

Protective effect of cordycepin on experimental renal ischemia/reperfusion injury in rats

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Summary *Aim: To date, various molecules have been investigated to reduce the effect of renal ischemia/reperfusion (I/R) injury. However, none have yet led to clinical use. The present study aimed to investigate the protective effect of cordycepin (C) on renal I/R injury in an experimental rat model.*

Materials and methods: Twenty-four mature Sprague Dawley female rat was randomly divided into three groups: Sham, I/R, I/R+C. All animals underwent abdominal exploration. To induce I/R injury, an atraumatic vascular bulldog clamp was applied to the right renal pedicle for 60 minutes (ischemia) and later clamp was removed to allow reperfusion in all rats, except for the sham group. In the I/R + C group, 10 mg/kg C was administered intraperitoneally, immediately after reperfusion. After 4 hours of reperfusion, the experiment was terminated with right nephrectomy. Histological studies and biochemical analyses were performed on the right nephrectomy specimens. EGTI (endothelial, glomerular, tubulointerstitial) histopathology scoring and semi-quantitative analysis of renal cortical necrosis were used for histological analyses and superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA), total oxidant status (TOS) for biochemical analyses. Results: Histopathological examination of the tissue damage revealed that all kidneys in the sham group were normal. The I/R group had higher histopathological scores than the I/R + C group. In the biochemical analysis of the tissues, SOD, MDA, TOS values were found to be statistically different in the I/R group compared to the I/R + C group (p: 0.004, 0.004, 0.001 respectively).

Conclusions: Intraperitoneal cordycepin injection following ischemia preserve renal tissue against oxidative stress in a rat model of renal I/R injury.

KEY WORDS: Cordycepin; Ischemia/reperfusion injury; Kidney; Rat.

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INTRODUCTION

Renal ischemia is one of the important causes of acute renal failure. Acute renal failure is an important public health problem with high morbidity, mortality, and cost

worldwide (1). Hypotension, shock, sepsis, renal artery embolism, trauma, renal transplantation, and partial nephrectomy are the main conditions that cause renal ischemia. Renal tissue damage develops with the failure of oxygen and nutritional support of kidney cells due to a complete stop or decrease of blood flow. Ischemia/reperfusion (I/R) is defined as restoring blood flow after it is interrupted. In the case of reperfusion following renal ischemia, tissue damage continues. Necrosis, apoptosis, free oxygen radicals, and inflammation have been described as the main mechanisms that are responsible for I/R kidney damage. However, the mechanism of development of I/R kidney damage is not clear (2, 3). Various agents have been studied to protect the kidney from I/R damage. Doxycycline (by decreasing pro-inflammatory cytokine levels), ascorbic acid (by reducing antioxidant activity), leptin (by decreasing TNF alpha level and by increasing nitric oxide levels), iloprost (by suppressing lipid peroxidation) and levosimendan (antioxidant and NO/release) have been shown to have protective effects on I/R kidney damage (4). Cordycepin (C) is an adenosine analog and reported as the first nucleoside antibiotic isolated from Cordycepin militaris culture. Cordycepin has been shown to have protective effects on testicular I/R injury in rats, and its anti-inflammatory, anti-tumor and antioxidant properties have been reported (5-7). In this study, we aimed to investigate the effects of Cordycepin on experimental renal I/R injury.

MATERIALS AND METHODS

24 male Sprague-Dawley female rats (8 weeks old, weight 230-300 g) were obtained from the Karadeniz Technical University Laboratory Animals Research Centre (Trabzon, Turkey). The study was approved from the Animal Experiments Local Ethics Committee of Karadeniz Technical University (Trabzon, Turkey) (Approval Number/ID: 2018/21). The same environment and nutritional conditions were provided for all animals. Rats were entrained under a 12:12 h dark: light cycle (lights on 6 am-6 pm) with stable temperature (21 ± 2°C) and

No conflict of interest declared.

humidity ($60 \pm 5\%$). The rats had sterile water and food available ad libitum.

Experimental protocol and surgical procedure

The protocol is described in the previous study (8). Rats were randomly and equally divided into 3 groups; sham group, I/R group, I/R+C group. Ketamine hydrochloride (100 mg/kg, *Ketalar, Eczacibasi, Turkey*) and xylazine (10 mg/kg) were used intraperitoneally for anesthesia. A midline laparotomy incision was performed, and the right renal pedicle was dissected. Then, right renal ischemia was performed with bulldog clamp for 60 minutes in I/R and I/R+C groups. The clamp was removed for reperfusion and the renal artery pulse was visually confirmed. In the I/R+C group, 10 mg/kg Cordycepin was administered intraperitoneally following the beginning of reperfusion and saline in the I/R group. After controlling the bleeding, the skin layers were sutured. In the sham group, rats underwent a similar surgical procedure without renal occlusion. The rats were sacrificed 4 hours after reperfusion and the right nephrectomy was performed. Renal tissues were prepared for biochemical analyses and histopathological examination.

