ORIGINAL ARTICLE

The efficiency of oxerutin on apoptosis and kidney function in rats with renal ischemia reperfusion injury

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ABSTRACT

BACKGROUND: Background: Renal ischemia-reperfusion injury (RIRI) is the most frequent cause of acute renal failure in clinical conditions such as trauma and shock as well as renal surgeries. Oxerutin is a member of the flavonoid family and possesses antioxidant properties. The aim of this study was to investigate whether oxerutin has protective effects on RIRI.

METHODS: Twenty-eight male Wistar albino rats were randomly divided into three groups: sham control group (n=8), RIRI group (n=10), and RIRI + oxerutin group (n=10). RIRI was achieved by clamping the left renal artery for 30 min, followed 1-h reperfusion period. Thereafter, blood samples and left kidney tissue samples were taken for histopathological and biochemical examination. Blood urea nitrogen (BUN), urea, creatinine, and cystatin C levels, which are indicators of kidney function, as well as tumor necrosis factor-alpha, which is an indicator of inflammation were analyzed in blood samples. Total antioxidant status and total oxidant status (TOS), which are indicators of oxidative stress were analyzed on renal tissues. The apoptotic index, an indicator of kidney damage, as well as histopathological changes were evaluated on renal tissues.

RESULTS: The apoptotic index, TOS, tumor necrosis factor-alpha, BUN, and urea levels were lower in the RIRI + oxerutin group than in the RIRI group ($p<0.05$). The results demonstrated that the histopathological and biochemical properties of oxerutin protected rats from RIRI.

CONCLUSION: The findings obtained in this study show that prophylactic administration of oxerutin has protective effects on apoptosis and renal failure caused by RIRI. Therefore, oxerutin can be used as an effective prophylactic agent in the treatment of RIRI.

Keywords: Acute kidney injury; antioxidants; apoptosis; oxerutin; oxidative stress.

INTRODUCTION

Renal ischemia–reperfusion (I/R) injury (RIRI) remains the leading cause of acute renal failure (ARF) and is associated with increased morbidity and mortality rates. It is also associated with an increased treatment cost in both adult and pediatric patients.[1] RIRI is the most frequent cause of ARF in clinical procedures such as renal transplantations, nephron-sparing surgeries, and renal artery and suprarenal aortic aneurysm repairs as well as shock and trauma.[2]

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The precise mechanisms and pathophysiology of RIRI are still not fully understood. Reperfusion of ischemic kidneys increases the harmful effect of early ischemic injury due to the release of reactive oxygen species (ROS) and accumulation of activated neutrophils.[3] Although the kidneys have enzymatic antioxidant defense mechanisms to cope with this potential damage, free radicals lead to rapid depletion of endogenous antioxidant resources.[3,4] A study reported that the harmful effects of ROS can be reduced or eliminated completely by exogenous antioxidant substances.[4] The effects of antioxidant supplementation have been explored in detail. Studies have shown that antioxidant-containing diets prevent damage caused by free oxygen and nitrogen radicals.[4,5] Thus, appropriate prophylaxis might be a rational approach to prevent RIRI.[1]

Flavonoids are a large group of polyphenolic compounds with natural antioxidant properties and are present in vegetables, fruits, etc.[6] Their protective effects are attributed to their free radical-scavenging and metal ion-chelating activities.[6] Oxerutin, which has been the preferred therapeutic agent in chronic venous insufficiency, diabetic retinopathy, micro-angiopathy, and hemorrhoidal disease, is a member of flavonoids. Thus, this study aimed to investigate the possible protective effects of oxerutin on RIRI.

MATERIALS AND METHODS

Male Wistar albino rats weighing 200–300 g (n=28) were used in this experimental study, which was conducted at the Suleyman Demirel University Experimental Animal Laboratory. Rats were housed in a room maintained at 25°C±1°C with 55% relative humidity. They were given food and water ad libitum.

The study was conducted after obtaining approval from Suleyman Demirel University Ethics Review Committee. All experiments were performed based on the ethics principles reported in the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

RIRI Model and Study Groups

The rats were randomly divided into three groups. The same surgical procedure was performed for all groups. The rats were anesthetized by intraperitoneal injection of ketamine (40 mg/kg) and xylazine (10 mg/kg). The abdomen was shaved, povidone-iodine was applied, and midline laparotomy was performed. The small intestine was wrapped in gauze moistened with 3 ml of 0.9% sodium chloride (NaCl; 36–37°C) and placed outside the operating field.

