



Evaluation of the effects of dexmedetomidine on liver damage secondary to renal ischemia-reperfusion

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ABSTRACT

Background: The aim of this study was to evaluate the hepatic protective effects of dexmedetomidine in a rat model of renal ischemia-reperfusion (I/R) injury.

Methodology: We selected 18 albino rats and randomly divided them into 3 equal groups (n = 6); control group (Group C), ischemia/reperfusion group (Group I/R), and Group D+I/R, in which dexmedetomidine was given and I/R was administered. The right renal pedicle was ligated to induce I/R in Group-I/R and Group-D+I/R, the left renal pedicle was clamped with an atraumatic vascular clamp to induce ischemia for 120 min and then reperfusion was performed for 120 min. In Group D+I/R, dexmedetomidine 100 µ/kg was administered intraperitoneally 30 min before the administration of before renal I/R. Histopathological changes in liver tissue, caspase-3 activity, glutathione activity, and malondialdehyde level were evaluated through serum renal and liver function tests.

Results: After ischemia/reperfusion, the levels of malondialdehyde, glutathione, aspartate aminotransaminase, alanine aminotransaminase, blood urea nitrogen, creatinine, and caspase-3 were increased and these parameters were observed to be improved followed by the administration of dexmedetomidine. After ischemia/reperfusion, histopathological deterioration was also observed, and less histopathological deterioration was observed in rats given dexmedetomidine.

Conclusion: The effects of renal ischemia-reperfusion on hepatic tissue were evaluated histopathologically, immunologically, and biochemically. It was observed that renal and liver damage occurred after ischemia-reperfusion and dexmedetomidine reduced damages in both kidney and liver.

Key words: Renal Ischemia; Reperfusion; Dexmedetomidine; Liver

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INTRODUCTION

Renal ischemia-reperfusion (I/R) injury is an inevitable result of renal hypoperfusion after renal transplantation, partial nephrectomy, renal vascular surgery, aortic cross-clamping, shock,

and trauma.¹ It is cited that the liver, lung, and heart as remote organs are affected after renal I/R.² With the interruption of the renal arterial circulation, ischemia occurs in the distal area, and with the resumption of blood circulation hypoxic tissues are suddenly exposed to oxygen.

Reperfusion injury originated from free oxygen radicals due to inflammatory response in the hypoxic area and it may cause secondary remote organ damage.³

Increased free oxygen radicals in healthy tissue are removed by the antioxidant defense system. In case free oxygen radicals are increased in large amounts, the antioxidant system becomes insufficient and tissue damage occurs. Histopathological examination, lipid peroxidation, malondialdehyde (MDA), and glutathione (GSH) levels can be used to demonstrate tissue damage.^{4,5} Oxidative stress and lipid peroxidation have been shown to play a role in remote organ damage after I/R.⁶

Dexmedetomidine hydrochloride is an α_2 adrenergic agonist and has analgesic, sedative, neuroprotective, and anxiolytic effects.⁷ In rat studies, dexmedetomidine has been shown to inhibit secondary organ (liver, kidney) damage and inflammatory response, increase survival, have antiapoptotic activity,⁸⁻¹⁰ decrease plasma catecholamine levels, increase urinary output, and to have hemodynamic and renal protective effects.³ Dexmedetomidine has protective effects on other secondary remote organs, such as lungs and heart.^{3,8,9,12,13} However, there is no comprehensive study describing the effect of dexmedetomidine on liver injury as a remote organ secondary to renal I/R.

The aim of this study was to evaluate the renal and hepatic protective effects of dexmedetomidine biochemically and histopathologically in the renal I/R model in rats.

METHODOLOGY

A. Animals and Experimental Protocol

This study was carried out at the Animal Experiments Laboratory of Recep Tayyip Erdoğan University after the approval of the Animal Ethics Committee (2017/36). The study methodology was performed in accordance with the guideline for the protection and care of experimental animals.