Histological analysis

After the kidney tissue samples were fixed in 10% formaldehyde for 24-48 hours, routine histological follow-up was performed. Serial sections of 5-micron thickness were taken from the paraffin-embedded tissues. Subsequently, the samples were stained with hematoxylin-eosin and I/R related changes were evaluated under the light microscope. Besides, sections were taken from each paraffin block, and *Periodic acid-Schiff* (PAS) and Masson trichrome stain were applied for evaluation of fibrosis and Bowman capsule thickening. The histological evaluations of the renal tissue damage were graded as described in the study of *Medeiros et al.* (Table 1) (9). EGTI scoring system was also used (Table 2) for histological analyses (10). This system examines histological damage in 4 separate sections: Endothelial, Glomerular, Tubular, and Interstitial. The histological evaluations were made by examining each section one by one and considering the areas where the damage was most severe.

Biochemical analysis

The tissues were first cleaned by saline solution and stored at $-80\text{ }^{\circ}\text{C}$ until the analysis time. In the analysis process, first they were homogenized in cold *phosphate buffer solution* (PBS) (0.05 M, pH 7.4), and were centrifuged at 3000 rpm for 10 min to remove debris and to obtain clear supernatant fraction. Then, the analyses were performed in this fraction. *Malondialdehyde* (MDA), *Total Oxidant Status* (TOS), as well as enzyme activities of *Superoxide Dismutase* (SOD) and *Catalase* (CAT) were measured in this fraction. MDA levels in tissue samples were determined using the method described by Mihara and Uchiyama. Tetramethoxypropane was used as a standard, and tissue MDA levels were calculated as nmol/g wet tissue (11). TOS levels were determined using a colorimetric TOS kit as previously described by *Erel* (12). CAT activity was measured by modifying the method based on the

measurement of the absorbance of ammonium molybdate with H_2O_2 at 405 nm. CAT standard (Sigma C9322) was used as a standard, and tissue CAT activity was calculated as nmol/g protein (13). The SOD enzyme activity was determined by the method of Sun and Oberley. This method is based on the measurement of the absorbance of the purple-colored formazan molecule at 560 nm resulting from the reduction of nitroblue tetrazolium of O_2^- formed by the xanthine-xanthine oxidase system. Tissue SOD activity was calculated as nmol/g protein by using SOD standard (Sigma S8160) (14).

Statistical analysis

The data were transferred to SPSS 22 (*Statistical Package for the Social Sciences*) computer package program and evaluated statistically. Compliance with normal distribution was checked by the Kolmogorov-Smirnov test. One way ANOVA and post-hoc Tukey tests were used for the evaluation of more than two independent groups that fit the normal distribution, and the Kruskal-Wallis test was used for the evaluation of more than two parameters that did not fit the normal distribution, and Mann Whitney-U test was used for the binary parameter that did not fit the normal distribution. The values obtained were expressed as mean \pm standard deviation ($x \pm \text{SD}$) and $p < 0.05$ was considered statistically significant.

Table 1.
Scoring system for renal histopathology.

Score	Histopathological pattern
0	Normal
0.5	Small focal damaged areas
1	< 10% Cortical damaged zone
2	10-25% Cortical damaged zone
3	25-75% Cortical damaged zone
4	> 75% Cortical damaged zone

Table 2.
The EGTI histological (Endothelial, Glomerular, Tubular, Interstitial) scoring system.

Tissue type	Damage	Score
Tubular	No damage	0
	Loss of Brush Border (BB) in less than 25% of tubular cells.	1
	Integrity of basal membrane	2
	Loss of BB in more than 25% of tubular cells, Thickened basal membrane	3
	(Plus) Inflammation, cast formation, necrosis up to 60% of tubular cells	4
Endothelial	No damage	0
	Endothelial swelling	1
	Endothelial disruption	2
	Endothelial loss	3
Glomerular	No damage	0
	Thickening of Bowman capsule	1
	Retraction of glomerular tuft	2
	Glomerular fibrosis	3
Tubulo/Interstitial	No damage	0
	Inflammation, haemorrhage in less than 25% of tissue	1
	(Plus) necrosis in less than 25% of tissue	2
	Necrosis up to 60%	3
	Necrosis more than 60%	4

RESULTS

All rats in the sham group had normal renal tissue in the histopathologic examination. However, as shown in Table 3, 2 (25%) rats in the I/R group had small focal damaged areas, 3 (47.5%) < 10% cortical damage, 2 (12.5) had 10-25 % cortical damage and 1(12.5%) had 25-75% cortical damage. In I/R+C group, 5 (62.5%) had small focal damaged areas, 1 (12.5%) had < 10% cortical

Table 3.
Cortical damage score of all rats according to the groups.