Sham Control Group (no I/R, n=8): Two doses of 5 ml of isotonic solution (first dose, 24 h before the procedure; second dose, 2 h before the procedure) were administered to the rats by oral gavage. After making the incision for laparotomy, the left and right kidneys were exposed and isolated. Nothing was applied to the left renal pedicle for 30 min. Then, a moist sponge was layered on the laparotomy incision and left for 1 h. Thereafter, blood samples were collected, the left kidney was removed, and the rats were sacrificed.

RIRI Group (n=10): Two doses of 5 ml of isotonic solution (first dose, 24 h before the procedure; second dose, 2 h before the procedure) were administered to the rats by oral gavage. After making the incision for laparotomy, the left and right kidneys were exposed and isolated. A nontraumatic clamp was applied to the left renal pedicle for 30 min. During the 1-h reperfusion period, a moist sponge was layered on the laparotomy incision. Thereafter, blood samples were collected, the left kidney was removed, and the rats were sacrificed.

RIRI + Oxerutin Group (n=10): Two doses of oxerutin contained in 5 ml of isotonic solution (first dose, 24 h before the procedure; second dose, 2 h before the procedure) were administered to the rats by oral gavage at a dose of 500 mg/kg. After making the incision for laparotomy, the left and right kidneys were exposed and isolated. A nontraumatic clamp was applied to the left renal pedicle for 30 min. During the 1-h reperfusion period, a moist sponge was layered on the laparotomy incision. Thereafter, blood samples were collected, the left kidney was removed, and the rats were sacrificed.

Biochemical Analyses

A total of 90 min after the left kidney was exposed by laparotomy, 5 ml of blood was drawn from the inferior vena cava and collected into heparinized tubes. Serum urea and creatinine levels were measured by a spectrophotometric method using a commercial kit (Beckman Coulter® AU 5800, USA). Blood urea nitrogen (BUN) levels were calculated from urea values. The serum levels of tumor necrosis factor-alpha (TNF-α) and cystatin C (Cys C) were determined via enzyme-linked immunosorbent assay using commercial kits (BioVendor, Brno, Czech Republic and Invitrogen, Camarillo, CA, USA). All assays were studied twice, and the mean value was recorded.

A half of the left kidney was washed with 0.9% NaCl and stored at −80°C until homogenization. Kidney tissues were homogenized with 1:10 phosphate tamponade at two steps using a homogenizer (Janke and Kunkel Ultra-Turrax® T25, Germany) and a sonicator (UW-2070, Bandelin Electronic GmbH and Co, Germany). The total antioxidant status (TAS) and total oxidant status (TOS) of the tissues were analyzed using status assay kits (Reel Assay Diagnostics, Turkey) in accordance with the modified Erel method.[7,8] Protein levels of the homogenates were measured using spectrophotometry (Beckman Coulter® AU 5800, USA). TAS and TOS results were expressed as mmol Trolox Eq/gr and μmol H_2O_2 Eq/gr, respectively.

Histopathological Analyses and TUNEL Assay to Detection of Apoptotic Cells

A half of the left kidney was stored in 10% neutral formaldehyde for histopathological examination. Tissues fixed

in formalin were sliced into 4–5-μm-thick sections, and the sections were stained with hematoxylin–eosin and examined under a light microscope (Nikon, 400×). In the histological analysis, inflammation, tubular epithelial cell flattening, cytoplasmic vacuolization, cell necrosis–ischemic changes, and tubular lumen obstruction were investigated; these changes were graded as absent/mild (0), moderate (+), or severe (++).[9] After the deparaffinization protocol and antigen retrieval procedure, the slides were examined under a microscope to detect and quantify apoptosis using an in situ cell death detection kit (Roche Diagnostics GmbH, Germany).

Statistical Analyses

SPSS version 15.0 Data Analysis System (SPSS Inc., Chicago, IL, USA) was used for data analysis. Normal distribution and homogeneity tests were performed on all data. A one-way analysis of variance was conducted, and if shown to be significant, that Tukey post-hoc test was used to evaluate and determine the differences between the groups. The Pearson Chi-square test was used to compare renal pathology results. $p<0.05$ were considered significant.

