC)	Radiotherapy (RT)	Radiotherapy + L-Carnitine (RT + LC)	p*	Pairwise comparisons of histopathologic factors**
Tubular Degeneration *n (%)*	1 (0–1)	0.5 (0–1)	2.5 (1–3)	2 (1–3)	**< 0.001**	C vs LC, p = 1.000 C vs RT, **p = 0.009** C vs RT + LC, p = 0.052 LC vs RT, **p = 0.003** LC vs RT + LC, **p = 0.021** RT vs RT + LC, p = 0.403
Tubular Atropy *n (%)*	0 (0–1)	0 (0–0)	1 (0–2)	1 (0–2)	**0.006**	C vs LC, p = 1.000 C vs RT, p = 0.288 C vs RT + LC, p = 0.088 LC vs RT, p = 0.103 LC vs RT + LC, **p = 0.023** RT vs RT + LC, p = 1.000
Interstitial Fibrosis *n (%)*	0 (0–1)	0 (0–1)	1 (1–2)	1 (0–2)	**0.003**	C vs LC, p = 1.000 C vs RT, **p = 0.015** C vs RT + LC, **p = 0.021** LC vs RT, p = 0.115 LC vs RT + LC, p = 0.187 RT vs RT + LC, p = 1.000
Glomerular Damage *n (%)*	0 (0–0)	0 (0–0)	1.5 (0–3)	1 (0–2)	**0.002**	C vs LC, p = 1.000 C vs RT, **p = 0.024** C vs RT + LC, p = 0.058 LC vs RT, **p = 0.024** LC vs RT + LC, p = 0.058 RT vs RT + LC, p = 1.000

Median (Minimum – Maximum), * p values obtained from Kruskal Wallis test, ** p values obtained from Dunn test with Bonferroni correction after Kruskal-Wallis Test

Although the numbers of rats in all groups were the same at the beginning of the study, 50% of deaths occurred in the RT group, and 1 death occurred in the RT + L-Carnitine arm at the end of the study period (Fig. 4).

Discussion

Oxidative stress, which results from an imbalance between oxidants and antioxidants, damages cells. The kidney is a highly metabolic organ and vulnerable to damage caused by oxidative stress. In radiation-induced tissue damage, DNA damage caused by oxidative stress in the acute phase is an important pathomechanism in the progression of chronic kidney disease. Radiation-induced tissue damage in the kidney, which is referred to as RIN, is characterized by a chronic progressive reduction in renal functions and involves complex and dynamic interactions between glomerular, tubular, and interstitial cells. There is disagreement about the pathogenesis of RIN. While some researchers mainly prioritize glomerular damage, some researchers think that the pathology is related to tubular damage. Reactive oxygen species also play important pathogenic roles in RIN [19,20]. It has been shown that glomerular damage precedes tubular damage in RIN [21-23]. Therefore, it seems that the prevention of progressive glomerular damage using protective agents is vital for the management of RIN.

While antioxidant agents do not have a protective effect in the latent period after irradiation, it has been shown in experimental settings that administration before irradiation protects the oxidative system [24,25].

Carnitine, which is used clinically, is an agent that can be administered orally and intravenously and has minimal side effects. Carnitine therapy has been used as a replacement treatment for hereditary and acquired disorders and to prevent oil oxidation and ketogenesis in preterm newborn infants [26].

In this study, we aimed to evaluate the protective effect of L-carnitine on RIN in infant rats known to be in a naive period. First, in this study, while the kidney damage caused by irradiation was shown to be consistent with both scintigraphy findings and histopathology findings, it was shown that L-carnitine did not have any negative effects on the kidney.

As an antioxidant and free radical scavenger, L-carnitine has been shown to have protective effects against oxidative damage in several organs and tissues, including the kidney, as well as protective effects against damage to the cell membrane [11,18,27-30]. Inconsistent with this finding, we could not demonstrate the protective effect of L-carnitine on radiation-induced kidney damage, either scintigraphically or histopathologically.

There are some limitations of this study. The first and perhaps the most important limitation is the attempt to generate the RIN model with single-dose irradiation rather than through conventional methods. The second limitation of the study is that L-carnitine was given as a single dose, and its antioxidant effect on the tissue was not evaluated using molecular methods. When we look at the literature, several studies show the protective effect of L-carnitine on the kidney after single or repeated administration in adults [8,10,14-18,24,31-33].

