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Original Article

Protective effect of ibuprofen against renal ischemia-reperfusion injury

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Abstract

Aim: Ibuprofen is an older agent, but its intravenous form is a very new drug. The aim of this study was to investigate whether intravenous form of ibuprofen has protective effect against renal ischemia reperfusion injury at two different doses such as 10-30 mg/kg.
Material and Methods: Thirty-two Wistar Albino type female rats were divided into 4 groups as sham, control, IBU-10, IBU-30. In the control group, 60 minutes renal ischemia and 60 minutes reperfusion were performed. In the ibuprofen groups, at the 45th minute of ischemia, ibuprofen was administered in different doses at 10 mg/kg and 30 mg/kg through intraperitoneally. After 60 minutes of ischemia, the clamps were opened. Renal tissue and blood samples were collected from the rats at the end of the reperfusion period. Serum TAS, TOS and prolidase enzyme levels were analyzed in plasma samples. Both histopathological and biochemical evaluations were performed with kidney tissue.
Results: In the groups given intravenous ibuprofen, less cellular damage was always detected. Cellular damage indicators were significantly lower in the treated rats than in the control group. Serum and tissue prolidase values were different between groups ($p<0.001$, $p<0.001$). Serum TAS and TOS levels were also different between groups ($p=0.001$, $p=0.003$). Serum OSI levels were also different between groups ($p=0.017$).
Conclusion: The biochemical and pathological results obtained in our study suggest that intravenous ibuprofen, has a protective effect against kidney damage. We believe that our study will shed light on future clinical prospective studies.

Keywords: Intravenous ibuprofen; rat; experimental renal ischemia - reperfusion injury; proinflammatory biomarkers

INTRODUCTION

Ischemia-reperfusion (IR) is defined as a decrease in blood flow to the tissue or organ, and then a re-buildup of blood. Warm ischemia-reperfusion injury (IRI) may occur in the kidney during clinical conditions such as major trauma, systemic hypotension, hypovolemic shock, cardiac arrest, renovascular surgery, aortic clamping and organ damage. The severity of this injury increases in parallel with the duration of ischemia, resulting in different clinical conditions ranging from prerenal azotemia without significant tissue damage to severe acute renal failure owing to tubular or cortical necrosis (1). In surgical procedures such as transplantation in patients with a risk of kidney damage, the ideal nonsteroidal agent should be selected as the painkiller to protect renal function. But the ideal nonsteroidal agent to preserve renal function could still not be developed. Patients who need to use acute or chronic nonsteroidal agents face renal morbidity. Nonsteroidal anti-inflammatory agents are used for pain relief purposes and all have a risk of renal toxicity depending on the dose. In nonsteroidal agents, ibuprofen is an older agent, but its intravenous form is a very new drug (1-3).

Prolidase is actively involved in the destruction of collagen and the reintegration of proline into the collagen cycle. Collagen is not only a structural component of many organs and tissues, but also of the extracellular matrix, thus is affected by the pathology of these structures (4-6).

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Many drugs and antioxidants have been tried and are currently being studied on for the treatment of ischemia-reperfusion injury. In recent years, different approaches have been tried to prevent renal ischemia/reperfusion injury in the clinic (7,8).

Non-steroid anti-inflammatory drugs cause vasoconstriction and inhibit cyclooxygenase activation, stimulate rennin angiotensin aldosterone system (8). Ibuprofen can cause renal papillary necrosis and renal tubular toxicity when high doses are used, especially in older patients (3,8).We think that, regarding the intravenous form of ibuprofen in experimentally induced renal ischemia-reperfusion model, the evaluation of tissue and serum levels of TAS, TOS and prolidase enzyme, calculation of oxidative stress index (OSI index) and knowing if it is harmful to kidney tissue by histopathological examination and to what extent it damages kidney tissue will contribute significantly to human health and to the information in the literature (2).