RESULTS

The sham control group and two study groups successfully completed the study. As shown in Table 1 and Figure 1, the mean serum urea and BUN levels in the RIRI group were higher than those in the sham control group ($p<0.05$). In contrast, the mean serum urea and BUN levels in the RIRI + oxerutin group were lower than those in the RIRI group ($p<0.05$). The mean creatinine levels in the RIRI and RIRI + oxerutin groups were higher than the mean creatinine level in the sham control group (0.51±0.01 mg/dl) ($p<0.05$). However, when the RIRI and RIRI + oxerutin groups were compared (0.61±0.01 and 0.61±0.02 mg/dl, respectively), the difference between the groups was not statistically significant ($p>0.05$) (Fig. 1). Similarly, the mean Cys C level was not significantly different between the RIRI and RIRI + oxerutin groups ($p>0.05$). The mean TNF-α level was significantly lower in the RIRI + oxerutin group than in the RIRI group ($p<0.05$) (Table 1 and Fig. 1).

The mean tissue TAS in the RIRI group was lower than that in the sham control group, and the mean tissue TAS in the RIRI + oxerutin group was higher than that in the RIRI group, and the difference was statistically significant ($p<0.05$) (Fig. 2). The mean tissue TOS in the RIRI group was the highest among all the groups and the difference between the mean levels was statistically significant ($p<0.05$). Moreover, the mean tissue TOS in the RIRI + oxerutin group was lower than that in the RIRI group, and this difference was statistically significant ($p<0.05$) (Table 2 and Fig. 2).

On comparison of histopathological changes between the RIRI group and the sham control group, we observed inflammation, tubular epithelial flattening, cytoplasmic vacuolization, cell necrosis–ischemic changes, and tubular lumen ob-

Table 1. The mean serum Urea, BUN, Creatinine, Cystatin C, and TNF-α level in all experimental groups

Parameters	Sham control	RIRI	RIRI + Oxerutin
	Mean±SD	Mean±SD	Mean±SD
Urea (mg/dl)	45.77±2.76	57.70±1.49*	42.11±1.72†
BUN (mg/dl)	21.38±1.27	26.90±0.67*	19.80±0.74†
Creatinine (mg/dl)	0.51±0.01	0.61±0.01*	0.61±0.02*
TNF-α (pg/ml)	68.29±2.55	55.98±2.76*	52,34±2.42*†
Cystatin-C (mg/L)	1.31±0.09	1.57±0.14	1.65±0.13

*Compared with Sham control group; $p<0.05$. †Compared with RIRI Group; $p<0.05$. BUN: Blood urea nitrogen; TNF-α: Tumor necrosis factor-alpha; RIRI: Renal ischemia-reperfusion injury.

Table 2. The mean kidney TAS, TOS, and Apoptotic index level in all experimental groups

Parameters	Sham control	RIRI	RIRI + Oxerutin
	Mean±SD	Mean±SD	Mean±SD
TAS (mmol Trolox Eq/gr)	0.20±0.01	0.19±0.01*	0.21±0.01†
TOS (μmol H_2O_2 Eq/gr)	2.65±0.47	3.05±0.42*	2.87±0.42†
Apoptotic index (%)	17.5±2.85	55±3.05*	45.2±2.55*†

*Compared with Sham control group; $p<0.05$. †Compared with RIRI Group; $p<0.05$. TAS: Total anti-oxidant status; TOS: Total oxidant status; RIRI: Renal ischemia-reperfusion injury.

