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Research article
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Comparison of Protective Effects of Melatonin and Amifostine on Radiation-Induced Renal Oxidative Stress in Rats

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ABSTRACT. In this study, we aimed to compare the protective effects of melatonin and amifostine on radiation-induced oxidative stress. Fifty female Wistar rats (3-4 months old, weighing 200±25 g) were divided into five groups (with ten rats each) and treated as follows: control (Cont), radiotherapy alone (RT), radiotherapy + amifostine (RT+AMI), radiotherapy + melatonin (RT+MEL), radiotherapy + amifostine + melatonin (RT+AMI+MEL). Rats were irradiated individually with a single dose of 8 Gy and amifostine (200 mg/kg) and melatonin (10 mg/kg) was administered to rats 30 minutes before irradiation. At the end of this follow-up period (72 hours) the rats were sacrificed. Spectrophotometric Analysis has been performed to kidney tissue samples. As a result of statistical comparison between groups after RT, total antioxidant capacity (TAC) decreased, total oxidant status (TOS) and oxidative stress index (OSI) increased, although the statistically significant change was only for OSI ($p = 0.030$). Addition of AMI or MEL to RT increased TAC and OSI significantly ($p = 0.000$), but there was no additive effect for TAC and OSI when both drugs were given together ($p = 1.000$, $p = 0.172$, respectively). In terms of TOS, statistically significant increasing was only for AMI ($p = 0.000$). There was protective effect when both drugs were given together against on Radiation-Induced Renal Oxidative Stress.

Keywords: melatonin, amifostine, radiation-induced renal oxidative stress, rats

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INTRODUCTION

After exposure to radiation, free radicals occur in cells within milliseconds. The subsequent alterations in intracellular processes following irradiation are due to the initial oxidative damage caused by these free radicals. The physiological signs of these radiation-induced alterations have been suggested to contribute to adaptive responses, bystander effects, cytotoxicity, radiosensitization, genomic instability, inflammation, and fibrosis. While most of the molecular changes associated with the initial production of free radicals at the time of irradiation are known, the contribution of metabolic processes to biological outcomes following exposure to radiation have been identified recently (Spitz, Azzam, Li, & Gius, 2004). Superoxide anion (O_2^-), hydroxyl radical (OH^-), and hydrogen peroxide (H_2O_2) are the reactive oxygen species (ROS) that form after the radiolysis of water (Kaushal, Chandrashekar, & Juncos, 2019; Zhang et al., 2019). There are some protective enzymes in cells such as superoxide dismutase, catalase, and glutathione peroxidase that are increased in radiation-induced oxidative stress (Bhosle, Huilgol, & Mishra, 2005; Musa, Shabeeb, & Alhilfi, 2019). In this context, O_2^- can be eliminated by Superoxide dismutases (SOD), and Glutathione peroxidase (GSH-Px) is the major antioxidant enzyme responsible for hydrogene proxide (H_2O_2) detoxification (Sun, Chen, Li, & Ge, 1998). Amifostine (WR-2721), as an organic thiophosphate, is the only FDA-approved radioprotectant agent used in radiotherapy and capable of ROS scavenging (Cakmak, Severcan, Zorlu, & Severcan, 2016). Melatonin (N-acetyl-5-methoxytryptamine), a hormone majorly secreted in the pineal gland, has abilities to scavenge free radicals as well as antioxidant effects by stimulating antioxidant enzymes (Musa, Shabeeb, & Alhilfi, 2019).

In this study, we aimed to compare the protective effects of melatonin and amifostine on radiation-induced oxidative stress. No functional endpoints were tested.