The study was carried out on 18 male Wistar albino rats weighing 250-300 g, aged 10-12 weeks. The animals were allowed to reach free water and food for 2 h before the procedure with a 12-h dark-light cycles in standard metal cages (at 20-24° C).

Rats were randomly divided into 3 equal groups (n = 6 each); control group (Group-C), ischemia / reperfusion group (Group-I/R), and group to which dexmedetomidine was given and I/R was administered (Group-I/R+D).

All procedures were performed in the supine position. Inj ketamine hydrochloride (Ketalar®, Parke-Davis, Istanbul, Turkey) 100 mg/kg was administered intraperitoneally (IP) to provide anesthesia. Fluid and drug infusion was administered through tail vein cannulation. Ketamine at a dose of 50 mg/kg was repeated IP during the procedure.

In the control group, the abdomen was opened and closed only with a median incision. In groups I/R and D+I/R, the abdomen was opened by median incision, the right renal pedicle was ligated, and the left renal pedicle was clamped with atraumatic vascular clamp for 120 min ischemia and then 120 min reperfusion was performed to induce I/R.

In Group D+I/R, dexmedetomidine 100 μ g/kg in saline (SF) 2 mL was administered IP 30 min before laparotomy and renal I/R. During the procedure, 2 ml/h normal saline infusion was given from the tail vein.

After the reperfusion period was completed, blood samples were taken from the inferior vena cava and the liver tissue was removed and rats were sacrificed. Tissues were sent to the laboratory under appropriate conditions for examination.

B. Tissue Parameters of Oxidative Status

Liver tissue samples taken at 2 h of I/R, 20 mM 1L sodium phosphate + 140 mM potassium chloride (pH 7.4) were prepared as described previously.¹⁴ 100 ml of tissue was homogenized by adding 1 ml of homogenization solution onto

the tissue and the homogenates were centrifuged at 800 g speed for 10 min at 4° C. Glutathione, GSH, and MDA were determined by the supernatant that was obtained.

Evaluation of MDA: MDA was evaluated according to the method of Ohkawa et al.¹⁵ 200 µL of tissue supernatant; 50 µL 8.1% SDS (sodium dodecyl sulfate); 375 µL of 20% acetic acid (v/v) pH 3.5; 375 µL of 0.8% thiobarbituric acid (TBA) were added. The mixture was vortexed and the reaction was left for incubation for 1 h in a boiling water bath. After incubation, it was cooled in ice water for 5 min and centrifuged at 750 g for 10 min. The resulting pink color was read on a spectrophotometer at 532 nm. The results were calculated as nmol/g tissue.

Evaluation of GSH (Total thiol group): -SH groups were evaluated by using Ellman's reagent. 100 µL of 3M Na₂HPO₄ and 25 µL of DTNB was placed on 25 µL of supernatant (4mg DTNB was prepared in 10 mL of sodium citrate 1% solution) and after gentle agitation, the yellow color formed was read on a spectrophotometer at 412 nm. The results were determined by the prepared graph of 1000 µM-62.5 µM reduced glutathione standard and calculated as nmol/g tissue.

C. Biochemical Analysis

After 2 h of ischemia and 2 h of reperfusion injury, blood samples were taken from the rats by using non-anticoagulant tubes. After fibrin formation, centrifugation was performed and serum was separated. Creatinine, blood urea nitrogen (BUN), aspartate aminotransaminase (AST), and alanine aminotransaminase (ALT) measurements were performed by using Abbott architect c16000 autoanalyzer in a routine biochemistry laboratory.

