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Hepatoprotective Effect of Dexmedetomidine Against Radioiodine Toxicity in Rats: Evaluation of Oxidative Status and Histopathologic Changes

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Based on the anti-inflammatory, antioxidant, and anti-apoptotic properties of Dexmedetomidine (DEX), the present study was conducted to investigate the possible radioprotective effects of DEX against hepatic radioiodine (I-131) toxicity. Thirty-six rats were randomly divided into 3 groups as untreated control (Group 1); oral radioiodine (RAI, 111 MBq) administrated rats (Group 2), and DEX group (oral radioiodine and daily intraperitoneal 25 μg/kg DEX administrated rats, Group 3). In the third group, DEX administration was started 2 days before and continued for 5 days after RAI administration. Twenty-four hours after the administration of the last dose of DEX, liver samples were taken for evaluation of oxidative stress parameters and histopathologic changes. The tissue malondialdehyde and advanced oxidation protein product levels in DEX group were significantly lower than RAI group. The total tissue sulphydryl and catalase levels of DEX group were higher than RAI group and the difference was statistically significant. The histopathologic damage in the DEX-treated group was

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significantly less than the damage in the RAI group ($P < 0.05$ for all pathologic parameters). Treatment with DEX decreased the histopathologic abnormalities when compared with the RAI group. It was presented that DEX had radioprotective effect on the liver after I-131 therapy and anti-inflammatory and antioxidant activities are likely to be involved in the mechanism underlying the radioprotective effects of DEX. After further studies, DEX might be used as a hepatoprotective treatment regimen before administering radioactive iodine therapy particularly in patients with hepatic disease.

Key words: Dexmedetomidine — Radioiodine — Liver — Oxidative stress — Histopathology

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Iodine-131 (I-131) is a well-known radionuclide that radiates beta as well as gamma rays. It has been one of the main treatment tools for hyperthyroidism as well as thyroid carcinoma since 1940s.[1,2] I-131 whole-body scan (I-131 WBS) is a fairly sensitive and specific tool to detect local recurrence, residual thyroid tissue, and functional metastasis after thyroidectomy for differentiated thyroid cancer. With I-131 WBS, in addition to normal and neoplastic thyroid tissue, physiologic activity has been demonstrated in the salivary glands, stomach, intestines, oropharynx, breast tissue, urinary tract, and bladder. Furthermore, diffuse hepatic I-131 uptake has been observed during WBS, when high-dose radioactive iodine (RAI) treatment is utilized.[3] Liver plays a major role in thyroid hormone metabolism and is likely to get exposed to radioiodine. Therapeutic exposure to I-131 is susceptible to trigger the generation of the oxidative stress and concentrated radioiodine could also cause cellular damage in target organs.[2]

Dexmedetomidine (DEX) is a highly selective and potent α2-adrenoreceptor agonist approved for short-term use as a sedative agent for patients undergoing mechanical ventilation in the intensive care setting. It exerts its activity by acting as a full agonist at both pre- and postsynaptic α2-adrenoreceptors, providing sedation and the additional benefit of reducing anesthetic and opioid requirements. Alpha-2 adrenoreceptors agonists expose sedative, hypnotic, analgesic, anxiolytic, and sympatholytic effects. The advantages of DEX in producing moderate-to-deep sedation and analgesia without a respiratory depression have promoted its use.[4,5]

Several studies have revealed that DEX could be utilized to protect the experimental ischemia-reperfusion injury in various organs, namely rat skeletal muscle, intestine, heart, brain, and kidney. The positive effects of DEX are emanated from the anti-inflammatory, antioxidant, and anti-apoptotic properties of this compound.[6–10]

Moreover, preclinical studies on DEX have indicated that DEX could be a good option for treating T cell-mediated liver injury,[11] and it has beneficial effects on the liver in experimental liver injury models including ischemia-reperfusion and obstructive jaundice.[12,13] It was concluded that these effects of DEX might also be due to its antioxidant and anti-inflammatory activities.

Based on the anti-inflammatory, antioxidant, and anti-apoptotic properties of DEX, the present study was conducted to investigate the possible radioprotective effects of DEX against hepatic radioiodine (I-131) toxicity. To the best of the author's knowledge, the radioprotective effect of DEX has not been previously investigated in the literature. The present study is also the first study assessing the short-term damage and the oxidative stress generating effects of I-131 on the liver tissue.