MATERIALS AND METHODS

Study design and animals

All experiments were conducted adhering to the guidelines of the institutional animal ethics committee (TUHDYEK-2012/18). This work was supported by the Scientific Research Projects Coordination Unit of Trakya University (Project Number: TUBAP:2012/104). As a result of the power analysis performed for the study design, it was planned to recruit 10 rats to each group for %95 reliability. Inclusion cirteria: Weight between 170 g and 230 g, female rats, survival after treatment. Exclusion criteria: The weight less than 150 g or greater than 280 g, male rats, the dead rats after treatment. Fifty female Wistar rats, 3-4 months old, weighing 200 ± 25 g, maintained under standard temperature and humidity conditions, were used in the study. The animals had free access to sterile water and food and were housed in a polypropylene cage containing sterile paddy husk for bedding throughout the experiment. All animals received humane care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health. The animals were divided into five groups (with ten rats each) and treated as follows:

- Group 1: control (Cont);
- Group 2: radiotherapy alone (RT);
- Group 3: radiotherapy + amifostine (RT+AMI);
- Group 4: radiotherapy + melatonin (RT+MEL);
- Group 5: radiotherapy + amifostine + melatonin (RT+AMI+MEL).

Animals in the RT group were treated with 0.9% saline solution (SS) 30 minutes before irradiation. Amifostine was administered to the rats in the RT+AMI and RT+AMI+MEL groups 30 minutes before irradiation. Animals in the RT+AMI and RT+AMI+MEL groups received amifostine (200 mg/kg, ER-KIM Ilac, Istanbul, Turkey) by intraperitoneal injection before irradiation (Cosar et al., 2012). Melatonin was administered to the rats in the RT+MEL and RT+AMI+MEL groups 30 minutes before irradiation. Animals in the RT+MEL and RT+AMI+MEL groups received melatonin (10 mg/kg, Sigma Chemical Co, St. Louis, USA) by intraperitoneal injection before irradiation (Sener, Jahovic, Tosun, Atasoy, & Yegen, 2003). All experimental procedures were performed on anesthetized rats. Anesthesia was performed via intramuscular ketamine (100 mg/kg, Pfizer Ilac, Istanbul, Turkey) and xylazine (3.9 mg/kg, Interhas A.S., Istanbul, Turkey) during irradiation. The follow-up period was 72 hours in all groups. At the end of this follow-up period, after all rats were anesthetized, the rats were sacrificed using cervical dislocation method (Cosar et al., 2012). After irradiation, the animals were closely monitored until they recovered

from anesthesia. No animals died due to irradiation or medication.

Irradiation

Rats were anesthetized and fixed on their blocks across a blue Styrofoam (Med-Tec, Orange City, IA, USA) treatment couch in prone position. RT, RT+AMI, RT+MEL and RT+AMI+MEL groups were irradiated individually with a single dose of 8 Gy using a 60Co treatment unit (Cirus, cis-Bio Int., Gif-sur-Yvette, France). Dose rate was 1.15 Gy/min.

Spectrophotometric Analysis

Kidney tissue samples were excised, weighed, and immediately stored at −50ºC for later spectrophotometric analyses. The kidney tissues cleaned with 1.15% ice-cold KCl, minced, and then homogenized in five volumes (w/v) of the same solution. The homogenates were spun at 14000 rpm for 30 min at +4ºC, and assays were performed on the resultant supernatant. The protein concentration of the tissue was measured using the Lowry method (Lowry, Rosebrough, Farr, & Randall, 1951). The total antioxidant capacity (TAC) of supernatant fractions was evaluated using a novel automated and colorimetric measurement method developed by Erel et al. (Erel, 2004). Hydroxyl radicals, the most potent biological radicals, are produced in this method. In the assay, the ferrous ion solution present in Reagent 1 is mixed with hydrogen peroxide, which is present in Reagent 2. The subsequently produced radicals, such as brown-colored dianisidine radical cations produced by the hydroxyl radicals, are also potent radicals. Using this method, the antioxidative effect of the sample is measured against the potent-free radical reactions initiated by the produced hydroxyl radicals. The assay has excellent precision values lower than 3%. TAC results are expressed as µmole Trolox equivalent/mg protein. The total oxidant status (TOS) of supernatant fractions was evaluated using a novel automated and colorimetric measurement method developed by Erel (Erel, 2005). Oxidants present in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction is increased by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion makes a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide, and the results are expressed in terms of µmole H_2O_2 equivalent/mg protein (Ozturk et al., 2011). The ratio of TOS to TAC was regarded as the oxidative stress index (OSI). The units for kidney tissue TOS and TAC values were converted to µmole H_2O_2 Equiv./gram protein. The kidney tissue OSI value was calculated as follows: OSI = ((TOS, µmole H_2O_2 Equiv./gram protein)/(TAC, µmole H_2O_2 Equiv./gram protein) × 100) (Aycicek, Erel, & Kocyigit, 2005).