Rats	Sham Group	I/R Group	I/R+C Group
1	0	0.5	0.5
2	0	1	2
3	0	3	0.5
4	0	2	0.5
5	0	2	0.5
6	0	0.5	0.5
7	0	1	1
8	0	1	2

Table 4.
ECTI scores of all rats according to the groups.

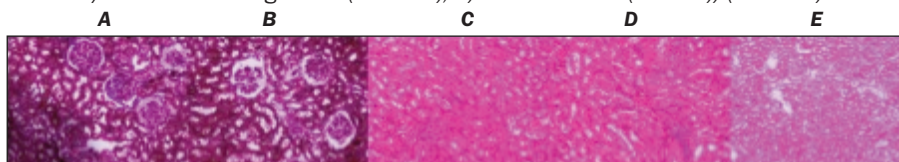
Rats	Sham Group	I/R Group	I/R+C Group
1	0	6	5
2	0	5	3
3	0	4	3
4	0	6	5
5	0	5	5
6	0	6	2
7	0	4	4
8	0	4	7

Table 5.
Results of superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA), total oxidant capacity (TOC) of groups.

Mean ± SD	Sham Group (n: 8)	I/R Group (n: 8)	I/R+C Group (n: 8)	P value
SOD (U/Gprotein)	46.39 ± 2.65	28.84 ± 6.74	45.76 ± 6.91	0.004* 0.749**
CAT (U/Gprotein)	7.19 ± 1.02	4.37 ± 0.74	6.46 ± 1.16	0.056
MDA (nmol/Gtissue)	39.8 ± 4.9	65.5 ± 3.5	45.6 ± 2.8	0.004* 0.055**
TOS (µmol/L)	8.5 ± 1.74	17.8 ± 3.33	15.83 ± 1.53	0.001* 0.324**

* I/R vs I/R+C. ** sham vs I/R+C.

Figure 1.
Histological images of the rat renal cortex sections.
a) Glomerular damage: Glomerular Fibrosis (x40 Masson Trichrome) (Score: 3),
b) Glomerular damage: Glomerular retraction (x40 Masson Trichrome) (Score: 2),
c) Tubular damage: necrosis up to 60% in tubule cells, tubular dispersion (x40 HE) (Score: 3),
d) Tubulo/interstitial damage: Inflammation, hemorrhage in less than 25% (x40 HE) in tubulo/interstitial damage area (Score: 1), e) Normal cortex (x20 HE)) (Score: 0).



damage and 2 (25%) had 10-25% cortical damage. EGTI scores of the rats in each group are shown in Table 4, separately. Histological images are shown in Figure 1. The biochemical analysis results are shown in Table 5. SOD in the I/R group decreased significantly compared to the I/R+C group (p = 0.004) but was similar in the sham and I/R+C groups (p: 0 = 749). CAT in the I/R group was lower than the sham and I/R+C groups but not statistically significant (p = 0.056). MDA and TOS in the I/R group increased significantly compared to the I/R+C group (p = 0.004, p = 0.001) but were similar in the sham and I/R+C groups (p = 0.055, p = 0.324).

DISCUSSION

Ischemia-reperfusion injury of the kidney continues to be an important clinical condition since it is not an effective agent that has been used in the treatment (1). Although the formation of I/R damage is a complex process that is not fully understood, significant progress has been made in this regard. The main components of this complex pathophysiological condition are inflammation, oxidative stress-lipid peroxidation, mitochondrial dysfunction, nitrite, and nitric oxide, the complement system, and the renin-angiotensin system.

Homeostatic control of kidney functions is dependent on the production of mitochondrial adenosine triphosphate (ATP), nitric oxide (NO), and reactive oxygen species (ROS), but is only possible with adequate oxygen supply to the kidney tissue (15). Circulatory impairment causes hypoxia and oxidative stress in the kidney tissue and subsequent NO, ROS, and oxygen imbalance. Ischemic damage inhibits the Na-K ATPase enzyme bound to the cell membrane, as a result, intracellular H₂O and sodium increase and edema develop (16).

Interstitial edema and vascular permeability cause a further reduction in blood flow.

