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ORIGINAL ARTICLE

The protective effects of tadalafil on renal damage following ischemia reperfusion injury in rats

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Abstract Ischemia-reperfusion injury can cause renal damage, and phosphodiesterase inhibitors are reported to regulate antioxidant activity. We investigated the prevention of renal damage using tadalafil after renal ischemia reperfusion (I/R) injury in rats. A total of 21 adult male Wistar albino rats were randomly divided into three groups of seven, including Group 1-control, Group 2-I/R, and Group 3-tadalafil + I/R group (I/R-T group) received tadalafil intraperitoneally at 30 minutes before ischemia. Inducible nitric oxide synthase, endothelial nitric oxide synthase, malondialdehyde, and total antioxidant capacity levels were evaluated, and histopathological changes and apoptosis in the groups were examined. Tadalafil decreased malondialdehyde levels in the I/R group and increased the total antioxidant capacity level. Histopathological and immunohistochemical findings revealed that tadalafil decreased renal injury scores and the ratios of injured cells, as measured through apoptotic protease activating factor 1, inducible nitric oxide synthase, and endothelial nitric oxide synthase levels. We suggest that tadalafil has protective effects against I/R-related renal tissue injury.

Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

Renal ischemia leads to the depletion of cellular energy, accumulation of intracellular sodium, calcium, reactive oxygen species (ROS), and activation of multiple enzyme systems, including proteases, nitric oxide synthases (NOSs), phospholipases, and endonucleases; these result in cell damage and death [1]. Following reinstitution of blood flow, the final stage of injury occurs during reperfusion, called reperfusion injury (I/R injury). I/R injury is an immediate nonspecific inflammatory response [2].

Nitrogen oxide (NO) is an important mediator of the physiological and pathological processes during renal I/R injury [1,2]. Renal reperfusion following ischemia activates NOS and increases its expression [3]. Phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil, tadalafil, and vardenafil, comprise the first-line therapy for treating erectile dysfunction in males. Inhibiting phosphodiesterase also decreases renal injury [4–7].

In this study, we investigated the effect of tadalafil on renal I/R injury.

Methods

This study was approved by the Ethics Council of Bülent Ecevit University Medical Faculty, Zonguldak, Turkey.

Twenty-one Wistar albino rats (weight, 400–450 g) were divided into three groups. General anesthesia was administered with 40 mg/kg ketamine hydrochloride (Ketalar, Eczacıbaşı, Turkey) with intraperitoneal injection. An approximate 3 cm skin incision was made in the abdominal region. The groups were divided as the following. Group 1, Control group: No treatment was given. The abdominal median laparotomy was conducted, blood was taken, and a bilateral nephrectomy was performed. Group 2, I/R group: The right kidney pedicle was clamped for 1 hour with a nontraumatic microvascular clamp (bulldog clamp), and the kidney was subjected to ischemia. No clamp was put on the left kidney pedicle. Following ischemia, the right kidney pedicle clamp was removed, and the kidney was perfused for 1 hour. Blood was then taken, and a bilateral nephrectomy was performed. Group 3, Tadalafil + I/R group (I/R-T group): Before subjecting the rat to ischemia, a 1 mL suspension of 10 mg/kg tadalafil was injected intraperitoneally. Then, the right kidney pedicle was clamped for 1 hour, as described for the I/R group. Following ischemia, the right kidney was subjected to 1-hour reperfusion by removing the clamp from the right kidney pedicle. Blood was then collected, and a bilateral nephrectomy was performed.

Tissue sampling

At the end of the experiment, the blood samples were centrifuged at 500*g* for 3 minutes and stored at −80°C for biochemical evaluation of malondialdehyde (MDA) and total antioxidant capacity (TAC).

After cutting each kidney into two parts, one part was stored at −80°C for biochemical evaluations, and the other was fixed in 10% formalin for histological studies.

Biochemical analyses

Preparation of tissue samples

Tissues were homogenized on ice with an homogenizer (Ultra Turrax Type T25-B, IKA Labortechnic, Germany) by adding 0.1M Tris-hydrochloride buffer solution including 0.1% Tween 80 [8]. Then, the homogenates were centrifuged at 800*g* and 4°C. Protein concentrations of supernatants were assessed using the Lowry et al [9] method.