Statistical Analysis

All statistical evaluations were made using the SPSS 19 package program. One way analysis of variance and Mann-Whitney U test (post hoc with Bonferoni correction) were used to determine differences between the groups. All parameters were given as mean ± SD. Significance was considered at $p < 0.05$.

RESULTS

All the animals were included in the analysis. After radiotherapy, although TAC decreased, TOS and OSI increased, although only the change in OSI was statistically significant (p=0.03). Addition of amifostine or melatonin to radiotherapy increased TAC significantly (p=0.00), but there was no additive effect for TAC when both drugs were given together. In terms of TOS, there was an increase, but this was statistically significant only for amifostine. Results for OSI were similar to TAC results (Table 1 and table 2).

Table 1. Spectrophotometric analysis results

Group		TAC (µmole H_2O_2 Equiv./gram protein)	TOS (µmole H_2O_2 Equiv./gram protein)	OSI = ((TOC, µmole H_2O_2 Equiv./gram protein)/ (TAC, µmole H_2O_2 Equiv./gram protein) × 100)
1	Control	3.58±0.45	0.99±0.34	0.02±0.009
2	RT	2.98±0.67	2.11±0.91	0.07±0.030 A*
3	RT+AMI	4.16±0.21 E***	6.7±1.53 E***	0.15±0.030 E***
4	RT+MEL	4.50±0.62 F***	3.02±1.27	0.07±0.039
5	RT+AMI+MEL	2.89±0.48	2.92±0.71	0.10±0.30

Data are given as mean±SD. * p< 0.05, ** p<0.01, ***p<0.001. Group Comparisons: A: 1 and 2, B: 1 and 3, C: 1 and 4, D: 1 and 5, E: 2 and 3, F: 2 and 4, G: 2 and 5. Abbreviations: AMI, Amifostine; MEL, Melathonin; RT, Radiotherapy; TAC, Total Antioxidant Capacity; TOS, Total Oxidant Status; OSI, Oxidative Stress Index

Table 2. The statistical comparison of the groups for TAC, TOS and OSI

	Groups	1	2	3	4
TAC	2	.131			
	3	.147	**.000**		
	4	**.002**	**.000**	1.000	
	5	.050	1.000	**.000**	**,000**
TOS	2	.208			
	3	.000	.000		
	4	**.001**	.581	**.000**	
	5	**.002**	.888	**.000**	1,000
OSI	2	**.030**			
	3	.000	.000		
	4	**.029**	1.000	**.000**	
	5	**.000**	.172	**.001**	.178

Abbreviations: AMI, Amifostine; MEL, Melathonin; RT, Radiotherapy; TAC, Total Antioxidant Capacity; TOS, Total Oxidant Status; OSI, Oxidative Stress Index , Group 1: control (Cont), Group 2: radiotherapy alone (RT), Group 3: radiotherapy + amifostine (RT+AMI), Group 4: radiotherapy + melatonin (RT+MEL), Group 5: radiotherapy + amifostine + melatonin (RT+AMI+MEL),

DISCUSSION

The main finding of this study is melatonin and amifostine may have some protective effect on radiation-induced renal oxidative stress. Radiation is an important inducer of oxidative stress, and chronic oxidative stress after total body irradiation is thought to be the cause of radiation nephropathy in rats (Ozbek, 2012). In our study, whole body irradiation of rats provoked oxidative stress in the kidney, identified by elevated levels of TOS and decreased levels of TAC compared to their respective values in control rats. The decrease in antioxidants might result from their increased utilization to neutralize the excess of free radicals, as well as their release to the blood stream resulting from radiation-induced cell membrane damage (Saada Helen & Azab Khaled, 2001). In addition, protein oxidation may contribute to the partial inactivation of enzymes (Kregel & Zhang, 2007).