In our study, we intend to primarily explore the position of intravenous ibuprofen, which is a current nonsteroidal anti-inflammatory agent, after renal ischemia-reperfusion injury, in the benefit/harmful balance of kidney tissue. The secondary aim of our study was to investigate the effects of different doses of ibuprofen on kidney tissue. In summary; the aim of this study was to explore whether intravenous form of ibuprofen has protective effect against renal ischemia- reperfusion injury at two different doses such as 10-30 mg / kg.

MATERIAL and METHODS

Thirty-two female Wistar Albino rats, weighing between 250-300g, collected from the Experimental Animal Research Center of Samsun Ondokuz Mayis University, were brought to the Experimental Animal Breeding Research and Application Center in Ordu University. This study was carried out in the School of Medicine Experimental Research Center in Ordu University. Ethical permission was obtained from Ordu University, School of Medicine, Local Ethics Committee of Experimental Animals. (Date: 28.03.2017, Decision number: 2017/06). During the in our study, all experimental and surgical practices were execute following the Guide to the Care and Use of Experimental Animals published by the US National Health Institutes, and considering ethics rules.

All rats used in the study were housed at 24±2°C room temperature and 50-60% dampness. Animals were fed with standard laboratory feed and water. The rats underwent the experimental procedure after being stored in the experimental animals laboratory in Ordu University at 22±2º C room temperature, 50%±10% humidity and circulation of 12 hours daytime and 12 hours night lights. The weights of the experimental animals were preferred to be between 250 and 300 grams. All the Wister Albino female 32 rats were used in the experiments.

Ischemia Reperfusion Injury Model

On the day of the study, the rats were brought to the research laboratory and weighed. The rats were sedated with intraperitoneal (i.p) 50 mg/kg dose of ketamine. After anesthesia was applied to the rats, they were cleaned with povidone-iodine and sterile gauze in supine position. The abdomen layers were crossed with a midline incision of approximately 3 cm, the intestines were removed with a wet gauze, and the kidneys were carefully reached. Renal ischemia was established by placing a small atraumatic vascular clamp on the left renal artery and vein. After ensuring that the arterial pulsations were completely cut, a warm saline was soaked gauze was placed over the exposed abdomen area to prevent fluid and heat loss. Intravenous ibuprofen was administered intraperitoneally (IP) at the 45th minute of ischemia. After all of the ischemia period of 60 minutes, the clamps were opened and the flow of renal artery and vein were seen to be continuing. Left nephrectomy was done and tissue samples were taken for histopathological and biochemical analysis after one hour of reperfusion (9). Intracardiac blood samples were taken for the serum measurements of proinflammatory biomarkers. The removed kidney tissue was divided in two equal parts and stored in two equal parts for histopathological and biochemical examinations. For histopathological examinations, they were placed in 50 ml storage containers, each containing 10% formaldehyde solution, and sent to the Departments of Pathology and Biochemistry of the School of Medicine in Ordu University. Blood samples were taken into biochemistry tubes and transferred to the Department of Biochemistry of the School of Medicine in Ordu University in nitrogen tanks.

Experimental Groups

All rats were randomly separated to four equal experimental groups (n=8). All of the rats included in the experimental study were anesthetized intraperitoneally with ketamine 50 mg/kg (Ketalar , Eczacıbası, Istanbul, Turkey).

Group 1 (Sham): Laparotomy was performed, and left nephrectomy was performed after 120 minutes. Blood and tissue samples were collected. No active agent was administered during the experiment.

Group 2 (Control): After laparotomy, 60 minutes of ischemia and 60 minutes of reperfusion, nephrectomy was performed to the left kidney, and tissue and blood samples were taken. No active agent was administered during the experiment.

Group 3 (IR + ibuprofen 10 mg / kg): Laparotomy and 60 minutes of ischemia were performed, and 10 mg/kg of ibuprofen intraperitoneally was administered at the 45th minute of ischemia, so in the other words 15 minutes before reperfusion. After 60 minutes of reperfusion, nephrectomy was performed on the left kidney, and tissue and blood samples were taken.