MDA working procedure

Serum and tissue MDA levels were evaluated with high-performance liquid chromatography (HPLC) using an Agilent 1200 HPLC (Agilent Technologies, Munchen, Germany). MDA was measured using commercial immunodiagnostic kits (Merck, Bensheim, Germany). Solutions of 1,1,3,3-tetraethoxypropane (TEP), trichloroacetic acid, 2-thiobarbituric acid, and dinitrophenylhydrazine (DNPH), sodium hydroxide, perchloric acid, hydrochloric acid, sulfuric acid, methanol, and ethanol were obtained from Merck (Frankfurter, StraBe 250, Germany). Acetonitrile was obtained from Sigma-Aldrich (Frankfurter, StraBe 250, Germany). Fifty μL of 6M sodium hydroxide was added to 0.250 mL serum and then incubated in a 60°C water bath for an hour. The hydrolyzed sample (0.125 mL) was acidified with 0.125 mL of 35% (v/v) perchloric acid. After centrifugation (500*g*) for 10 minutes, 0.250 mL supernatant was mixed with 25 μL of 5mM DNPH solution and incubated in dark for half an hour. One hundred μL of the reaction mixture was directly injected into HPLC system [10]. MDA standard was prepared by dissolving 25 μL TEP in 100 mL of water to give a 1mM stock solution. Working standard was prepared by dilution of 1 mL stock solution in 50 mL of 1% sulfuric acid and incubation for 2 hours at room temperature. The resulting MDA standard of 20 μmol/L was further diluted with 1% sulfuric acid to yield different concentration. The 0.250 mL of standard was mixed with 25 μL DNPH solution and incubated in dark for 30 minutes. One hundred microlitres of the reaction mixture was directly injected into HPLC system. The analytical column was 125 mm × 4 mm ODS-2 C18 reserve phase column with particle size of 5 μm (Thermo, Theale/Berkshire, UK). The mobile phase was acetonitrile-distilled water (34:66, V/V) containing 0.2% (V/V) acetic acid. All separations were performed at isocratic conditions with a flow rate of 1 mL/min. MDA peaks were determined according to its retention time and confirmed by spiking with added exogenous standard. Concentrations of MDA were calculated from standard curve prepared from TEP.

The detection limit of this procedure was 0.15μM and linearity was 100μM.

TAC working procedure

The TAC measurement principle is based on the reaction of antioxidants with hydrogen peroxide in the sample. The antioxidants sample was taken, with the same amount of hydrogen peroxide. Antioxidants in the sample bind to the hydrogen peroxide, and the increased hydrogen peroxide converts TMB (3,3′,5,5′-tetramethylbenzidine) to a colored

compound by an enzymatic reaction. The newly formed colored compound is assayed with a photometric procedure. The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay to determine the amount of human TA in a biological sample (MyBioSource, San Diego, CA, USA).

According to the standards' concentration and the corresponding optical density values, the standard curve linear regression equation was calculated, and then applied to the optical density values of the sample on the regression equation to calculate the corresponding sample's concentration.

TMB is a noncarcinogenic substitute (Ames test negative) for benzidine1, suitable as a peroxidase substrate for use in enzyme-linked immunosorbent assay procedures. The substrate produces a soluble end product that is pale blue in color and can be read spectrophotometrically at 370 nm or 620–650 nm. The TMB reaction may be stopped with 2M sulfuric acid (resulting in a yellow color), and read at 450 nm.

Pathological evaluations

Histomorphological evaluation

The hematoxylin and eosin stained sections were evaluated for histological changes, such as loss of the nucleus, cell swelling, cytoplasmic vacuolization, brush border loss, tubular dilatation, hyaline caste formation in the tubular lumen, and interstitial congestion, and edema in the kidney tubules. A semiquantitative evaluation of the histopathological changes in the kidney tubules was carried out according to the following criteria: 0 = no change; 1 = change of 0–10%; 2 = change of 11–25%; 3 = change of 26–50%; 4 = change of 51–75%; and 5 = change of 76–100%.

Immunohistochemical evaluation

Cytoplasmic staining for inducible nitric oxide synthase (iNOS), endothelial NOS (eNOS), and apoptotic protease activating factor 1 (APAF-1) was performed, and the ratio of immunopositive cells to the total number of tubular cells was evaluated. A semiquantitative evaluation according to staining intensity was carried out according to the following criteria: 0 = no staining; 1 = minimal; 2 = moderate; and 3 = strong staining.