D. Immunohistochemical Analysis

In our study, an immunohistochemistry kit containing Caspase-3 (ab4051, Abcam, United Kingdom) primary antibodies, an apoptosis biomarker, was used. After paraffin blocks were cut with a microtome (Leica RM2125RT,

Germany), 2-3µm sections were taken on positively charged slides (Patolab, China) and then stored in the incubator and xylol (Merck, Darmstadt, Germany) and deparaffinized. After deparaffinization, liver tissue sections were left for 3 min in a 3% H₂O₂ solution. In the next step, they were incubated in the secondary blocking solution for 20 min. After endogenous peroxidase procedure, sections were incubated in primary antibody solutions followed by secondary antibody solution (Goat Anti-Rabbit IgG H&L (HRP) (ab205718, Abcam, United Kingdom). Finally, after incubation in a solution of diaminobenzidine chromogen (DAB Chromogen, Abcam, United Kingdom) for imaging, tissues were stained as counterstaining with Harris Hematoxylin (Merck, Darmstadt, Germany).

E. Semi-Quantitative Analysis

Histopathological analysis observed in liver tissue sections was performed blindly by two independent histopathologists as in thirty different areas randomly determined in each preparation without overlap in each preparation. Histopathologists were blinded for treatment groups (TM and LT). In addition, evaluation of liver tissues showing caspase-3 positivity was analyzed as shown in Table 1. Scoring of immune positive bone tissues was evaluated by two blinded histopathologists (TM and LT) with thirty different sites in each preparation.

Table 1: Caspase-3 Staining Positivity Score

Grade	Caspase-3 Staining Positivity
0	None (less than 5%)
1	Mild (involvement 6-25%)
2	Moderate (involvement 26%-50%)
3	Severe (more than %51)

Histopathological Analysis

Samples of liver tissue obtained from the subjects were fixed for 24 h in a 10% formalin solution (Sigma-Aldrich, Germany) and then dehydrated in 50%, 70%, 80%, 90%, 96% and 100% alcohol, respectively. In the next step, tissue samples of liver tissue were stored in

xylol (Merck, Darmstadt, Germany), and then embedded in paraffin blocks (Merck, Darmstadt, Germany). Samples, 4-5 µm thick, were taken from liver tissue obtained in paraffin blocks and stained with Harris hematoxylin (Merck, Darmstadt, Germany) and Eosin G (Merck, Darmstadt, Germany). Sections of liver tissue were examined under a light microscope (Olympus Co., BX51, Japan) and photographed with a digital camera (Olympus Co., DP71, Japan). Histopathological Activity Index (HAI) described by Knodell et al.¹⁶ was used for histopathological evaluation (Table 2).

Table 2: Histopathological Activity Index (HAI) for Knodell et al. modified.

Score	Periportal (+/-) bridging necrosis
0	None
1	Mild piecemeal necrosis
3	Moderate piecemeal necrosis (less than 50%)
4	Severe piecemeal necrosis (more than 50%)
5	Moderate piecemeal necrosis + bridging necrosis
6	Severe piecemeal necrosis + bridging necrosis
10	Multilobular necrosis
Intralobular degeneration and focal necrosis	
0	None
1	Mild hepatocellular necrosis (less than 1/3)
2	Moderate (involvement of 1/3-2/3)
3	Severe (more than 2/3)

Statistical analysis:

All data obtained from the analyses were calculated using SPSS 18.0 (IBM, Armonk, NJ, USA). Compliance with normal distribution was checked by the Kolmogorov-Smirnov test. In the evaluation of more than two independent groups with normal distribution, analyses were performed by using one-way ANOVA, followed by LSD test and the numerical data of the groups were analyzed. For nonparametric data, analyses were performed using the Kruskal

Wallis test followed by Tamhane test using differences between groups and then expressed as mean ± standard deviation considering maximum and minimum values.

A p < 0.05 was considered as significant.

RESULTS

1. Analysis of tissue oxidative status parameters (MDA & GSH)

GSH activity was increased in Group-I/R and decreased in Group-I/R+D. There was a significant difference between the Group-C and Group-I/R (p = 0.014), and Group-I/R and Group-I/R+D (p = 0.012).

MDA level was increased in Group-I/R and decreased in Group-I/R+D. There was a significant difference between the control and the I/R groups (p = 0.037) and the I/R and I/R+D groups (p = 0.001). There was a difference between the control group and Group-I/R+D, but this difference was statistically not significant (Table 3).