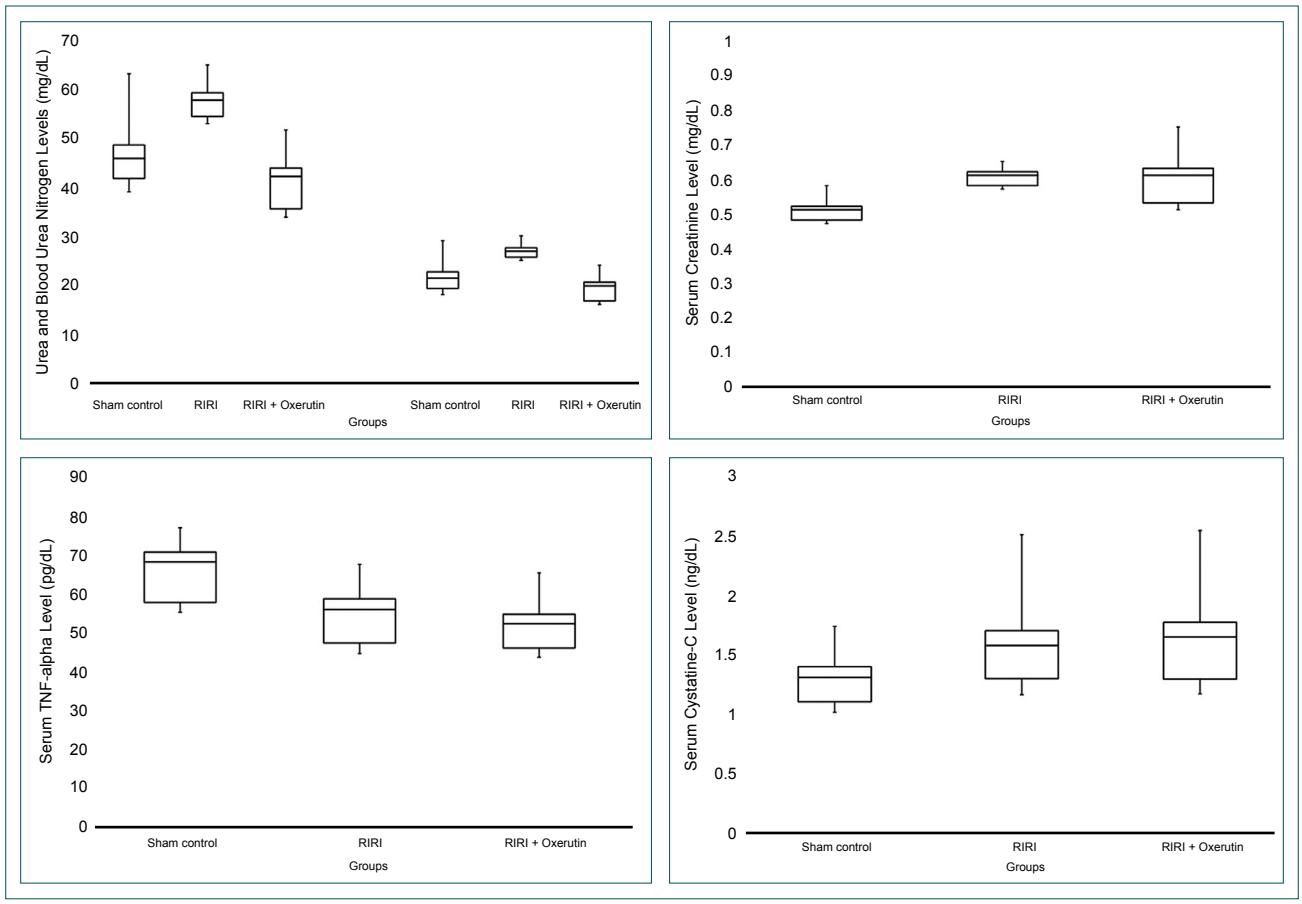

Figure 1. Comparison of the mean serum urea, blood urea nitrogen, creatinine, tumor necrosis factor-alpha and cystatin C levels among the groups.