The semiqualitative evaluation was performed according to the following criteria based on the rate of immunopositive cells: 0 = no reaction; 1 = 1–9% of the cells reacted; 2 = 10–49% of the cells reacted; and 3 = $\geq$ 50% of the cells reacted.

The statistical analyses were carried out using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). The Mann–Whitney *U* test was used to compare the tissue and blood MDA and TAC levels, as well as the histopathological and immunohistochemical scores of the groups. A value of $p < 0.05$ indicated statistical significance.

Results

MDA values

Right kidney tissue MDA levels were significantly increased in the I/R group versus the control group ($p = 0.011$; Table 1).

The right kidney tissue MDA values were significantly higher in the I/R-T group than those in the control group ($p = 0.026$). However, no significant difference was observed between I/R group and I/R-T group ($p > 0.05$; Table 1).

Tissue MDA values in the left kidney were not different among the three groups ($p > 0.05$; Table 1).

Blood MDA levels in the control group were significantly lower than those in both the I/R ($p = 0.001$) and I/R-T groups ($p = 0.001$). Blood MDA levels in the I/R-T group were significantly lower than those in the I/R group ($p = 0.017$; Table 1).

TAC values

TAC levels in right kidneys of the I/R group were significantly lower than those in the control group ($p = 0.038$). However, no differences were observed between the I/R-T and control groups for right kidney tissue ($p > 0.05$; Table 2).

Additionally, no differences were observed in the TAC values of the left kidney among the groups ($p > 0.05$; Table 2).

Blood TAC values in the I/R group were significantly lower than those in the control group ($p = 0.026$). No significant difference was found between the I/R-T group and the control group ($p > 0.05$); however, TAC levels were significantly higher in the I/R-T group compared with the I/R group ($p = 0.026$; Table 2).

Table 1 Renal tissue and blood levels of malondialdehyde (μmol/g tissue).

	Right kidney MDA	Left kidney MDA	Blood MDA
Group control ($n = 7$)	2.71 ± 1.37*,**	2.36 ± 1.79	1.01 ± 0.61*,**
Group I/R ($n = 7$)	6.30 ± 3.03	3.91 ± 3.24	7.53 ± 1.71
Group I/R-T ($n = 7$)	5.06 ± 2.11	1.98 ± 0.47	4.72 ± 1.79***

Data are presented as mean ± standard deviation.
*$p < 0.05$ (Group control vs. Group I/R), Mann–Whitney *U* test.
**$p < 0.05$ (Group control vs. Group I/R-T), Mann–Whitney *U* test.
***$p < 0.05$ (Group I/R-T vs. Group I/R), Mann–Whitney *U* test.
I/R = ischemia/reperfusion; MDA = malondialdehide; T = tadalafil.

Table 2 Renal tissue and blood sample total antioxidant capacity (μmol/g tissue).

	Right kidney TAC	Left kidney TAC	Blood TAC
Group C ($n = 7$)	59.41 ± 34.15*	39.20 ± 20.88	342.29 ± 31.12*
Group I/R ($n = 7$)	30.61 ± 7.77	26.08 ± 18.02	265.29 ± 76.99
Group I/R-T ($n = 7$)	61.97 ± 58.48	58.64 ± 45.89	339.57 ± 23.59**

Data are presented as mean ± standard deviation.
*$p < 0.05$ (Group C vs. Group I/R), Mann–Whitney *U* test.
**$p < 0.05$ (Group I/R-T vs. Group I/R), Mann–Whitney *U* test.
C = control; I/R = ischemia-reperfusion; T = tadalafil; TAC = total antioxidant capacity.

Histopathological findings

The right kidneys of five rats in the I/R group had histopathological change levels of 51–75% and two had levels of 76–100%. Histopathological changes, such as loss of the nucleus, cell swelling, cytoplasmic vacuolization, brush border loss, tubular dilatation, hyaline cast formation, interstitial congestion, and edema in tubular structures, were observed.

The structural histopathological changes in the I/R group were significantly different compared with those in the control group ($p = 0.01$).

Significant histopathological structural defects were observed in the I/R-T group compared with those in the control group ($p = 0.001$). However, the damage was significantly less in the I/R-T group compared with the I/R group ($p = 0.026$; Figure 1).