Materials and Methods

This study was conducted in the Husnu Sakal Experimental and Clinical Practice Center, Ankara, Turkey. The procedures in this experimental study were performed in accordance with the National Guidelines for the Use and Care of Laboratory Animals and the Animal Ethics Committee of Ankara Education and Research Hospital (Ankara, Turkey) granted approval for the study.

Animals

The study was carried out on 36 Wistar-Albino female rats weighing 225–275 g. The rats were allowed to adapt to laboratory conditions for 1 week before experimental use. The animals were housed under standard laboratory conditions with constant temperature (21°C ± 2°C) and a relative humidity of

65%–70% with 12-hour light-dark cycle. They were housed in polypropylene cages using disposable absorbent cloths under sterile paddy husks to avoid contamination from radioactive urine. The animals were fed with standard laboratory chow and water ad libitum. No enteral or parenteral antibiotics were administered during the study.

Experimental design

The rats were randomized and divided into 3 groups of 12 animals in each. The first group was the untreated control (UC) group, which received no RAI therapy or DEX (n = 12). Radioiodine (MONIYOT-131 Eczacıbaşı/Monrol Nukleer Urunler Sanayi ve Ticaret Anonim Şirketi Gebze, Kocaeli, Turkey) was applied at 111 MBq (3 mCi) after replacing nasogastric sondage to the rats in groups 2 and 3. No other medication was given to the rats in Group 2 (RAI group, n = 12). The rats in the third group (DEX group, n = 12) were treated with daily intraperitoneal injection of 25 μg/kg body weight DEX (Hospira, Inc. Rocky Mount, North Carolina), which was started 2 days before RAI administration and continued for five days after the RAI therapy. Twenty-four hours after the administration of the last dose of DEX, the animals were sacrificed by high-dose diethyl ether inhalation. Liver samples were taken for biochemical and histopathologic evaluation.

Evaluation of oxidative stress

The evaluation of oxidative stress parameters was performed in the Biochemistry Department of Ankara Education and Research Hospital. Tissues were stored at –80°C until the assays. Tissue malondialdehyde (MDA), total-SH (sulphydryl) levels, advanced oxidation protein products (AOPP) levels, and catalase (CAT) enzyme activities were measured.

MDA levels were calculated by the fluorometric method, as described by Wasowicz *et al*.[14] After the reaction of thiobarbituric acid (TBA) with MDA, the reaction product was extracted in butanol and was measured spectrofluorometrically at wavelengths of 525 nm for excitation and 547 nm for emission. 0-5 μmol/L 1,1′,3,3′-tetraethoxypropane solution was used as standard. For the measurement of tissue MDA levels, 50 μL of homogenate was added and introduced into 10 mL glass tubes containing 1 mL of distilled water. After the addition of 1 mL of the solution containing 29 mmol/L TBA in acetic acid and mixing, the samples were placed in a water bath and heated for 1 hour at 95°C–100°C. The samples were then cooled, 25 μL of 5 mol/L hydrochloric acid (HCL) was added and the reaction mixture was extracted by agitation for 5 minutes with 3.5 mL n-butanol. After separation of the butanol phase by centrifugation at 1500*g* for 10 minutes, the fluorescence of the butanol extract was measured with a fluorometer (Hitachi F-2500, Tokyo, Japan) at wavelengths of 525 nm for excitation and 547 nm for emission. Solutions of 0–5 μmol/L 1,1′,3,3′-tetraethoxypropane were used as standard. MDA levels were presented as μmol/g wet tissue.[14]

Total SH groups were measured spectrophotometrically using the method suggested by Sedlak and Lindsay.[15] Aliquots of 250 μl of the supernatant fraction of the tissue homogenate were mixed in 5 mL test tubes with 750 μl of 0.2 M Tris buffer, pH 8.2, and 50 μl of 0.01 M 5,5″-dithiobis (2-nitrobenzoic acid) (DTNB). The mixture was brought to 5 mL with 3950 μl of absolute methanol. A reagent blank (without sample) and a sample blank (without DTNB) were prepared in a similar manner. The test tubes were stoppered with rubber caps, the color was developed for 15 minutes and the reaction mixtures were centrifuged at approximately 3000*g* at room temperature for 15 minutes. The absorbance of supernatant fractions was read in a spectrophotometer (Schimadzu CL-770, Kyoto, Japan) at 412 nm.[15]