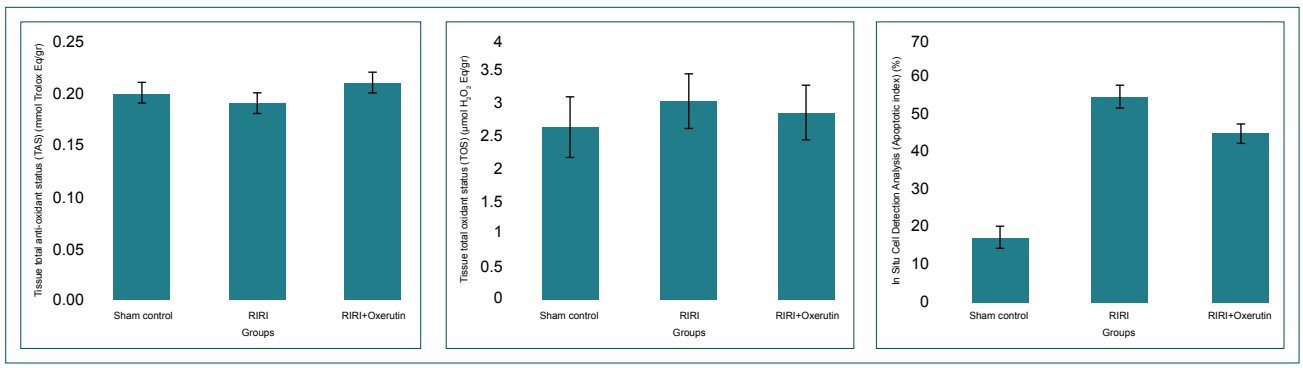

Figure 2. Comparison of the mean tissue total antioxidant status, tissue total oxidant status and apoptotic index levels among the groups.

struction at various degrees in the RIRI group (Fig. 3). These changes were less common in the RIRI + oxerutin group (Fig. 4). Histopathological changes are shown in Figure 4.

The mean apoptotic indexes of the RIRI and RIRI + oxerutin groups were higher than the mean apoptotic index of the sham control group ($p<0.05$), and the mean apoptotic index in the RIRI + oxerutin group was lower than that in the RIRI group ($p<0.05$) (Table 2 and Fig. 2). The apoptotic indexes were coherent with the histopathological changes (Fig. 3). TUNEL positive cells, an indicator of apoptotic cell death, were observed at a high rate in the kidneys of the RIRI group. Oxerutin treatment reduced the number of TUNEL positive cells (Fig. 5).

DISCUSSION

The kidneys are one of the organs most affected by RIRI, which occurs in clinical conditions requiring emergency intervention such as trauma and hemorrhagic shock.[1] Therefore, it is essential to develop effective medical treatment strategies. In the literature, some flavonoid derivatives such as rutin and flavangenol have been used in the RIRI model, and their effects have been investigated.[10,11] Oxerutin,

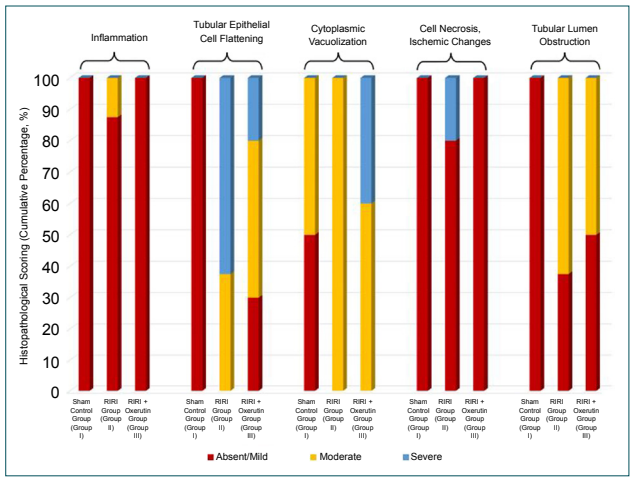

Figure 3. Comparison of the histopathological scores in terms of inflammation, tubular epithelial flattening, cytoplasmic vacuolization, cell necrosis–ischemic changes, and tubular lumen obstruction within cumulative percentages with a grading scale of absent/mild (0), moderate (+), and severe (++).

a member of the flavonoid family, has been widely used as therapeutic agent in chronic venous insufficiency and hemorrhoidal disease at cardiovascular and general surgery practice for many years. To the best of our knowledge, there is no research on effects of oxerutin in experimental model of early-stage RIRI, and this study is the first time demonstrating the protective effects of oxerutin in the early stage RIRI model. This protection is primarily due to the inhibition of apoptosis and reduced histopathological damage, as well as clearly associated by our findings that pretreatment with oxerutin decreased oxidative stress and inflammatory response.