Table 3: Oxidative status parameters of rat liver tissue (mean ± SD)

Group	MDA (nmol/g doku)	GSH (nmol/g doku)
Control	1.76 ± 0.20	16.5 ± 2.2
I/R	2.06 ± 0.27a	20 ± 2.4a
D+I/R	1.53 ± 0.21b	16.4 ± 1.7b

^ap < 0,05; Versus to Control group,

^bp = 0.05; Versus to I/R group

MDA: Malonildialdehyde

GSH: Glutatyon

ANOVA, LSD test

2. Biochemical Tests

ALT levels were increased in Group-I/R and decreased in Group-I/R+D. There was a significant difference between the control and I/R groups (p = 0.000), the control group and I/R + DEX group (p = 0.048), and I/R and I/R + DEX groups (p = 0.021).

AST levels were increased in Group-I/R and decreased in Group-I/R+D. There was a

significant difference between the control and I/R ($p = 0.005$) groups and I/R and I/R + DEX groups ($p = 0.005$).

Creatinine level was increased in Group-I/R and decreased in Group-I/R+D. There was a significant difference between Group-I/R with control group ($p = 0.000$), Group-I/R+D with control group ($p = 0.000$) and Group-I/R with Group-I/R+D ($p = 0.027$).

BUN level was increased in Group-I/R and decreased in Group-I/R+D. There was a significant difference between Group-C and Group-I/R ($p = 0.000$), Group-C and Group-I/R+D ($p = 0.000$) and Group-I/R and Group-I/R+D ($p = 0.025$) (Table 4).

Table 4: Comparison of biochemical (AST, ALT, creatinin and BUN) values

	AST (U/L)	ALT (U/L)	Creatinin (mg/dL)	BUN (mg/dL)
Control	357.14 ± 154.208	86.48 ± 15.58	0.44 ± 0.055	44.43 ± 7.15
I/R	559.63 ± 130.43a	316 ± 167.32a	1.02 ± 0.078a	84 ± 2.77a
I/R+D	358.13 ± 90.15b.c	191.25 ± 41.36b	0.94 ± 0.09b.c	78.38 ± 2.5b.c

AST: aspartate aminotransaminase

ALT: alanine aminotransaminase

BUN: blood urea nitrogen

Kruskall Wallis, Tamhane T2 test

^a $p < 0.05$; Versus to Control group, ^b $p < 0.05$; Versus to I/R group, ^c $p < 0.05$; Versus to Control group

Table 5: Caspase-3 Positivity Score (mean ± SD)

Group	Score
Control	0.00 ± 0.46
I/R	3.00 ± 0.71a
I/R+D	1.00 ± 0.53b

^a $p = 0.000$ I/R Group vs. Control group

^b $p = 0.000$; I/R+D Group vs I/R group

Kruskall Wallis, Tamhane T2 test

Table 6: Histopathological Activity Index (HAI; mean ± SD)

Group	Periportal bridging necrosis	Intralobular degeneration and focal necrosis	HAI
Control	0.00 ± 0.35	0.00 ± 0.46	0.00 ± 0.52
I/R	3.00 ± 0.83a	3.00 ± 0.83a	6.00 ± 1.16a
I/R+D	0.00 ± 1.10b	1.00 ± 0.96b	1.00 ± 1.30b

^a $p < 0.05$; I/R Group vs. Control group

^b $p < 0.05$; I/R+D Group vs I/R group

Kruskall Wallis, Tamhane T2 test

3. Immunohistochemical Analysis We observed that the number of Caspase-3 (Figures 2 (E-F); Table 5; Caspase-3 positivity score: 1.00 ± 0.53 ; $p = 0.00$).

4. Semi-quantitative Analysis

In the I/R group, we found that periportal bridging necrosis, intralobular degeneration, focal necrosis, and HAI scores were significantly increased compared to the control group (Table 6; $p = 0.000$; $p = 0.000$; $p = 0.000$, respectively); however, in the I/R+D group, we observed that all the three were decreased compared to the I/R group. ($p = 0.001$; $p = 0.002$; $p = 0.000$; respectively).