AOPP were determined according to the method described by Witko-Sarsat *et al*.[16] AOPP were measured by spectrophotometrically and were calibrated with Cloramin-T solutions that in the presence of potassium iodide absorb at 340 nm. In standard tubes, 50 μL of 1.16 M potassium iodide was added to 1000 μL of chloramine-T solution (0–100 mmol/L) followed by 100 μL of acetic acid. In test tube, 1000 μL of tissue homogenate diluted 1/5 in PBS, 50 μL 1.16 M KI and 100 μL of acetic acid were mixed, and the absorbance of the reaction mixture was immediately read at 340 nm on the spectrophotometer against blank containing 1000 μL PBS, 100 μL acetic acid, and 50 μL 1.16 M KI.

CAT activity was assayed using the method suggested by Yasmineh and Theologides.[17] The absorbance change of hydrogen peroxide, which was degraded by CAT activity, was monitored at 240 nm. CAT activity was calculated by using change of absorbance per minute, molar absorptivity coefficient of hydrogen peroxide, and dilution factor. Results were expressed as units per milligram (U/mg) protein.

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Table 1 Grading of histopathologic changes of the groups

Hyperemia	Presence of inflammatory cells	Steatosis (microvesicular)
Grade 0: no hyperemia	Grade 0: absent	Grade 0: absent
Grade 1: mild hyperemia	Grade 1: few inflammatory cells	Grade 1: mild steatosis
Grade 2: severe hyperemia	Grade 2: severe inflammatory cells	Grade 2: severe steatosis
Grade 3: very severe hyperemia	Grade 3: very severe inflammatory cells	Grade 3: very severe steatosis
Cellular changes (multiple nucleus)	Bile duct proliferation	Fibrosis
Grade 0: absent	Grade 0: absent	Grade 0: absent
Grade 1: mild cellular changes	Grade 1: mild proliferation	Grade 1: mild fibrosis
Grade 2: severe cellular changes	Grade 2: severe proliferation	Grade 2: severe fibrosis
Grade 3: very severe cellular changes	Grade 3: very severe proliferation	Grade 3: very severe fibrosis
Venous lesions	Capsule thickening	Granuloma formation
Grade 0: absent	Grade 0: absent	Grade 0: absent
Grade 1: mild lesions	Grade 1: mild thickening	Grade 1: mild granuloma formation
Grade 2: severe lesions	Grade 2: severe thickening	Grade 2: severe granuloma formation
Grade 3: very severe lesions	Grade 3: very severe thickening	Grade 3: very severe granuloma formation

Histopathologic examination

The histopathologic analyses were performed in the Pathology Department of Harran University Faculty of Veterinary Medicine. For light microscopic analyses, the samples were obtained from the liver and fixed in 10% neutral buffered formalin solution for 2 days. The tissues were washed in running water and were dehydrated with increasing concentrations of ethanol (50%, 75%, 96%, 100%). After dehydration, the specimens were put into xylene to obtain transparency and were then infiltrated with and embedded in paraffin. The embedded tissues were cut into 5-μm thick sections using a Leica RM 2125 RT microtome (Nussloch, Germany) and stained with hematoxylin and eosin. Histopathologic examinations were performed with a light microscope (Olympus BX-50, Tokyo, Japan) by a pathologist blinded to the study design. Histopathologic parameters including hyperemia, presence of inflammatory cells, steatosis, capsule thickening, cellular changes (multiple nucleus), bile duct proliferation, fibrosis, venous lesions (endothelial loss, subintimal thickening and fibrosis), and granuloma formation were evaluated semiquantitatively according to modified histologic activity index (HAI).[18,19] The scoring system of these parameters is given in Table 1.

Statistical analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 15.0 for Windows (SPSS Inc, Chicago, Illinois). All variables were normally distributed about the mean. Data were presented as mean ± SD. Differences between the groups were evaluated by one-Way analysis of variance (ANOVA) or Kruskal–Wallis variance analysis, whichever was appropriate. When the P values from the variance analysis were statistically significant, the Tukey honestly significant difference (HSD) or Mann-Whitney U multiple comparison test was used to determine which group was different from the others. A value of $P < 0.05$ was considered to be statistically significant.

Results

Oxidative stress parameters

The mean levels of the oxidative stress parameters for the liver (MDA, total SH, AOPP and CAT) are summarized in Table 2.