Immunohistochemical findings

A minimal degree of cytoplasmic staining for iNOS, eNOS, and APAF-1 was observed in bilateral kidneys of the control group and the left kidneys in the I/R and I/R-T groups (Table 3).

The right kidneys in the I/R group showed moderate cytoplasmic staining for APAF-1 in six kidneys and strong staining in one kidney, moderate iNOS staining in six kidneys, and minimal staining in one kidney, and minimal staining for eNOS in all kidneys.

All right kidneys in the I/R-T group showed moderate staining for APAF-1; there was minimal staining for eNOS in one kidney and moderate staining in six kidneys.

The tubular cells in the right-side kidneys showed significantly higher cytoplasmic staining for APAF-1 in the I/R group and I/R-T group than in the control group

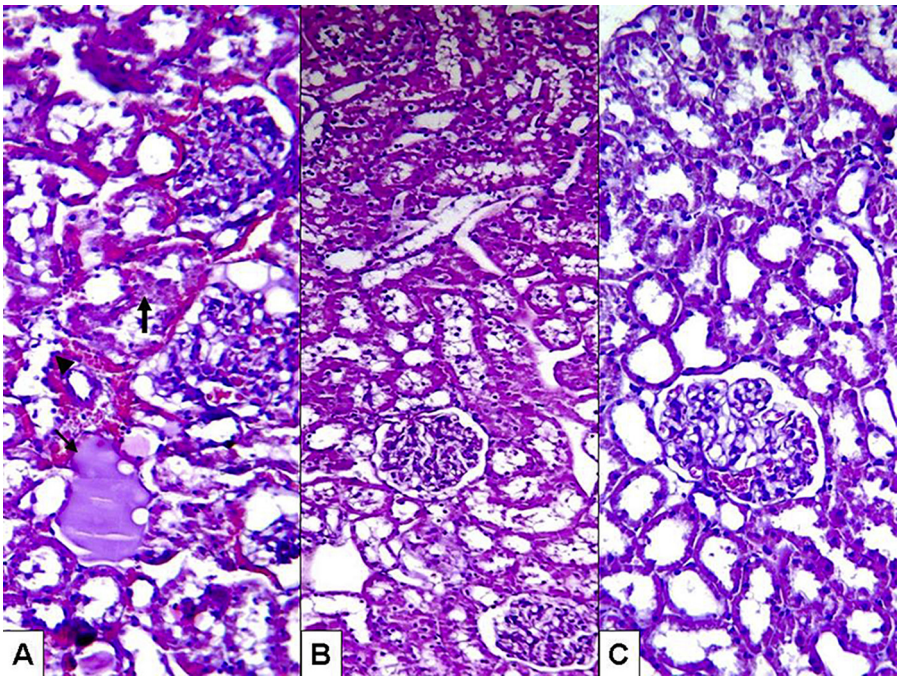

Figure 1. Histopathological changes in right-sided kidney tubules. (A) I/R group: loss of nuclei, cell swelling (thick arrow), cytoplasmic vacuolization, brush border loss, tubular dilatation (arrow head), hyaline cast formation (thin arrow), interstitial congestion, and edema. (B) I/R-T group: decreased histopathological changes. (C) Control group: normal renal parenchyma. Hematoxylin and eosin stain: (A) × 200; (B) × 100; (C) × 200. I/R = ischemia reperfusion; T = tadalafil.

Table 3 Cytoplasmic staining for apoptotic protease activating factor-1, inducible nitric oxide synthase, and endothelial nitric oxide synthase.

Group	Right kidney			Left kidney		
	APAF-1	iNOS	eNOS	APAF-1	iNOS	eNOS
Control ($n = 7$)	0.71 ± 0.48*,**	1.14 ± 0.37*	1.28 ± 0.48*	1.00	1.00	1.00
I/R ($n = 7$)	2.57 ± 0.53	1.85 ± 0.37	2.57 ± 0.53	1.00	1.14 ± 0.37	1.00
I/R-T ($n = 7$)	1.71 ± 0.48***	1.00 ± 0.00***	1.71 ± 0.48***	1.00	1.00	1.00

Data are presented as mean or mean ± standard deviation.
*$p < 0.05$ (Group control vs. Group I/R), Mann–Whitney *U* test.
**$p < 0.05$ (Group control vs. Group I/R-T), Mann–Whitney *U* test.
***$p < 0.05$ (Group I/R-T vs. Group I/R), Mann–Whitney *U* test.
APAF-1 = apoptotic protease activating factor-1; eNOS = endothelial nitric oxide synthase; iNOS = inducible nitric oxide synthase.