Group 4 (IR + ibuprofen 30 mg/kg): Laparotomy and 60 minutes of ischemia were performed, and 30 mg/kg of ibuprofen was administered intraperitoneally was administered at the 45th minute of ischemia, so in the

other words 15 minutes before reperfusion. After 60 minutes of reperfusion, nephrectomy was performed on the left kidney, and tissue and blood samples were taken (9).

Histopathological Examination

For histopathological examination, tissue samples were fixed in 10% buffered neutral formaldehyde solution for 24 hours. All of the samples were routinely followed up in tissue tracking device and paraffin blocks were prepared. For each tissue sample, serial sections of 5 µm width were prepared with microtome (RM 2255; Leica Instruments, Nussloch, Germany) from these paraffin blocks and stained with hematoxylin eosine (H&E). They were subjected to histopathological examination with light microscope (BX51, Olympus, Tokyo, Japan). Renal tissues were evaluated for tubular cell swelling, interstitial edema, tubular dilatation, medullary congestion, epithelial necrosis and hyaline cast formation parameters. These parameters were rated as negative (-) or positive findings (+). Positive findings were rated as mild (+), moderate (++) or severe (+++). The mean scores of the histopathological findings according to groups were calculated as follows: 0 points for negative findings (-), 1 point for mild findings (+), 2 points for moderate findings (++) and 3 points for severe findings (+++) (10).

Measurement of Prolidase Enzyme Activity (Optimized Chinard Method)

Serum and tissue prolidase level was measured spectrophotometrically on the basis of the principle of creating a colored compound (pink color) with ninhydrin by the heat effect of enzyme-mediated proline using glycyl-proline as a substrate. The tissue mixture was homogenized for 15min (Ultra Turrax T25; Rose Scientific Ltd, Edmonton, Canada). The homogenates were filtered and centrifuged at 4º C. The supernatants formed were used in biochemical processes (11-13).

Principle

The Fe2+- o-dianisidine complex creates a Fenton type reaction with hydrogen peroxide to form the OH- radial. This potent reactive oxygen type reducing agent reacts with colorless odianisidine molecule at low pH to form yellow-brown dianisidyl radicals. They participate in advanced oxidation reactions to increase color formation. Nevertheless, antioxidants in the samples suppress these oxidation reactions and stop the formation of color. This reaction was evaluated spectrophotometrically (UV-1601; Shimadzu Co., Kyoto, Japan) at 240 nm on the automatic analyzer (mmolTroloxEqv./L) (10).

Total Oxidant Level (TOS)

Principle

Oxidants in the sample: ferrous ion-o-dianisidine complex, ferric ion oxides. The glycerol present accelerates this reaction, triples its speed. Ferric ions form a colored complex with xylenol orange in acidic environment. The intensity of the color associated with the amount of oxidants in the sample was measured spectrophotometrically (µmol H2O2 Eqv./L) (5).

Oxidative Stress Index (OSI)

Oxidative Stress Index (OSI) was calculated by dividing Total Oxidant Level (TOS) by

Total Antioxidant Level (TAS) and multiplying by 100.

Oxidative Stress Index (OSI) = Total Oxidant Level (TOS) / Total Antioxidant Level (TAS) (Arbitrary Unit (AU)) × 100 (5)

The rats were sacrificed with cervical dislocation (Ketalar®, Eczacıbası, Istanbul, Turkey) under anesthesia 2 hour after the experimental procedures.

Statistical Analysis

The data were analyzed with IBM SPSS (Statistical Package for Social Sciences) for Windows v.23 (IBM Inc.,Chicago,IL,USA). The distribution conformity of the data was analyzed with the Shapiro-Wilk test. One-way analysis of variance (ANOVA) was used to compare the data with normal distribution according to groups. All of the multiple comparisons were performed with Tukey HSD because the variances were homogeneous. The chi-square test was used to analyze categorical data. The relationship between the variables was examined with Pearson correlation. Analysis results were presented as mean ± standard deviation for quantitative data and frequency (percentage) for qualitative data. Significance level was taken as $p<0.05$.