There was a significant difference in tissue MDA levels between the RAI group and the other groups ($P < 0.05$). The highest tissue MDA levels were detected in the RAI group. The levels in DEX group were significantly lower than the RAI group ($P < 0.05$). The MDA levels were lower in the control group than the DEX group and the difference was statistically significant ($P < 0.05$).

Like MDA level comparison, total tissue SH levels were significantly different between the RAI group and other groups ($P < 0.05$). The total tissue SH levels were lowest in the RAI group. The levels of DEX group were higher than the RAI group and the difference was statistically significant ($P < 0.05$). The total SH levels were higher in the control group when compared with DEX group ($P < 0.05$).

For CAT activities, the differences between the RAI and other groups were significant. The lowest CAT values were found in the RAI group. The DEX group reacted better than the RAI group, implied by the higher CAT values, and the difference was

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Table 2 Mean oxidative stress parameter levels of the groups

Groups	MDA	Total SH	AOPP	CAT
Group 1 (control)	2.28 ± 0.24	157.37 ± 22.90	15.50 ± 3.14	77.73 ± 16.24
Group 2 (RAI)	3.16 ± 0.47[a]	114.29 ± 15.28[a]	29.20 ± 2.45[a]	44.89 ± 13.94[a]
Group 3 (DEX)	2.53 ± 0.21[a,b]	125.36 ± 13.07[a,b]	19.62 ± 3.43[a,b]	58.64 ± 8.55[a,b]

AOPP, advanced oxidation protein products; CAT, catalase; DEX, dexmedetomidine; MDA, malondialdehyde; RAI, radioiodine; SH, sulphydryl.

[a]Significantly different, control versus other groups.

[b]Significantly different, RAI versus dexmedetomidine group.

statistically significant ($P < 0.05$). The CAT activities were higher in the control group when compared with the DEX group ($P < 0.05$).

There was a significant difference in tissue AOPP levels between the RAI group and the other groups ($P < 0.05$). The highest tissue AOPP levels were determined in the RAI group. The levels of DEX group were significantly lower than the RAI group ($P < 0.05$). The AOPP levels were lower in the control group than the DEX group and the difference was statistically significant ($P < 0.05$).

Histopathologic results

The mean scores of the histologic activity index (HAI) of the groups are given in Table 3. When statistical analyses of the HAI scores were performed, it was found that the histopathologic damage in the DEX-treated group was significantly less than the damage in the RAI group ($P < 0.05$ for all pathologic parameters). The HAI scores of the control group were significantly better than the RAI group ($P < 0.05$ for all parameters). There was a statistically significant difference between the control and DEX groups for inflammation, capsular thickening, and cellular changes ($P < 0.05$). However, no significant difference was found between the control and DEX groups for other pathologic parameters ($P > 0.05$; Table 3).

Table 3 Mean pathologic scores of the groups

	Group 1 (Control)	Group 2 (RAI)	Group 3 (DEX)
Hyperemia	0.08 ± 0.02	1.41 ± 0.41[a]	0.50 ± 0.09[b]
Inflammation	0.00 ± 0.00	1.33 ± 0.38[a]	0.33 ± 0.07[a,b]
Steatosis	0.08 ± 0.02	1.41 ± 0.41[a]	0.50 ± 0.09[b]
Capsular thickening	0.00 ± 0.00	1.16 ± 0.24[a]	0.33 ± 0.07[a,b]
Cellular changes	0.00 ± 0.00	1.08 ± 0.21[a]	0.33 ± 0.07[a,b]
Bile duct proliferation	0.00 ± 0.00	0.91 ± 0.18[a]	0.83 ± 0.11[b]
Fibrosis	0.00 ± 0.00	1.33 ± 0.38[a]	0.08 ± 0.02[b]
Venous lesions	0.00 ± 0.00	1.08 ± 0.21[a]	0.16 ± 0.05[b]
Granuloma formation	0.00 ± 0.00	1.41 ± 0.41[a]	0.08 ± 0.02[b]

DEX, dexmedetomidine; RAI, radioiodine.

[a]Significantly different, control versus other groups.

[b]Significantly different, RAI versus dexmedetomidine group.