Although we could not show the protective effect of L-carnitine on radiation-induced kidney damage in this study, we would like to draw attention to the number of rats that died, especially in the RT-administered groups. Although it is known that deaths may be due to different reasons, the mortality rate in the RT group was 50%, while the mortality rate in the RT + L-carnitine group was 10%. This situation and the limitations of the study that are mentioned above necessitate molecular and biochemical evaluations in future studies.

Conclusion And Recommendations

In conclusion, kidney damage due to irradiation was successfully induced in infant rats, but the protective effect of L-carnitine could not be demonstrated in our study. The limitations of the study need to be overcome to demonstrate the protective effects of L-carnitine on the development of RIN in infant rats.

Declarations

Authors' contributions

The authors confirm their contributions to the paper as follows: study conception and design: RC, AO, GDA, SP, and FOP; analysis and interpretation of results: NS; manuscript draft preparation: RC, AO, KI, DN, and TO. All authors reviewed the results and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon request.

Ethics approval and consent to participate

The study was performed after obtaining ethical clearance from Trakya University and all animal experiments were conducted according to the guidelines of the Institutional Animal Ethics Committee (TUHDYEK 2012/13).

Consent for publication

This manuscript does not contain any person's data.

Competing interests

The authors declare that they have no conflicts of interest.