In addition, oxidative stress and increased prostaglandin synthesis in damaged tubules further disrupts oxygen transmission and causes the local no-reflow phenomenon (17, 18). The long-term consequence of microvascular circulation disorder is the development of hypoxia and finally renal fibrosis as a result of Transforming growth factor-beta (TGF-β) stimulation with decreased *Vascular endothelial growth factor* (VEGF) response secondary to the decrease in peritubular capillary density (19). The inflammatory cascade is triggered with I/R damage, which further aggravates the kidney damage. The main mediators of inflammatory damage are chemokines. Chemokines regulate pro-inflammatory cytokine activity, adhesion molecule expression, leukocyte infiltration and activation. IL 6 and TNF-alpha are cytokines that play a major role in the development of renal dysfunction (4). Activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway mediates the release of multiple pro-inflammatory cytokines that

cause progression of renal I/R injury (20). Various agents have been studied in reducing inflammation in I/R injury. Dexmedetomidine (a highly selective α_2 -adrenoreceptor agonist) has a cytoprotective effect by reducing the level of IL6 and TNF alpha by inhibiting the phosphorylation of JAK/STAT proteins (21). Nicotine has a renoprotective effect by reducing leukocyte infiltration and chymokine release with its anti-inflammatory cholinergic properties (22). Celastrol (*Tripterygium wilfordii*), also found in China (china herb), is used in chronic nephritis and autoimmune diseases with its anti-inflammatory and antioxidant properties. Although Celastrol has been reported to have a positive effect on I/R damage by suppressing neutrophil infiltration, lipid peroxidation, and proinflammatory mediator synthesis such as cyclooxygenase-2 (COX2), there are also counter studies reporting that it increases I/R damage by COX-2 upregulation and prostaglandin E2 synthesis (23, 24).

ROS produced in excess during I/R injury causes changes in mitochondrial oxidative phosphorylation, ATP consumption, intracellular calcium increase and membrane phospholipid protease activation (25-27). This process causes damage to the lysosome membrane, leakage of lysosome enzymes and deterioration of the cell structure (28). Free oxygen radicals that cause lipid peroxidation are generated during the reperfusion phase of I/R injury. Lipid peroxidation and oxidative damage contribute to apoptosis and cell death by making DNA and protein damage. In addition, down-regulation of the antioxidant enzyme system consisting of catalase, superoxide dismutase and glutathione peroxidase enzymes may be responsible for I/R damage (25-27).

Studies have shown that free radical scavengers and antioxidants can be beneficial in protecting against I/R damage. Propofol, melatonin, ulinastatin, picroliv, naringin, and aqueous garlic extract, are some of the antioxidants and radical scavengers that have been of interest to researchers (4).

In our study, the biochemical and histopathological effects of cordycepin (3'-deoxyadenosine) on renal I/R injury in a rat model were investigated. Cordycepin is widely used in the treatment and prevention of many diseases (circulatory, immune, respiratory, and glandular systems illness) in East Asian countries (29). Cordycepin has been reported to be an effective anti-inflammatory and antioxidant (7). Cordycepin exerts its anti-inflammatory and analgesic effect by inhibiting IL-1 β , IL-6, TNF- α , induced nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) enzymes (5). It has been reported that ROS production induced by platelet-derived growth factor (PDGF) can be reduced by cordycepin and it attenuates neointima formation in vascular smooth muscles in rats (29, 30). Also, Li *et al.* reported that cordycepin showed a renoprotective effect by inhibiting myofibroblast activation (31).

In previous studies, Cordycepin's protective effect on the brain and testis in ischemia-reperfusion injury was reported (7, 32). In the study of Han *F et al.*, the effectiveness of Cordycepin at different doses (2 mg/kg, 4 mg/kg, 8 mg/kg) in rats with renal ischemia-reperfusion injury was investigated (33). In this study, in which Cordycepin was administered with oral gavage for 7

days, it was reported that increasing doses reduce pathological damage, oxidative stress, and apoptosis. In the same study, serum creatinine and BUN values were observed to be statistically lower in the Cordycepin treated groups compared to the I/R group. In our study, unlike the study of Han *et al.*, 20 mg/kg Cordycepin was administered intraperitoneally at the beginning of reperfusion, and nephrectomy was performed 4 hours later. In the biochemical analysis, SOD, MDA, and TOS values were found to be statistically different in the C + I/R group compared to the I/R group. As a limitation of the study, serum creatinine and BUN values were not measured since we did not perform left nephrectomy.

CONCLUSIONS

Intraperitoneal Cordycepin administration has been shown to support the endogenous antioxidant defense system and reduce oxidative stress in renal ischemia/reperfusion injury in rats.

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