RESULTS

Tubular swelling did not show difference according to all groups ($p=0.446$). While 62.5% of the cases in the sham group were mild, 25% of the control group, 62.5% of the IBU 10 group and 46.9% of the IBU 30 group were mild observed as tubular swelling. Tubular cell degeneration showed difference according to groups ($p=0.013$). While 87.5% of the cases in the sham group were mild, 37.5% of the control group, 87.5% of the IBU 10 group and 100% of the IBU 30 group were found to have mild level tubular cell degeneration. Hyaline cast formation did not show difference according to groups ($p=0.077$). While 100% of the cases in sham group were mild, 50% of the control group, 87.5% of the IBU 10 group and 87.5% of the IBU 30 group had mild hyaline cast formation. Interstitial lymphocyte value was obtained as mild in all groups. Medullar congestion showed difference according to groups ($p<0.001$). Mild medullary congestion was observed in 100% of the sham group, 12.5% of the control group, 62.5% of the IBU 10 group and 75% of the IBU 30 group. Interstitial edema showed difference according to groups ($p=0.003$). Similarly, tubular dilatation also showed difference according to groups ($p=0.003$). The results of our pathological data analysis are presented in Table 1.

Histopathological findings shown Figure 1 and 2.

Serum prolidase mean values showed difference according to groups ($p<0.001$). The mean values were 349.88 in the control group, 318.75 in the sham group, 340.13 in the IBU 10 group and 328.38 in the IBU 30 group. There is no serum prolidase value difference between the sham group and the IBU 10 group, and the others are different from each other. The mean values of tissue prolidase showed difference according to groups ($p<0.001$). The mean

values of tissue prolidase were 3593.5 in the control group, 2652.88 in the sham group, 3512.25 in the IBU 10 group and 3144.13 in the IBU 30 group. There is no difference between the mean values of the sham group and the IBU 10 group, and the others are different from each other. Serum Total Antioxidant status mean values showed difference according to groups (p=0.001). The mean values were 1.79 in the sham group, 1.39 in the control group, 1.43 in the IBU 10 group and 1.68 in the IBU 30 group. Serum Total Oxidant Status mean values showed difference according to groups (p=0.003).The mean serum TOS values were 28.66 in the control group, 16.79 in the sham group, 16.91 in the IBU 10 group and 18.51 in the IBU 30 group. There was no difference between the sham and control groups. The mean value in the control group was higher than the IBU 10 and IBU 30 groups. Mean values also showed difference between the control and IBU 30 groups. Tissue Total Antioxidant Status mean values did not show difference according to groups (p=0.217). Tissue TAS values were 1.55 in the sham group, 1.30 in the control group, 1.77 in the IBU 10 group and 1.81 in the IBU 30 group. Tissue Total Oxidant Status mean values showed difference according to groups (p=0.002). Tissue TOS values were 13.58 in the control group, 10.62 in the sham group, 12.25 in the IBU 10 group and 13.16 in the IBU 30 group. Serum Oxidative Stress Index mean values showed difference according to groups (p=0.017). Serum OSI index mean values were 1573.13 in the control group, 977.75 in the sham group , 1181.5 in the IBU 10 group and 1320.5 in the IBU 30 group. There was a difference between the sham and control groups, and the mean value was higher in the control group. TOS mean values did not show difference according to groups (p=0.168). Tissue OSI index mean values were 975.5 in the control group, 641.63 in the sham group, 849.75 in the IBU 10 group and 899.5 in the IBU 30 group.

The comparison of biochemical values according to groups is presented in Table 2.

There was a statistically significant negative correlation between serum prolidase and tissue total antioxidant status in the control group (r=-0.749; p=0.033). There was a statistically significant negative correlation between serum prolidase and tissue total oxidant status in the IBU 10 group (r=-0.799; p=0.017). Similarly, there was a statistically significant negative correlation between serum prolydase and tissue oxidative stress index in the IBU 10 group (r=-0.750; p=0.032). There was a statistically significant negative correlation between serum total oxidant status and tissue total oxidant status - tissue oxidative stress index in the IBU 30 group (r values were -0.770 and -0.793, p=0.025,p= 0.019 respectively). There was a statistically significant negative correlation between serum oxidative stress index and tissue total oxidant status - tissue oxidative stress index in the IBU 30 group (r values were -0.757 and -0.804, p=0.030, p=0.016 respectively).