The histopathologic findings are presented in Figs. 1 and 2. Liver tissue sections from the control group exhibited almost normal morphology. RAI caused marked hyperemia, inflammatory cell infiltration, steatosis, capsule thickening, cellular changes, bile duct proliferation, fibrosis, venous lesions, and granuloma formation. Treatment with DEX decreased the histopathologic abnormalities when compared with the RAI group.

Discussion

In recent years, radioactive I-131 has frequently been administered during therapeutic treatment of patients having thyroid carcinoma after the surgical procedure of total or partial thyroidectomy.[20] RAI treatment is commonly utilized due to its easy-to-administer nature, its availability, and its effectiveness in most patients.[21] Although the radioactive I-131 is mainly toxic to thyroid cells that accumulate iodine from bloodstream, it could also be biodistributed to the entire body and other organs. In total thyroidectomized patients, it has been shown that the lower gastrointestinal tract, kidney, stomach, heart wall, and liver absorb relatively high doses per unit of administered iodine activity.[22] Ideally, I-131 treatment should only ablate residual micro/macroscopic tumor cells in the thyroid and/or distant metastasis but not affect healthy tissues in the body. However, the posttherapy scans frequently reveal diffuse I-131 uptake in the liver.[3,23] After ingesting orally, I-131 is absorbed through the stomach and intestines, then passes to the liver and reaches the systemic circulation via the portal vein.[24] Hepatic radioiodine uptake was positively correlated with the dose of administered I-131. Several factors, including age, sex, nutritional factors, the period of disease, and the size of the goiter, are able to augment the RAI-induced hepatotoxicity.[21]

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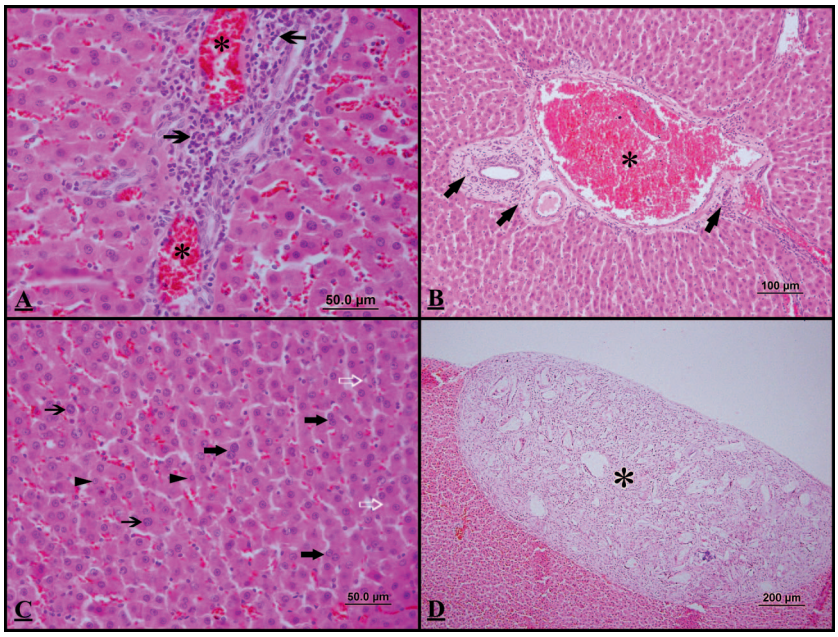

Fig. 1 Histopathologic findings of radioiodine group (Group 2). G2a: Severe perivascular and perilobular inflammatory cell infiltration (arrows) and intense inflammatory hyperemia (stars). Hematoxylin and eosin (H&E), ×400. G2b: Severe perivascular and perilobular fibrosis (arrows) and intense inflammatory hyperemia (star). Hematoxylin and eosin (H&E), ×200. G2c: Multiple double-nucleated hepatocytes (arrows), dense hepatocytes with macronuclei (thin arrows), micronucleus structure (arrowhead), and cytoplasmic vacuoles (white arrows). Hematoxylin and eosin (H&E), ×400. G2d: Large granuloma formation in the liver (star). Hematoxylin and eosin (H&E), ×40.

Atilgan *et al*[25] evaluated the histopathologic changes in rat livers at the third month following 131-I treatment and found that I-131 caused significant hyperemia, steatosis, cellular changes, bile duct proliferation, fibrosis, venous lesions, capsule thickening, and granuloma formation. They also found that montelukast sodium effectively protected the liver against this morphologic damage.