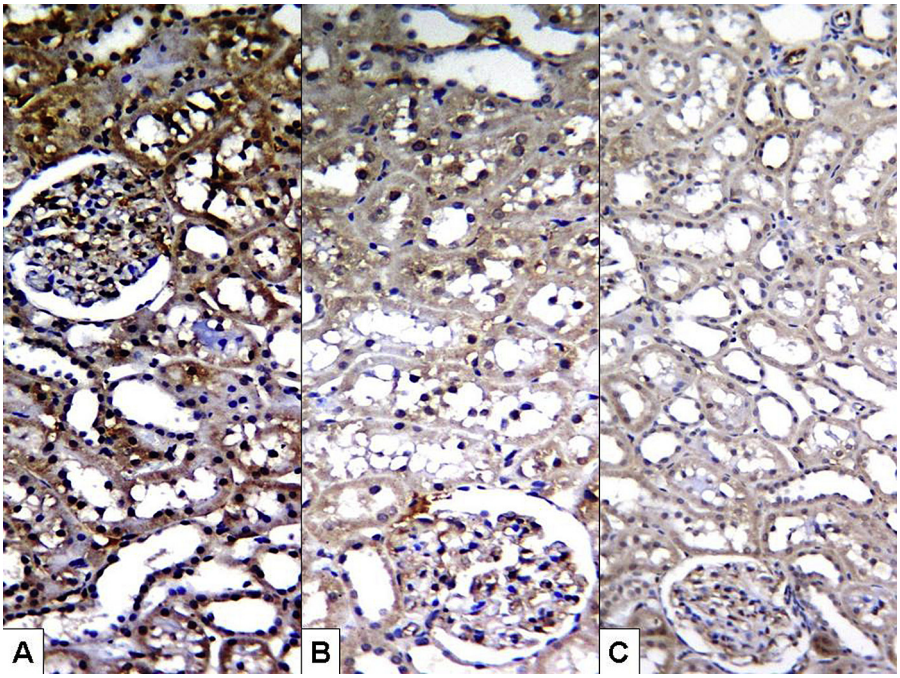

Figure 2. Apoptotic protease activating factor-1 immunostaining for apoptosis in right-sided kidney tubules. (A) I/R group: strong cytoplasmic staining. (B) I/R-T group. (C) Control group: minimal cytoplasmic staining. Biotin-streptavidin peroxidase system, diaminobenzidine: (A) × 200; (B) × 200; (C) × 200. I/R = ischemia reperfusion; T = tadalafil.

($p = 0.001$ and $p = 0.011$, respectively). APAF-1 staining in the I/R-T group was lower than that in the I/R group ($p = 0.026$; Figure 2, Table 3).

The tubular cells in the right-side kidneys showed higher cytoplasmic staining for iNOS in the I/R group than that in the control group ($p = 0.026$; Figure 3, Table 3).

No differences were observed between the control group and I/R-T group ($p > 0.05$).

Cytoplasmic staining scores for iNOS in the I/R-T group were lower than those in the I/R group ($p = 0.004$).

Cytoplasmic staining for eNOS was lower in the control group than that in the I/R group ($p = 0.004$); however, no difference was observed between the I/R-T group and control group ($p > 0.05$). Cytoplasmic staining for eNOS in the I/R-T group was lower than that in the I/R group ($p = 0.026$; Figure 4, Table 3).

Immunopositive tubular cell rates

INOS immunoreactivity in tubular cell structures of the left-sided kidneys in the I/R group revealed six kidneys with a rate of 1–9% and one with a rate of 10–49%. For eNOS, five left-sided kidneys had a rate of 1–9%, and two had a rate of 10–49%. All left-sided kidneys in the I/R group showed a 1–9% APAF-1 staining rate.

INOS immunoreactivity in tubular cell structures in the I/R-T group revealed five left-sided kidneys with a rate of 1–9% and two with a rate of 10–49%. All left-sided kidneys in the I/R-T group exhibited a 1–9% APAF-1 staining rate.