An ischemic period approaching 1 h is sufficient for temporary loss of function, and exposure to the ischemic period for 3 h leads to permanent kidney damage.[12] Many studies have shown that the duration of ischemia for the development of RIRI is 30 min.[13–15] However, reperfusion times ranging from 1 h to 24 h were evaluated in the studies.[13–16] Since we considered that the improvement of early-stage RIRI will be a positive recovery sign for the late-stage renal functions, we conducted our RIRI model in such a way that 30 min of ischemia followed by 1 h of reperfusion. In the histopathological examinations and apoptotic index evaluations, the kidney tissues in the sham control group had a normal histopathological appearance and low apoptotic index, but those in the RIRI and RIRI + oxerutin groups exhibited deteriorated histopathological structure and apoptotic index at varying levels. These findings suggest that RIRI model was successfully generated in our study and the early stage RIRI is particularly due to apoptosis and deteriorated histopathological structure.

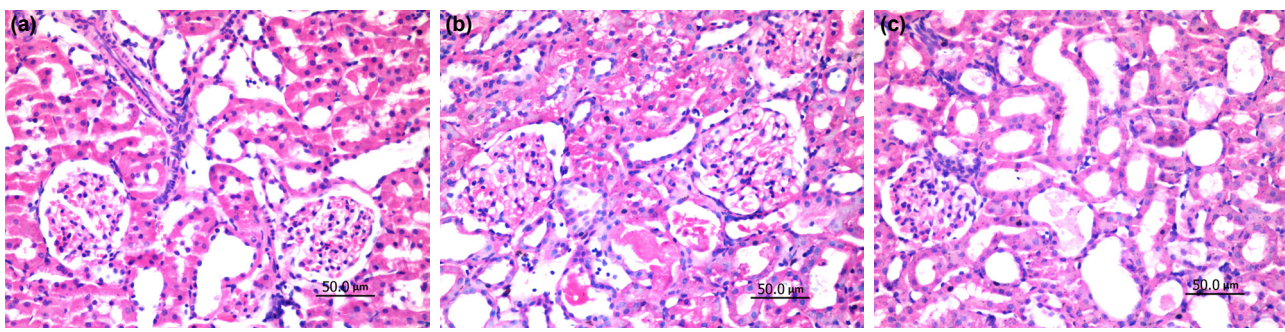

Figure 4. Hematoxylin and eosin (H&E) stain of kidney tissue and histopathological assessment of the all groups (H&E; 400×). **(a)** Sham control group, the renal tubules and glomerulus displayed normal renal histological structure; **(b)** Renal ischemia–reperfusion injury (RIRI) group, severe tubular epithelial flattening, moderate cytoplasmic vacuolization, and tubular lumen obstruction detected; **(c)** RIRI + oxerutin group, moderate tubular epithelial flattening, and focal tubular dilatation detected.

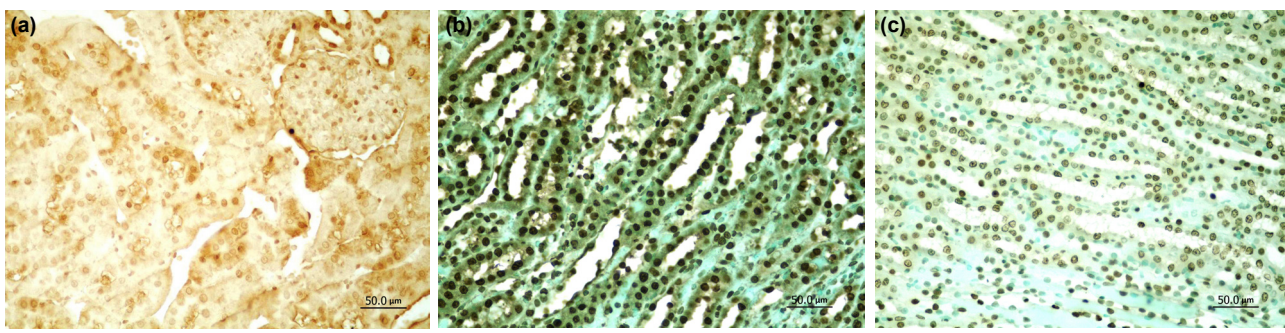

Figure 5. Terminal deoxynucleotidyltransferase-mediated dUTP digoxigenin nick end labeling (TUNEL) analysis for apoptotic cells shown (TUNEL; 400×). Nuclei of TUNEL-positive cells are stained brown, in contrast to blue-stained TUNEL-negative cells. **(a)** Sham control group, low apoptotic index was detected in glomeruli and proximal tubules; **(b)** Renal ischemia-reperfusion injury (RIRI) group, high apoptotic index was detected in distal tubule structures; **(c)** RIRI + oxerutin group, moderate apoptotic index was detected in the distal tubule structures.