5. Histopathological Analysis

In the control group, typical Remark cords and sinusoids with normal hepatocytes were present in the sections of the liver tissue [Figure 1 (A-C); Table 6; HAI score: 0.00 ± 0.52 ($p = 0.000$)]. On the other hand, in the I/R group, widespread vacuoles localized around the central vein and numerous intralobular focal necrotic hepatocytes were observed. In addition, we observed diffuse pycnotic hepatocytes accompanying with nuclear shrinkage and dilatations in sinusoids [Figure 1 (D-F); Table 6; HAI score: 6.00 ± 1.16 ($p = 0.000$)]. However, we found that necrotic and apoptotic hepatocytes were decreased in the Group I/R+D [Figure 1 (G-I); Table 6; HAI score: 1.00 ± 1.30 ($p = 0.000$)].

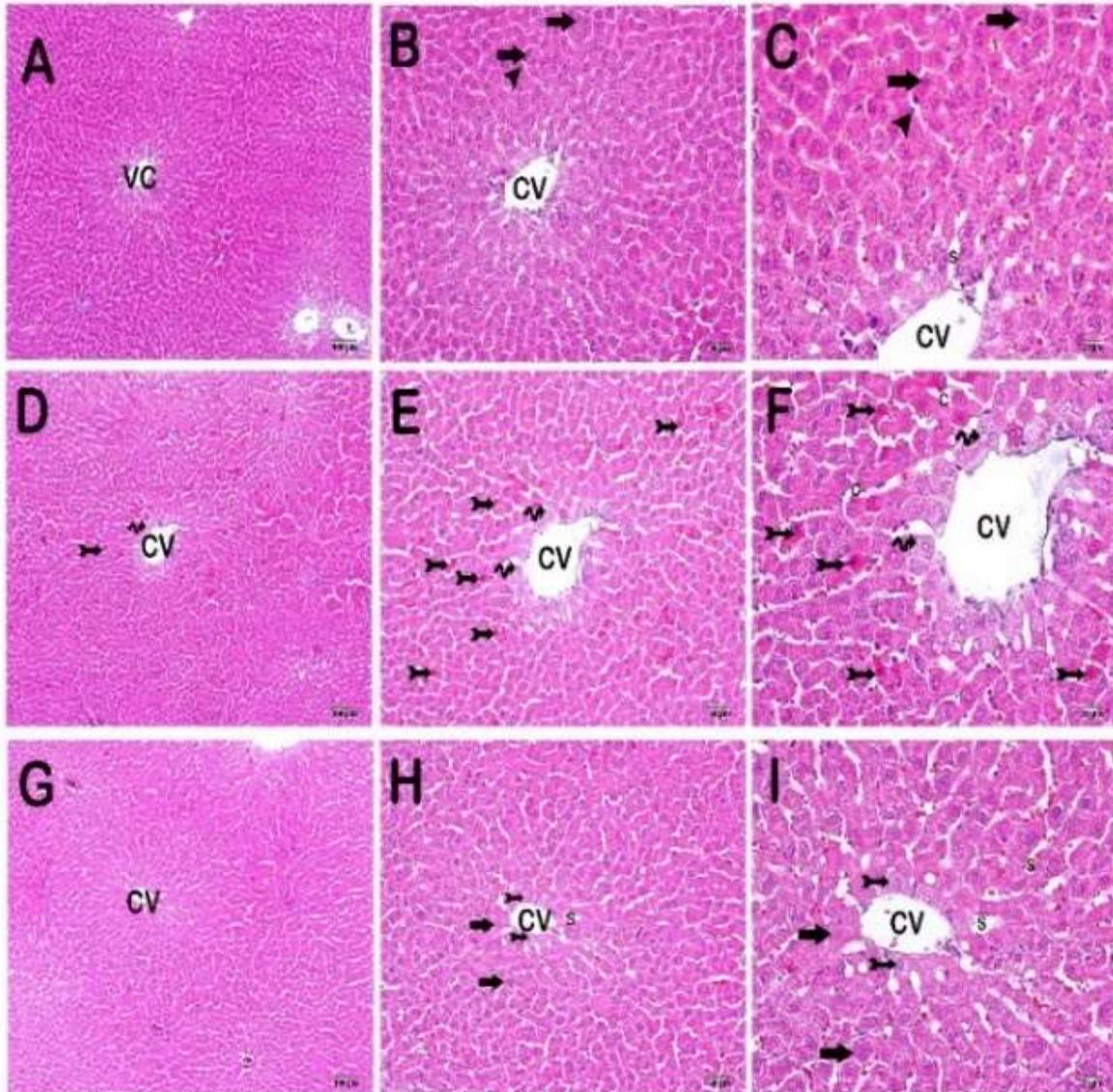


Figure 1: Representative photographs of liver tissue by light microscope (H&E)

A (x10) - B (x20) - C (x40): Normal sections of the hepatocytes (arrow) and sinusoids (s) in the control group. Central vein (CV). Kupfer cell (arrowhead) (HAI score 0.00 ± 0.52). **D. (x10) – E. (x20) – F. (x40):** In the I/R group, focal necrotic hepatocytes (spirally arrows) containing diffuse vacuoles and in the formation of ballooning around the central vein. Also, dilatation of sinusoids (c) and diffuse apoptotic hepatocytes (tailed arrows). Central vein (CV). Kupfer cell (arrowhead) (HAI score 6.00 ± 1.16). **D. (x10) – E. (x20) – F. (x40):** Although a small number of necrotic hepatocytes (tailed arrows) were observed around the central vein in the dex treatment group, normal hepatocytes (arrows) were diffuse. (HAI score 1.00 ± 1.30).