The ratio of immunopositive cells in tubular structures of right-sided kidneys was also evaluated. INOS immunoreactivity in tubular cell structures in right-sided kidneys of the I/R group revealed five kidneys with a rate of 10–49% and two

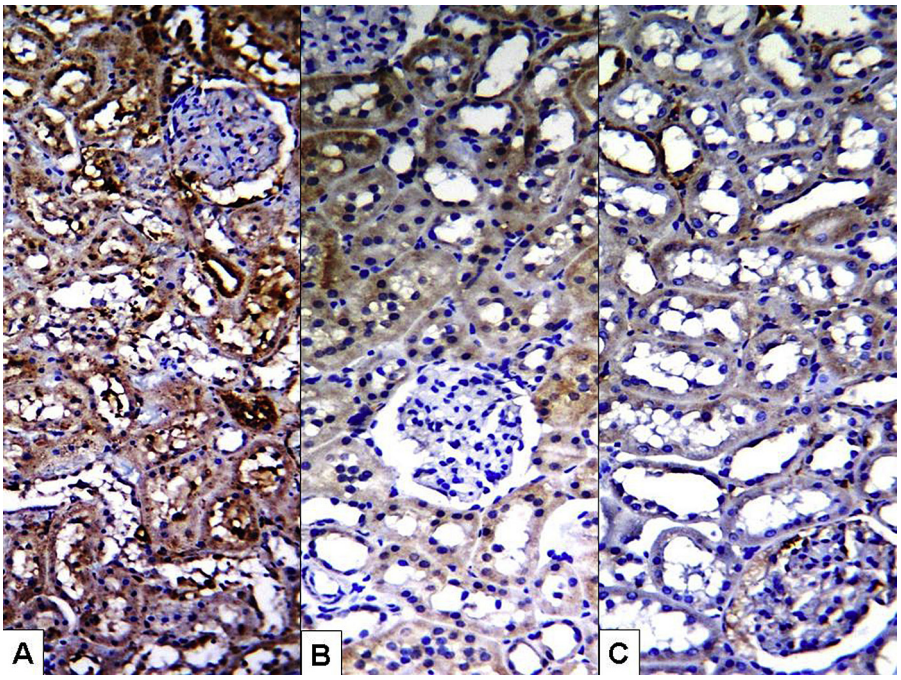

Figure 3. Endothelial nitric oxide synthase immunostaining in right-sided kidney tubules. (A) I/R group: strong cytoplasmic reaction. (B) I/R-T group. (C) Control group: minimal cytoplasmic reaction. Biotin-streptavidin peroxidase system, diaminobenzidine: (A) × 200; (B) × 200; (C) × 200. I/R = ischemia reperfusion; T = tadalafil.