The inflammatory and oxidative process in RIRI causes acute tubular necrosis due to disruption in the integrity of the glomerular and tubular epithelium, which clinically manifests as ARF.[5,17] Serum levels of biomolecules such as BUN, urea, creatinine and Cys C are elevated in ARF.[14,18–20] In this study, the findings that the mean BUN and urea levels in the RIRI group were significantly higher than those in the sham control group indicated that the experimental model was established correctly. The similarity of the mean BUN and urea levels in the RIRI + oxerutin and sham control groups supported to the protective effect of oxerutin in RIRI. When the mean creatinine and Cys C levels were compared, no significant difference was found between the groups, but differences in creatinine and Cys C levels may not be observed in the early stage of renal injury.[20,21] In addition, the fact that the mean creatinine and Cys C levels tend to increase in RIRI group compared to sham control group suggests that creatinine and Cys C levels will increase in late-stage RIRI.

Various levels of inflammatory markers have been used to evaluate the inflammatory response in RIRI. Many studies have reported that RIRI increases the production of some proinflammatory cytokines.[5,16,18] To determine the effects of oxerutin on the inflammatory response in kidneys, the level of the inflammatory factor TNF-α was evaluated. Zografos et al.[16] reported that there was no statistically significant difference between the groups in terms of TNF-α in early stage renal ischemia damage. In our study unlike the study of Zografos et al.,[16] the mean TNF-α levels were significantly different in the RIRI and RIRI + oxerutin groups compared to the sham control group. However, the fact that oxerutin pretreatment significantly decreased the mean TNF-α level suggests that oxerutin will show a protective effect by reducing the inflammatory response in RIRI.

Oxidative stress and antioxidant status can be evaluated by various markers and methods.[5,18,22,23] However, measuring these markers separately is both time-consuming and costly. Therefore, in this study, we used TOS and TAS, which are commonly used in recent years, to evaluate the oxidative stress status.[7,8,22] Turgut et al.[24] and Toprak et al.[22] reported that RIRI resulted in lower TAS and higher TOS levels. In agreement with these previous studies, we showed that lower TAS and higher TOS levels were in the RIRI group compared the sham control group. Meanwhile, we demonstrated that oxerutin pretreatment significantly decreased TOS levels and increased TAS levels. These results provided evidence that oxerutin protects the kidneys in RIRI owing to its powerful antioxidant and strong scavenger properties.

Ischemia-induced damage leads to apoptosis and necrosis of renal tubular cells.[18] This condition leads to some histopathological changes, including inflammation, tubular epithelial flattening, cytoplasmic vacuolization, cell necrosis–ischemic changes, and tubular lumen obstruction.[9,22,25] Many recent studies have shown that both histopathological changes occur in RIRI and these changes are reduced by various agents.[16,26,27] This study revealed that similar to previous studies, oxerutin pretreatment significantly relieved the severity of histopathological changes. To our knowledge, apoptosis, one of the important mechanisms of cell death, is an important prognostic factor in the development of ARF induced by I/R injury.[28] Therefore, in the present study, apoptotic cell death was also evaluated in contrast to the above studies. Our results showed that the mean apoptotic index and the number of TUNEL-positive cells were higher in the RIRI group than in the sham control group, which subsequently decreased with oxerutin pretreatment. Based on the obtained histopathological and apoptotic index data, we consider that oxerutin will provide improvement in kidney functions in the late stage as provided improvement in early-stage RIRI histopathologically.

The main limitations of our study are the lack of other oxidative stress biomarkers for biochemical assessment and the long-term effect of oxerutin had not been investigated. However, strengths of our study are that we focused on the early stage of the I/R injury, and could demonstrate that oxerutin significantly reduced inflammatory response and oxidative damage, inhibited apoptosis, as well as improved histopathologically in the early stage of RIRI.

Conclusion

In conclusion, in this study, we successfully established an early-stage RIRI model, and this is the first study to show that pretreatment of oxerutinin is effective in preventing RIRI. Currently, there is no specific treatment to reduce RIRI as most of the relevant pathogenetic mechanisms have not been fully clarified. We consider that developing emergency treatment strategies that can be applied in early-stage RIRI will protect from late-stage renal dysfunction. Therefore we believe that future studies on the development of treatment strategies to prevent oxidative stress due to free oxygen radicals, such as oxerutin, will help successfully prevent renal dysfunction due to RIRI.