The relationship between serum and tissue biochemical values is presented in Table 3.

A significant positive correlation was found between tissue prolidase and tissue oxidative stress index in the control group (p=0.015, r=0.809). In the IBU 10 group, a strong negative correlation was found only between tissue total oxidant status (p=0.017, r= -0.799).

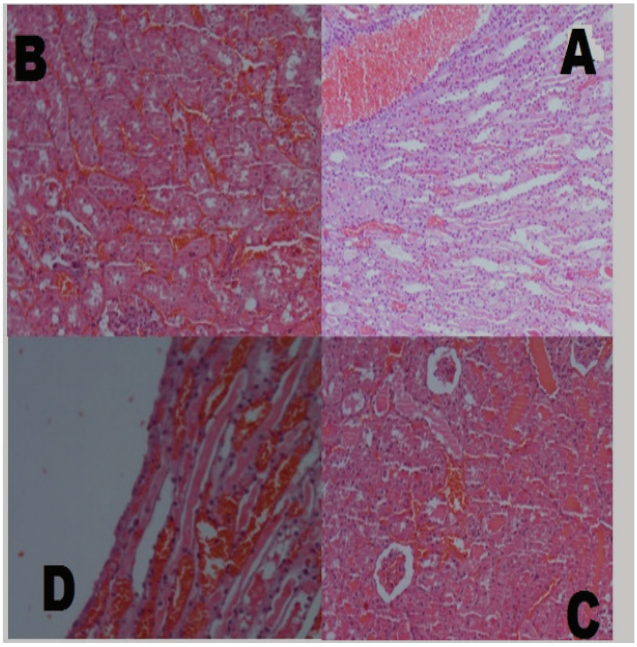

Figure 1. A- hyaline cast in control group (H&E X100),B- intense congestion in the cortex in the control group (H&EX100),C- degeneration in the control group (H&EX100), D- (H&EX200) hyaline cast in control group

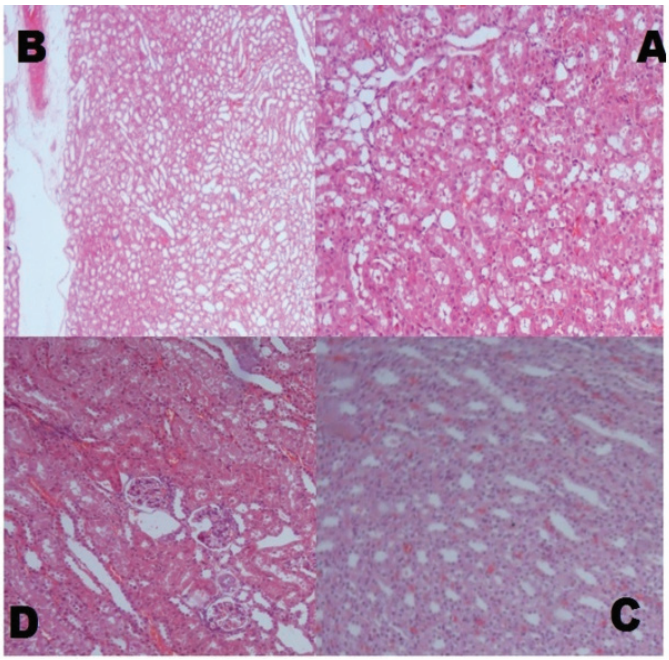

Figure 2. A- mild congestion in the IBU 10 group (H&EX100),B- mild degeneration in the IBU 10 group (H&EX40),C- normal appearance in medulla in sham group (H&EX100),D- sham group, normal appea-rance (H&EX100)