Acknowledgment

Not applicable

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Figures

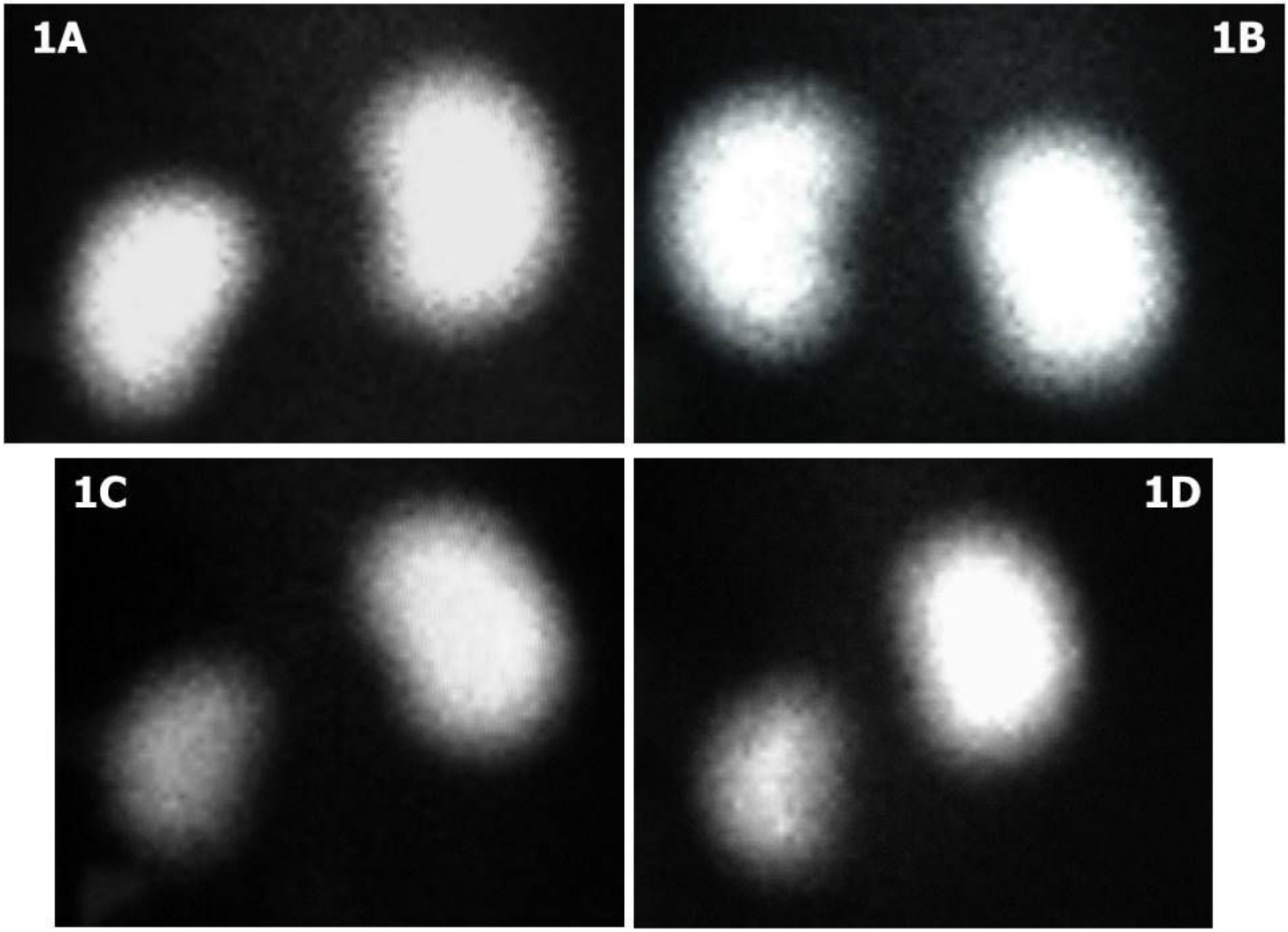

Figure 1

(a-d) The posterior views of the 99mTc-DMSA scan are shown by the group. The percentages of left kidney function were similar between the RT and RT + L-Carnitine groups; Control group (Left 51%) **(a)**, L-Carnitine group (Left 53%) **(b),** RT group (Left 25%) **(c),** RT + L-Carnitine group (Left 28%) **(d)**.

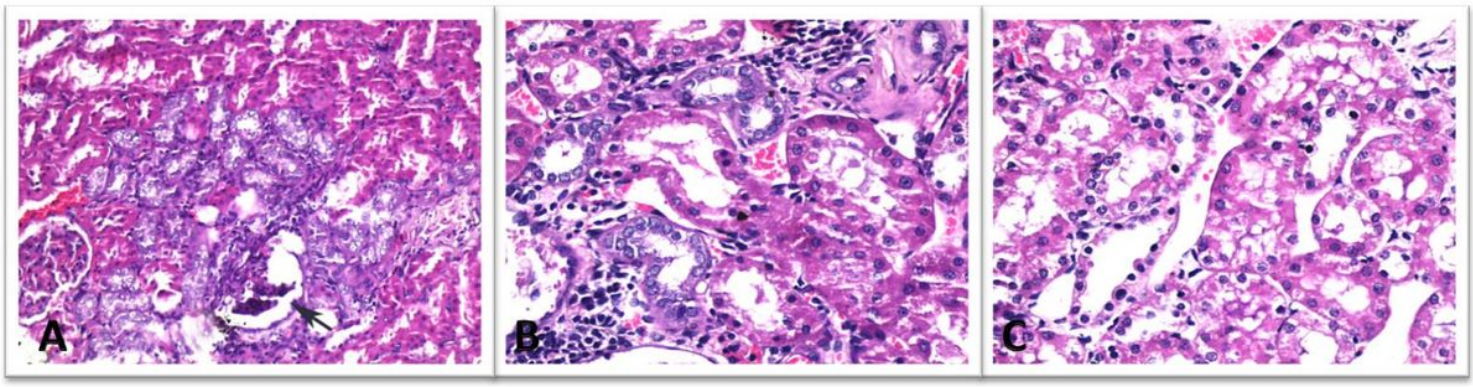

Figure 2

(a-d) RT group; capillary loop collapse (arrow) **(a)**, regenerative changes in the periglomerular tubules with lymphoid infiltration and fibrosis **(b)**, vacuolar degeneration of the proximal tubules **(c)**; additionally, nuclear enlargement and hyperchromasia of the tubular epithelial cells were observed (H&E x 100, 200, 200).