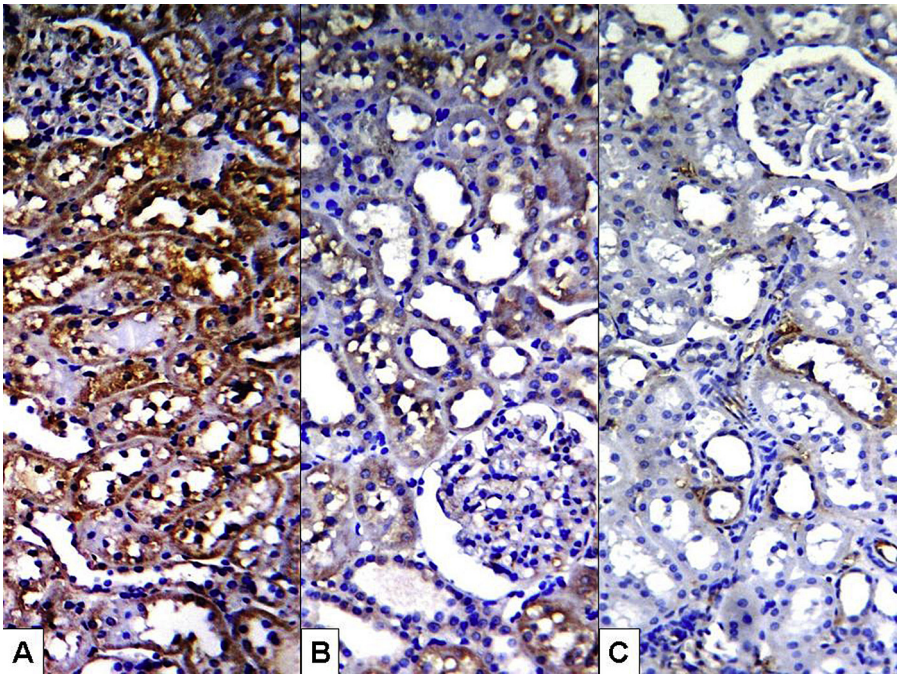

Figure 4. Inducible nitric oxide synthase immunostaining in right-sided kidney tubules. (A) I/R group: strong cytoplasmic staining. (B) I/R-T group. (C) Control group: minimal cytoplasmic staining. Biotin-streptavidin peroxidase system, diaminobenzidine: (A) × 200; (B) × 200; (C) × 200. I/R = ischemia reperfusion; T = tadalafil.

kidneys with a rate of $\geq$ 50%. For eNOS, two right-sided kidneys had a rate of 10—49%, and five kidneys had rates $\geq$ 50%.

By contrast, APAF-1 immunoreactivity in right-sided kidney tissues in the I/R-T group showed a rate of 1—9% in two kidneys and 10—49% in five kidneys. INOS immunoreactivity in right-sided kidney tissues in the I/R-T group revealed that three kidneys had a rate of 1—9% and four kidneys had a rate of 10—49%. For eNOS, 10—49% immunopositive tubular cell structures were observed in all right-sided kidneys.

No significant difference in the immunopositive cell rates of APAF-1, iNOS, and eNOS, was observed between left- and right-sided kidneys ($p > 0.05$, Table 3).

The APAF-1 immunopositive tubular cell ratio in the right-sided kidneys in the I/R group was significantly higher than that in the control group ($p = 0.002$). Also it was reduced significantly in I/R-T group ($p = 0.038$) compared with the I/R group (Table 3).

The iNOS immunopositive tubular cell ratios in right-sided kidneys in the I/R group were significantly higher than those in the control group ($p = 0.002$). No difference was observed in the iNOS immunopositive tubular cell ratio between the control group and I/R/-T groups ($p > 0.05$, Table 3).

The eNOS immunopositive tubular cell ratios were significantly higher ($p = 0.026$) in the I/R group compared with those in the control group and it was lower in I/R-T group compared with those in the I/R group ($p = 0.026$, Table 3).

Discussion

Reperfusion following renal ischemia may cause acute inflammation and secondary tissue damage. Development of ROS at this stage may increase damage. Endogenous antioxidant enzymes exert protective effects on cells by decreasing the effects of ROS. The amounts of these enzymes differ depending on the severity of the oxidative stress [3]. In particular, vascular endothelial damage develops during renal ischemia [1,2]. While NO is released by the renal vascular endothelium and the balance between NO and endothelin-1 is shifted. This decreases the elasticity of the renal vascular endothelium and thus increases vascular resistance [2]. NO is a mediator that acts through cyclic guanosine monophosphate (cGMP) [6,7,11].

Several studies have examined the effect of PDE5 inhibitors on renal I/R damage. Chintala et al [11] investigated the antithrombin effect of zaprinast, a PDE5 selective inhibitor, in rats treated with I/R. Guan et al [4] showed that zaprinast increases renal blood flow by stimulating intracellular cGMP in rats undergoing kidney failure. Liedo-Garcia et al [6] observed that kidneys recover during the early post-transplant period with warm ischemia.

Oruç et al [5] reported that when sildenafil is administered to I/R damaged kidneys during the ischemic phase, I/R damage was corrected due to reduced leukocyte infiltration. Vardenafil also plays a protective role in I/R damage; however, few studies have addressed the effects of tadalafil on I/R damage [12,13]. Tadalafil is a vasoactive agent used to treat erectile dysfunction that has a different chemical structure than sildenafil and vardenafil [14,15]. Tadalafil reaches maximum plasma concentration in 2 hours, and its plasma half-life is four-fold longer (17.5 hours) than those of sildenafil and vardenafil (4 hours) [15–17]. Because of this prolonged effect, it is considered more advantageous for lowering vascular resistance and treating ischemia.