Table 1. Examination of pathological values according to groups

	Sham	Control	IBU 10	IBU 30	Total	p*
Tubular swelling						
Mild	5 (62.5)	2 (25)	3 (37.5)	5 (62.5)	15 (46.9)	
Moderate	3 (37.5)	5 (62.5)	5 (62.5)	3 (37.5)	16 (50)	0.446
Severe	0 (0)	1 (12.5)	0 (0)	0 (0)	1 (3.1)	
Tubular cell degeneration						
Mild	7 (87.5)	3 (37.5)	7 (87.5)	8 (100)	25 (78.1)	0.013
Moderate	1 (12.5)	5 (62.5)	1 (12.5)	0 (0)	7 (21.9)	
Hyaline cast formation						
Mild	8 (100)	4 (50)	7 (87.5)	7 (87.5)	26 (81.3)	
Moderate	0 (0)	1 (12.5)	1 (12.5)	1 (12.5)	3 (9.4)	0.077
Severe	0 (0)	3 (37.5)	0 (0)	0 (0)	3 (9.4)	
Interstitial lymphocyte						
Mild	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	---
Medullary congestion						
Mild	8 (100)	1 (12.5)	5 (62.5)	6 (75)	20 (62.5)	
Moderate	0 (0)	0 (0)	3 (37.5)	2 (25)	5 (15.6)	<0.001
Severe	0 (0)	7 (87.5)	0 (0)	0 (0)	7 (21.9)	
Interstitial edema						
Mild	8 (100)	4 (50)	8 (100)	8 (100)	28 (87.5)	0.003
Moderate	0 (0)	4 (50)	0 (0)	0 (0)	4 (12.5)	
Tubular dilatation						
Mild	8 (100)	4 (50)	8 (100)	8 (100)	28 (87.5)	0.003
Moderate	0 (0)	4 (50)	0 (0)	0 (0)	4 (12.5)	

n(%), *Chi-square test

Table 2. Comparison of biochemical values according to all groups

	Control	Sham	IBU 10	IBU 30	p*
Serum prolidase (U/L)	349.88 ± 13.05b	318.75 ± 16.5a	340.13 ± 16.86b	328.38 ± 14.36c	<0.001
Tissue prolidase (U/L)	3593.5 ± 210.63a	2652.88 ± 194.36b	3512.25 ± 195.65a	3144.13 ± 168.5c	<0.001
Serum Total Antioxidant status (mmol Trolox Eq./L)	1.39 ± 0.14a	1.79 ± 0.24c	1.43 ± 0.2ab	1.68 ± 0.22bc	0.001
Serum Total Oxidant Status (µmol H2O2 Equiv./L)	28.66 ± 7.9a	16.79 ± 6.63b	16.91 ± 4.96b	18.51 ± 6.81b	0.003
Tissue Total Antioxidan Status (mmol Trolox Eq./L)	1.30 ± 0.26	1.55 ± 0.3	1.77 ± 0.23	1.81 ± 0.24	0.002
Tıssue Total Oksidan Status (µmol H2O2 Equiv./L)	13.58 ± 2.55	10.62 ± 4.11	12.25 ± 4.33	13.16 ± 4.04	0.434
Serum Oxidative Stress Index (Arbitrary Unit)	1573.13 ± 333.8a	977.75 ± 294.44b	1181.5 ± 304.93ab	1320.5 ± 452.72ab	0.017
Tissue Oxidative Stress Index (Arbitrary Unit)	975.5 ± 410.54	641.63 ± 249.66	849.75 ± 280.84	899.5 ± 226.56	0.168

*Variance analysis test, a-b: There is no difference between the groups with the same letter in terms of the relevant parameter.