Ethics Committee Approval: This study was approved by the Suleyman Demirel University Animal Experiments Local Ethics Committee (Date: 25.12.2012, Decision No: 03).

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: A.G., A.Ö., T.O., S.A.Ö., K.K.B., S.Y., E.U., A.C.U., P.A.K.; Design: A.G., A.Ö., T.O., SA.Ö., K.K.B., S.Y., E.U., A.C.U., P.A.K.; Supervision: A.G., A.Ö., T.O., SA.Ö., K.K.B., S.Y., E.U., A.C.U., P.A.K.; Resource: K.K.B., S.Y., E.U., A.C.U., P.A.K.; Materials: A.G., A.Ö., SA.Ö., K.K.B., E.U.; Data: A.G., T.O., S.Y., SA.Ö.; Analysis: K.K.B., E.U., A.C.U., P.A.K.; Literature search: A.G., A.Ö., T.O., SA.Ö.; Writing: A.G., A.Ö., T.O., SA.Ö.; Critical revision: A.G., A.Ö., T.O., SA.Ö., K.K.B., S.Y., E.U., A.C.U., P.A.K.

Conflict of Interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZ*

Böbrek iskemi reperfüzyon hasarlı sıçanlarda okserutinin apoptoz ve böbrek fonksiyonu üzerindeki etkinliği

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AMAÇ: Renal iskemi-reperfüzyon hasarı, böbrek cerrahilerinin yanı sıra travma ve şok gibi klinik durumlarda akut böbrek yetersizliğinin en sık nedenidir. Okserutin, flavonoid ailesinin bir üyesidir ve antioksidan özelliklere sahiptir. Bu çalışmanın amacı, okserutinin renal iskemi-reperfüzyon hasarı üzerinde koruyucu etkisinin olup olmadığını araştırmaktır.

GEREÇ VE YÖNTEM: Yirmi sekiz erkek Wistar albino sıçanı rastgele üç gruba ayrıldı: Sham kontrol grubu (n=8), renal iskemi-reperfüzyon hasarı grubu (n=10) ve renal iskemi-reperfüzyon hasarı + okserutin grubu (n=10). Renal iskemi-reperfüzyon hasarı sol renal arterin 30 dakika klemplenmesi ve ardından bir saatlik reperfüzyon periyodu ile sağlandı. Daha sonra histopatolojik ve biyokimyasal inceleme için kan örnekleri ve sol böbrek dokusu örnekleri alındı. Kan örneklerinde, böbrek fonksiyonunun göstergesi olan kan üre nitrojen, üre, kreatinin ve sistatin C düzeyleri ile enflamasyonun bir göstergesi olan tümör nekroz faktör-alfa değerleri incelendi. Oksidatif stresin göstergeleri olan total antioksidan kapasite ve total oksidan kapasite böbrek dokularında incelendi. Böbrek hasarının bir göstergesi olan apoptotik indeks ve ayrıca histopatolojik değişiklikler böbrek dokularında değerlendirildi.

BULGULAR: Apoptotik indeks, total oksidan kapasite, tümör nekroz faktör-alfa, kan üre nitrojen ve üre düzeyleri renal iskemi-reperfüzyon hasarı + okserutin grubunda renal iskemi-reperfüzyon hasarı grubuna göre daha düşüktü ($p<0.05$). Sonuçlar, okserutinin histopatolojik ve biyokimyasal özelliklerinin sıçanları renal iskemi-reperfüzyon hasarından koruduğunu gösterdi.

TARTIŞMA: Bu çalışmada elde edilen bulgular profilaktik okserutin uygulamasının renal iskemi-reperfüzyon hasarının neden olduğu apoptoz ve böbrek yetersizliği üzerinde koruyucu etkileri olduğunu göstermektedir. Bu nedenle okserutin, renal iskemi-reperfüzyon hasarının tedavisinde etkili bir profilaktik ajan olarak kullanılabilir.

Anahtar sözcükler: Akut böbrek hasarı; antioksidanlar; apoptoz; okserutin; oksidatif stres.

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