A study conducted by Vasil'ev *et al*[26] on liver and kidney function showed a decrease in absorptive and secretory hepatocytic function and a decline in total renal function after RAIT. The changes were of moderate nature, stable, and related both to hypothyroidism and to a radiation factor.

Jhummon *et al*[21] presented 2 cases of liver toxicity developing in previously healthy Graves' disease patients when treated with RAI, and subsequent improvement via hepatoprotective treatment regimens. They concluded that although hepatic toxicity after RAI treatment was scarce, physicians should be aware of this probable complication and might consider initiating early hepatoprotective treatment regimens before administering RAI.

Ran *et al*[27] indicated that 4 Gy of whole-body irradiation led to a substantial increase in the MDA level, whereas there was a prominent decline in the activities of antioxidant enzymes (SOD and CAT) and antioxidant molecular levels (GSH) in the liver and spleen. Reactive oxygen species (ROS), which are implicated in the process of DNA damage, cell killing, and tissue damage of organs, are produced by radiation. Both accidental exposure to radiation,

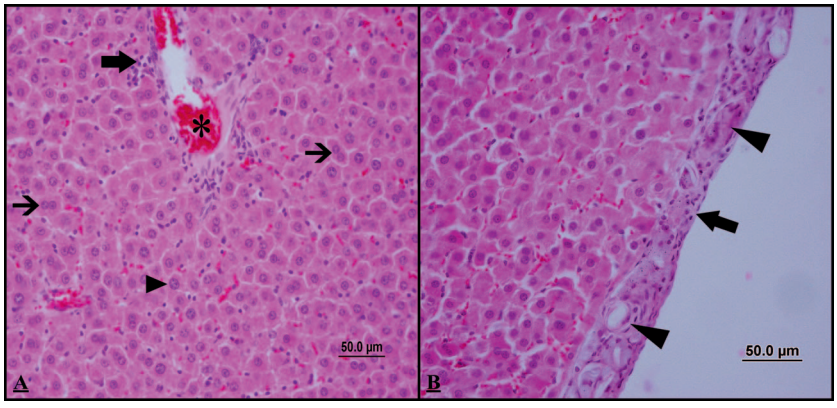

Fig. 2 The pathologic changes are less prominent in the DEX group than in the radioiodine group. G3a: Mild perivascular and perilobular inflammatory cell infiltration (arrow), mild hyperemia (star), rare double nucleated hepatocytes (thin arrows), and hepatocyte with macronucleus (arrowhead). Hematoxylin and eosin (H&E), ×400. G3b: Mild fibrosis and inflammatory reaction (arrow), improved granuloma pattern (arrowheads). Hematoxylin and eosin (H&E), ×400.

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as well as the therapeutic application of ionizing irradiation, are the main reasons for the generation of reactive oxygen species (ROS) in cells.

Unlike external radiation, radionuclides *in vivo* generally deliver a radiation dose over an extended period depending upon their physical and biologic half-life. The absorption of ionizing radiation by living cells could directly disrupt atomic structures, producing chemical and biologic alterations. It could also act indirectly through radiolysis of water, thereby generating reactive chemical species that might damage nucleic acids, proteins, and lipids. Combined direct and indirect radiation effects initiate a series of biochemical and molecular signaling events that might repair the damage or culminate in permanent physiologic changes or even cell death. Interestingly, the early biochemical modifications, which occur during or immediately after the radiation exposure, were considered to be responsible for most of the effects of ionizing radiation in mammalian cells. However, oxidative changes might persist for days and months after the initial exposure due probably to the continuous generation of reactive oxygen (ROS) and nitrogen (RNS) species. Ionizing radiation is a strong inducer of ROS and RNS.[28]

Although several drugs have been tested for the prevention of 131-I-related tissue damage, no medication has been widely accepted in clinical practice.