The major enzymatic antioxidants are SOD, catalase, and GSH-Px. SOD is generally thought to act as a bulk scavenger of superoxide radicals. H_2O_2 that is produced by the action of SOD or the action of oxidases, such as xanthine oxidase, is reduced to water by catalase and GSH-Px. Catalase exists as a tetramer composed of 4 identical monomers, each of which contains a heme group at the active site. Degradation of H_2O_2 is accomplished via catalase. Catalase also binds NADPH as a reducing equivalent to prevent oxidative inactivation of the enzyme by H_2O_2 as it is reduced to water (Kirkman, Rolfo, Ferraris, & Gaetani, 1999; Zelko, Mariani, & Folz, 2002). Enzymes in the redox cycle responsible for the reduction of H_2O_2 and lipid hydroperoxides (generated as a result of membrane lipid peroxidation) include GSH-Px. GSH-Px reduces H_2O_2 and lipid peroxides to their corresponding alcohols (Flohe, Gunzler, & Schock, 1973).

The role of melatonin as a protector against ionizing radiation has been investigated in different studies. These results suggest that the radioprotective effect of melatonin is not species-specific and acts in a similar way in different biological systems (Blickenstaff, Brandstadter, Reddy, & Witt, 1994; Vijayalaxmi, Reiter, & Meltz, 1995; Vijayalaxmi, Reiter, Sewerynek, et al., 1995). Melatonin is a remarkably efficient oxygen radical scavenger. In vitro, melatonin is fivefold better at neutralizing hydroxyl radicals than glutathione and twofold more effective at inactivating peroxyl radicals than vitamin E (Baldwin & Barrett, 1998; Haghi-Aminjan et al., 2018). Also, melatonin's protective effects in some subcellular compartments may be due to its indirect antioxidative actions such as stimulation of enzymes that either promote the synthesis of other antioxidants or metabolize reactive species to non-radical products (El-Sokkary, Omar, Hassanein, Cuzzocrea, & Reiter, 2002; Hara et al., 1997; Kotler, Rodriguez, Sainz, Antolin, & Menendez-Pelaez, 1998). Histopathological studies have shown that melatonin has a protective effect against radiation-induced nephrotoxicity (Kucuktulu et al., 2012; Ozen et al., 2013).

Amifostine is an organic thiophosphate ester prodrug and must be activated by alkaline phosphatase to be converted into an active sulfhydryl compound

(Kaldir et al., 2008; Levi et al., 2002). It has been shown that amifostine can ameliorate functional renal damage in rat kidneys (Caloglu et al., 2009; Rolleman et al., 2007). Amifostine is a broad-spectrum cytoprotective agent and selectively protects all normal tissues without decreasing the response of neoplastic tissues to the cytotoxic effects of radiation therapy. Normal tissues have higher alkaline phosphatase activity in the plasma membrane, higher interstitial pH, and better vascularity when compared with tumor cells (Hensley et al., 2009). It has been known from previous study that the sublethal dose of whole body ionizing radiation had a protective effect against amifostine damage to brain tissue (Cakmak et al., 2009). The protective effect of amifostine against renal oxidative stress has been shown (Jacevic et al., 2018; Stankiewicz & Skrzydlewska, 2003).

In our study, addition of amifostine or melatonin to radiotherapy increased TAC significantly. There was no statistically significant difference in TAC between amifostine and melatonin administration, and there was no additive effect on TAC and TOS when both drugs were given together. In terms of TOS, there was an increase, but this was statistically significant only for amifostine administration. An interesting finding of this study is that mean OSI levels in Group 3 almost two-fold higher in Group 2. This may be due to an increase in total oxidant capacity in kidney tissue. And finally, there was no significant protective effect of both drugs on OSI.

CONCLUSIONS

In conclusion, we suggest that melatonin and amifostine have some protective effects on radiation-induced renal oxidative stress.. For this reason, we think that this study is very important for the literature. Authors should discuss the results and how they can be interpreted in perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted. Strengths and limitations of the study should be discussed as well.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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