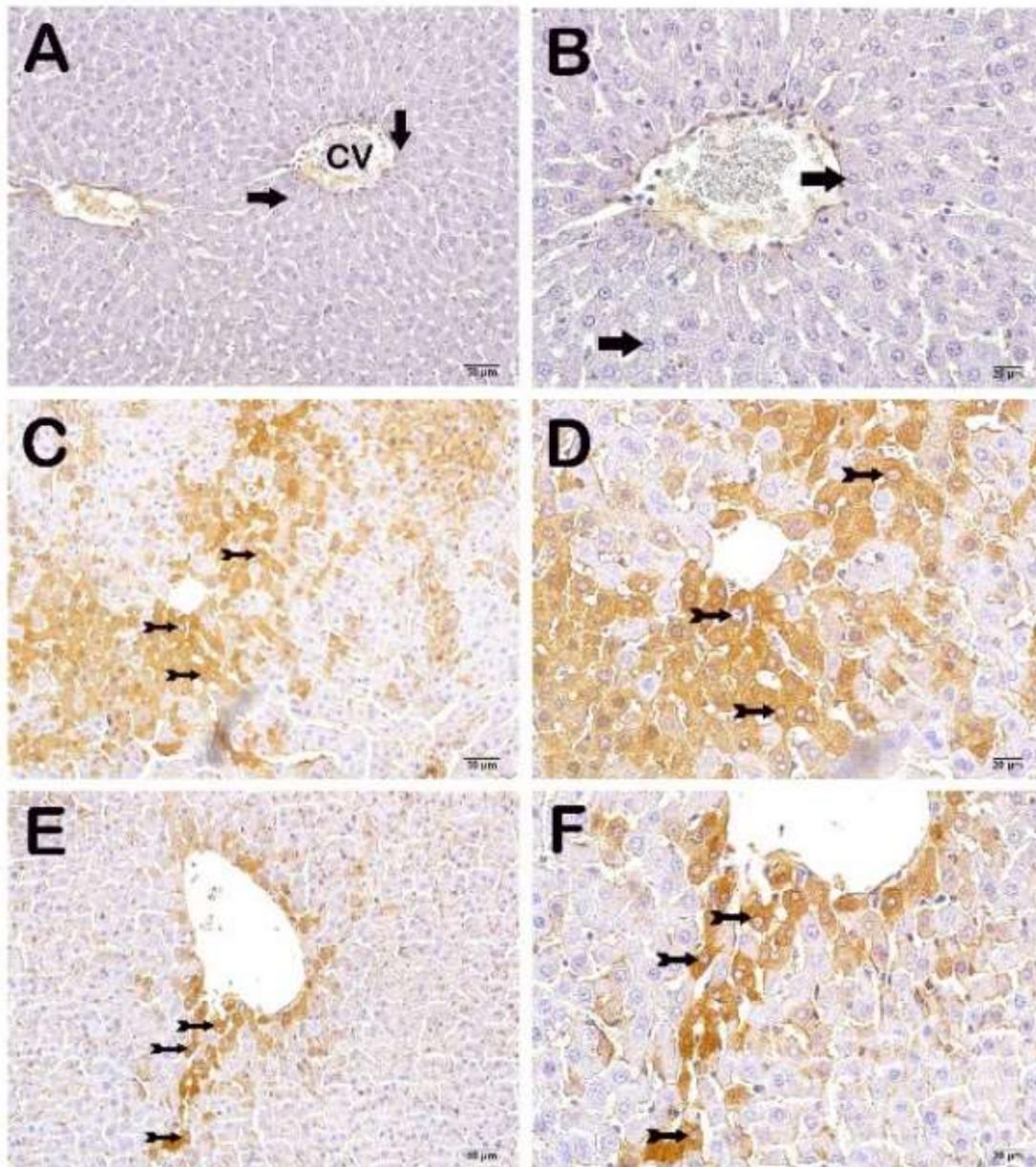


Figure 2: Representative photographs of liver tissue treated with Caspase-3 primary antibody by light microscopic images of sections. A. (x20) – B. (x40): Hepatocytes of normal structure (arrow) in the control group. Central vein (CV) (Caspase-3 positivity score 0.00 ± 0.46). **C. (x20) – D. (x40):** Diffuse apoptotic hepatocytes in the I/R group (tailed arrow) (Caspase-3 positivity score 3.00 ± 0.71). **E (x20) - F (x40):** Although a decrease in apoptotic hepatocytes (tailed arrow) was observed in the Dext treatment group, diffuse normal hepatocyte (arrows) were observed (Caspase-3 positivity score 1.00 ± 0.53).

DISCUSSION

In this study, dexmedetomidine was shown to alleviate liver damage from remote organs due to renal I/R. In our study, the parameters of oxidative stress (MDA and GSH levels) were evaluated by histopathological examination and caspase-3 activity level in the assessment of liver tissue damage. Lee et al. showed histopathologically, that there were necrotic areas in both liver and kidney as secondary organs in their rat study.⁶ Therefore, we planned our study on the same lines.

Various toxic products with lipid peroxidation have been observed after I/R procedures. The resulting protein products may disrupt DNA, and produce mutagenic effects.¹¹ MDA, which is one of the end products of lipid peroxidation, plasma, and tissue levels are accepted as good predictors of oxidative stress and systemic response following I/R and are mostly used in laboratory evaluation in I/R studies.^{9,17}

Liver tissue exhibits much higher GSH enzyme activity compared to other tissues; it is responsible for the cellular antioxidant defense mechanism, however, high GSH activity can be considered as a sign of the elimination of metabolites due to peroxidation and often shows damage caused by reactive oxygen products.^{9,18} Therefore, in many studies, MDA and GSH have been used as indicators to show I/R damage.¹⁹ Hence, we used these two as indicators. The low levels of MDA and GSH in Group-I/R+D suggest that dexmedetomidine was protective against I/R damage. Similarly, Erbatur et al. demonstrated the effect of dexmedetomidine on renal damage secondary to lower extremity I/R in diabetic rats.³ When MDA and GSH levels were evaluated histopathologically, they showed that dexmedetomidine reduced I/R damage.