Dexmedetomidine [DEX; (S)-4-[1-(2,3-dimethylphenyl)ethyl]-3H-imidazole], is a selective and potent α2-adrenergic receptor (α2-AR) agonist, which was approved by the US Food and Drug Administration in 1999 for sedation of patients hospitalized in intensive care units (ICUs). It is also beneficial to avoid additional cardiorespiratory workload and metabolic alterations caused by increased levels of catecholamines and other stress hormones.[29] It exerts its activity by acting as a full agonist at both pre- and postsynaptic α2-adrenoreceptors, providing for sedation and the additional benefit of reducing anesthetic and opioid requirements.[5] Furthermore, α2-AR agonists have a potential application as prophylactic agents in neuroprotection following neuroanesthesia and neurointensive care, which has attracted much research interest in their role in ischemia/reperfusion (I/R) injury in the brain and other critical organs. Since then, a growing number of research articles have aimed at investigating other possible applications, including use as a protective agent for I/R injury in various organs including the rat skeletal muscle, intestines, heart, kidneys, overs, lungs and liver.[6–10,29–31]

In addition, in other studies, the beneficial effects of DEX on liver injury have been analyzed under different experimental conditions including hepatic ischemia–reperfusion injury,[30,31] obstructive jaundice,[13] trinitrobenzene sulfonic acid (TNBS)-induced inflammatory bowel disease,[32] acid-induced acute lung injury,[33] and experimental sepsis models.[34]

Sahin *et al*[30] investigated the possible protection of DEX against IR-induced liver injury in rats and claimed that administration of DEX to the IR group reduced the MDA level while increasing the SOD, CAT, GSH, and GSH-Px activities. The histopathologic scores of sinusoidal congestion, hepatocytes with eosinophilic cytoplasms, and nuclear necrosis were significantly lower in the DEX groups. According to these results they concluded that both 10 μg/kg and 100 μg/kg doses of DEX protected against IR-induced damage in IR rat models. Tufek *et al*[31] also demonstrated that DEX markedly reduced the oxidative stress in serum, liver, and remote organs induced by hepatic IR injury, and ameliorated the histopathologic damage in the liver. Another study, conducted by Cekic *et al*,[35] showed that IR phenomenon during pneumoperitoneum caused oxidative stress and consumption of plasma antioxidants. DEX decreased oxidative stress caused by pneumoperitoneum and strengthened the antioxidant defense system.

Kuru *et al*[13] studied the possible hepatoprotective effects of DEX in experimental obstructive jaundice model and concluded that DEX had a significant hepatoprotective effect on the detrimental effects of obstructive jaundice. They suggested that these positive effects were due to its antioxidant and anti-inflammatory activities.

In a randomized controlled study, Wang *et al*[36] compared intestinal, hepatic, and other organ function after hepatic portal occlusion with or without DEX administration under general anesthesia. They stated that DEX administered perioperatively attenuated intestinal and hepatic injury in patients undergoing elective liver resection with inflow occlusion without any potential risk.

In a trinitrobenzene sulfonic acid (TNBS)-induced inflammatory bowel disease (IBD) model, Gul *et al*[32] investigated histopathologic, ultrastructural, and antioxidant effects of DEX on the liver. The results showed that the administration of DEX reduced the histopathologic and ultrastructural damage and enhanced the defense capacity against oxidative damage on the liver in the IBD mice model.

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DEX also had a protective effect on experimental liver injury induced by acid-induced acute liver injury[33] and experimental sepsis model.[34]

In the light of these studies, it was hypothesized by the authors of the current study that DEX would be effective against the radioiodine-induced lung injury induced by oxidative stress and inflammation after radioiodine treatment. Histopathologic parameters including hyperemia, presence of inflammatory cells, steatosis, capsule thickening, cellular changes, bile duct proliferation, fibrosis, venous lesions, and granuloma formation revealed that DEX protected rat liver against radioiodine-related liver damage. The mean scores of all these histopathologic parameters were lower in the DEX-treated rats (Group 3) and the differences were statistically significant when compared with the RAI group (Group 2; $P < 0.05$). When the oxidative stress parameters were evaluated, it was found that DEX treatment after RAI administration decreased MDA and AOPP levels, and increased the total SH levels and catalase activities. The results of the current study, in accordance with previously conducted studies mentioned earlier, indicated that DEX had significant anti-inflammatory and antioxidant activities.

To the best of our knowledge, this is the first study conducted on the evaluation of the radioprotective effects of DEX on the liver. The present study is also the first study assessing the early damage and the oxidative stress generating effects of I-131 on the liver. It was presented that DEX had radioprotective effect on the liver after I-131 therapy and anti-inflammatory and antioxidant activities are likely to be involved in the mechanism underlying the radioprotective effects of DEX. After prospective randomized clinical studies, DEX might be used as a hepatoprotective treatment regimen before administering radioactive iodine therapy particularly in patients with hepatic disease.

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