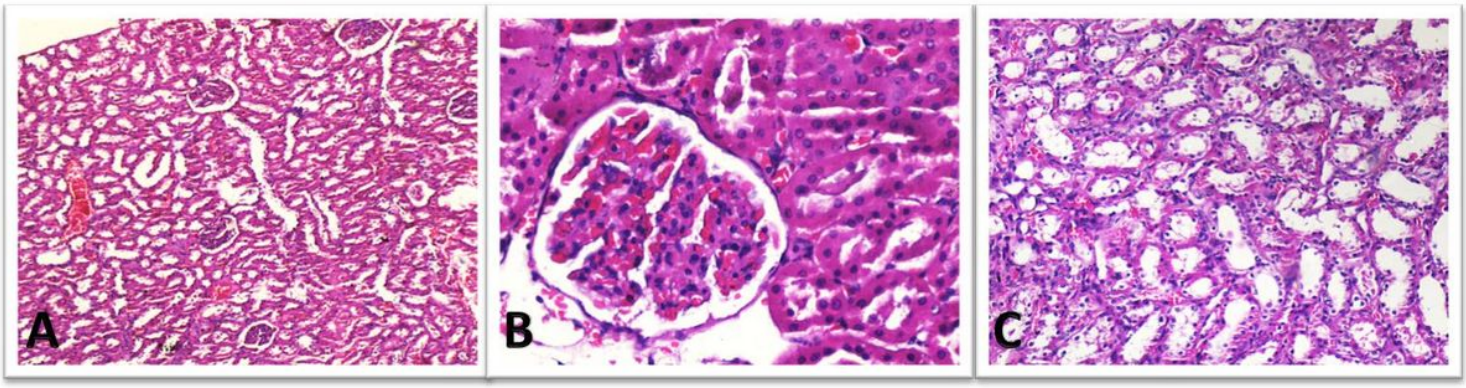

Figure 3

(a-d) L-Carnitine + RT group; Low-power view resembles Control and L-Carnitine group **(a)**, High-power view shows no glomerular damage **(b)**, Proximal and distal tubular degeneration was reduced **(c)**. However, nuclear enlargement and hyperchromasia were still remarkable (H&E x 50, 200, 100).

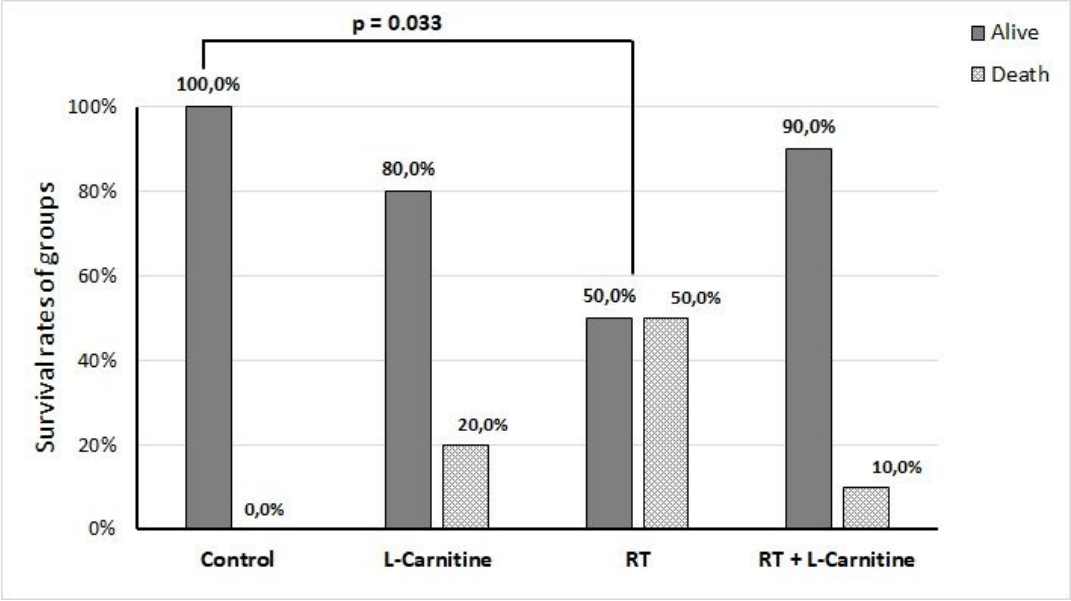

Figure 4

Comparison of the survival rates of the groups

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