Kucuk et al. showed that MDA levels were increased in hepatic I/R group in liver I/R study in rats and that MDA had become normal levels by giving dexmedetomidine which had a protective effect.⁹ There was no significant

difference in GSH-Peroxidase levels. It was though that remote organ damage was low because dexmedetomidine had local protective effects, anti-inflammatory, and organ protective effects on not only primary I/R tissues but also remote organs.⁷

This protective effect of dexmedetomidine was also observed in different designed I/R models. In rat intraabdominal sepsis model, Koca et al.¹² showed that dexmedetomidine had renal and lung-protective effects and significant improvement in serum creatine and MDA levels by using dexmedetomidine. Kip et al. investigated MDA and GSH levels in myocardial I/R model in rats, and they showed that dexmedetomidine had protective effects on lung tissue.¹³ In another study, Gu et al. showed that lung tissue damage was developed after Renal I/R and dexmedetomidine reduced this secondary injury.⁷

Yildirim et al. showed that dehydroepiandrosterone had protective effects against liver damage in rats after renal I/R by suppressing the oxidant system and supporting the antioxidant defense system.¹⁹ In our study, MDA levels in liver tissue were increased significantly in the I/R group compared to the control group. On the other hand, MDA levels were decreased significantly in the dexmedetomidine group compared to the I/R group. Dexmedetomidine was shown to reduce reperfusion injury and to protect tissues against cellular damage, which was consistent with the literature.¹⁹

In a study conducted by Erer et al., increased connective tissue around the central vein in the hepatic tissue and degeneration around endothelial cells, and necrotic hepatocytes were observed after myocardial I/R. A decrease in necrosis and apoptosis in hepatocytes was observed by dexmedetomidine administration.⁸ Our study was similar to this study. After I/R, damaged hepatocytes and dilated sinusoids were observed. A decrease in necrotic and apoptotic hepatocytes was observed by dexmedetomidine administration.

The breakdown of DNA due to activation of specific intracellular serine proteases (caspases) is described as apoptosis or programmed cell death.²⁰ Caspase -3 is used to evaluate the effect of dexmedetomidine on apoptosis in renal cells in sepsis and caspase-3 expression is shown to be decreased by dexmedetomidine.¹²

In the rat cerebral I/R model, dexmedetomidine was shown to suppress apoptotic activity.²¹ Similarly, in our study, it was shown histopathologically that caspase-3 activity was increased in liver tissue after renal I/R and then decreased by dexmedetomidine. This result was consistent with the literature we mentioned above.

Different doses (10-50 µg/kg) have been used for the protective effects of dexmedetomidine against I/R. Better protection against renal I/R damage at the dose of 100 µg /kg has been observed.^{22,23} In our study, 100 µg/kg was used for the maximal efficacy of dexmedetomidine in accordance with the literature.

Gonullu et al. observed the protective efficacy of dexmedetomidine against I/R damage in a precondition or postcondition application and the effect of both applications on renal I/R damage was observed histomorphological and histopathologically.²⁴ However, recent studies have emphasized that pre-I/R administration of dexmedetomidine suppresses inflammation and

has better long-term mortality and renoprotective efficacy, so this application has been more preferred (). In our study, dexmedetomidine was administered before ischemia in accordance with current literature.^{3,13}

CONCLUSION

In conclusion, the effect of dexmedetomidine on liver damage was assessed immunologically, biochemically and histopathological after renal ischemic-reperfusion injury and dexmedetomidine administration was found to reduce this damage.

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Conflict of interest:

1. This study was presented as a poster/oral presentation at the 6th Rize Thematic Anesthesia Meeting, 2019, Turkey
2. The authors report no conflicts of interest or financial support

Authors Contribution:

KS - designing and conducting the trial
SA - manuscript editing of the study
TL, MT - histopathological evaluations for the study
OA- Final approval of the study
YA - biochemical tests for the study
ST, AZ – *Concept, manuscript editing*

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