Antiapoptotic properties of PDE5 inhibitors have been reported [18]. Because sildenafil inhibits apoptosis by increasing cytochrome-c secretion and the Bcl-2/Bax ratio through NO [19], tadalafil may work through the same mechanisms.

Akgül et al [18] evaluated the effects of sildenafil, vardenafil, and tadalafil on renal apoptosis in a unilateral ureteral obstruction model. They determined that all three PDE5 inhibitors were effective in reducing the number of apoptotic cells [18]. In our study, the significantly lower APAF-1 level in the I/R-T group supports this finding.

The role of NO in renal damage remains debatable. NO exerts both proapoptotic and antiapoptotic effects [18], depending on the conditions. In previous studies, iNOS and eNOS expression were reported to increase during testicular ischemia reperfusion, and administration of tadalafil reduced this increase [20–24]. Increased iNOS and eNOS expression causes a rise in NO to toxic levels, resulting in testicular germ cell apoptosis [20,25].

Experimental studies have shown that high NO production leads to peroxynitrite formation. Peroxynitrite, a potent and aggressive cellular oxidant agent, causes the formation of 3-nitro-L-tyrosine [26].

Choi et al [27] reported that sildenafil lowers renal I/R damage by increasing iNOS and eNOS levels and maintaining NO at a particular level. Though this finding contradicts the findings in our study, it suggests that NO is protective at normal levels but has a toxic effect at high levels, and therefore, it regulates NO levels with PDE5 inhibitors. However, Elrod et al [28] reported that the protective effect of sildenafil may be independent of the NO/cGMP pathway.

Our results showed significant increases in eNOS and iNOS levels in the kidney tubular epithelium during renal I/R, and these levels were significantly lower in the group treated with tadalafil.

Guzeloglu et al [13] examined the effect of tadalafil on renal I/R damage and histopathological and TAC changes in tissue. Tadalafil regulates thrombocyte functions during I/R damage and intracellular calcium ion levels [11]. Guzeloglu et al [13] reported that TAC levels increased in the group treated with tadalafil but that total oxidant capacity levels were not different from those in a placebo group. They observed that tadalafil exerted a protective effect on tissues by increasing the antioxidant capacity. Similarly, we observed that blood TAC levels decreased significantly in the I/R group, but that this decrease was prevented by administering tadalafil 1 hour before ischemia (I/R-T group).

MDA is the end product of lipid peroxidation and is a well-known marker for free radical formation in post-ischemic tissue. Serarslan et al [29] determined that tadalafil lowers MDA and superoxide dismutase levels but increases levels of the antioxidant glutathione peroxide during spinal cord damage. In our study, blood MDA levels were decreased and TAC levels were increased in the tadalafil-administered group, suggesting a protective effect. Tissue MDA levels were lower in the I/R-T group than those in the I/R group, though the difference was not significant. Similarly, tissue TAC levels increased with tadalafil administration; however, the increase was not significant when compared to that in the I/R group. We believe that tadalafil should be injected intraperitoneally, rather than orally, and that its duration of action must be kept short to maximize efficacy.

A number of histological studies of I/R damage to kidneys and the effects of tadalafil have been conducted.

Guzeloglu et al [13] determined that kidney tubular necrosis, intracytoplasmic vacuolization in the tubular epithelium, congestion, and mononuclear cell infiltration in the interstitial region were minimal in a tadalafil-treated group of I/R rats [13].

In our study, the histopathological changes included loss of nuclei, cell swelling, cytoplasmic vacuolization, brush border loss, tubular dilatation, hyaline cast formation in the tubule lumen, interstitial congestion, and edema in the kidney tubules of the cortex and medullary region of rats treated with I/R. This renal damage was reduced in the tadalafil-treated group compared with that in the I/R group, with a meaningful decrease in renal damage scores.

Conclusion

Because tadalafil reduced renal damage, it could be a good alternative when clamping the aorta, particularly at the level of the renal artery. Although animal studies do not completely mimic the pathophysiology of renal I/R the need for novel treatment strategies for this condition is increasing because of the high mortality and morbidity rates. This need will be met by researching the effectiveness of agents that can reduce reperfusion damage.

We believe that studies on the protective effects of tadalafil on I/R damage that include administration of the drug at different times and by different methods will lead to the proper application of tadalafil in clinical practice.

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