Table 3. The correlation analysis serum and tissue biochemical values

Group	Parameter		Serum prolidase	Serum Total Antioxidant status	Serum Total oxidant status	Serum Oxida-tive Stress In-dex
Control	Tissue Prolidase	r	0.428	-0.027	0.267	0.455
		p	0.291	0.950	0.522	0.258
	Tissue Total Antioxidant status	r	-0.749*	0.113	-0.051	-0.112
		p	0.033	0.790	0.905	0.792
	Tissue Total oxidant status	r	-0.023	-0.541	-0.248	0.088
		p	0.957	0.166	0.555	0.836
	Tissue Oxida-tive Stress Index	r	0.473	-0.521	-0.136	0.196
		p	0.237	0.186	0.748	0.642
Sham	Tissue Prolidase	r	0.008	-0.669	-0.335	-0.151
		p	0.985	0.070	0.418	0.721
	Tissue Total Antioxidant status	r	0.459	0.025	0.247	0.278
		p	0.253	0.954	0.555	0.505
	Tissue Total oxidant status	r	-0.229	-0.252	-0.264	-0.207
		p	0.585	0.547	0.527	0.623
	Tissue Oxida-tive Stress Index	r	-0.443	-0.215	-0.340	-0.295
		p	0.272	0.608	0.411	0.478
IBU 10	Tissue prolidase	r	0.346	-0.105	0.208	0.325
		p	0.402	0.804	0.621	0.432
	Tissue Total Antioxidant status	r	0.024	0.298	0.459	0.368
		p	0.955	0.474	0.252	0.369
	Tissue Total oxidant status	r	-0.799*	0.144	-0.012	-0.091
		p	0.017	0.734	0.977	0.830
	Tissue Oxida-tive Stress Index	r	-0.750*	0.052	-0.162	-0.214
		p	0.032	0.903	0.702	0.610
IBU 30	Tissue Prolidase	r	-0.389	0.061	0.251	0.224
		p	0.341	0.886	0.548	0.594
	Tissue Total Antioxidant status	r	0.169	0.003	0.410	0.454
		p	0.689	0.995	0.314	0.259
	Tissue Total oxidant status	r	-0.210	-0.225	-0.770*	-0.757*
		p	0.617	0.592	0.025	0.030
	Tissue Oxida-tive Stress Index	r	-0.278	-0.190	-0.793*	-0.804*
		p	0.506	0.652	0.019	0.016

r: Pearson correlation coefficient

DISCUSSION

When we examined our pathological data analysis, statistically significant differences were found between all groups in the way of all parameters showing cellular damage except tubular swelling and hyaline cast formation. There were statistically significant differences between the groups in the way of tubular cell degeneration, medullary congestion, interstitial edema and tubular dilatation parameters. In the groups that were given

intravenous ibuprofen, always less cellular damage was detected. Cellular damage indicators were significantly lower in the treated rats than in the sham group. Examining the results of biochemical analysis yielded roughly the same situation. Serum prolidase and tissue prolidase values different between groups. Serum TAS and serum TOS levels were also different between groups. Serum OSI levels were also different between groups. Serum and tissue prolidase /serum TOS/serum OSI index/ Tıssue TOS/ Tıssue OSI index levels in control group were higher than given intravenous ibuprofen groups. Serum and tissue TAS levels in control group were lower than given intravenous ibuprofen groups. These results indicate that intravenous ibuprofen protects the kidneys from experimentally induced renal ischemia-reperfusion injury. Our pathological and biochemical analyzes results constitute the belief that intravenous ibuprofen out test doses protects the kidney tissue.

In an experimental study by Uzar et al., a cerebral ischemia/reperfusion injury was induced in rats and the protective effects of nebivolol and zofenopril were compared with pathological and biochemical biomarkers. They observed the serum TAS, TOS, malondialdehyde and nitric oxide levels. In pathological preparations, they evaluated the level of cell apoptosis (14).Although their study was different in terms of inducing cerebral ischemia/reperfusion injury, our results were similar. As with Uzar et al., in our study, we also reached the belief that intravenous ibuprofen protects kidney tissue against renal ischemia reperfusion.

In an experimental study by Sıvgın et al., they investigated the effect of intravenous ibuprofen and lornoxicam on erythrocyte deformability of leg and hip ischemia/ reperfusion injury. The authors suggested that intravenous ibuprofen and lornoxicam did not impair the erythrocyte deformability during the ischemia/reperfusion period and that they had no adverse effect (8). Although Sıvgın et al. studied ischemia reperfusion of a different area, they reported the fact that intravenous ibuprofen has a protective effect against ischemic tissues is similar to our study. Our results are partially compatible with the study of Sıvgın et al.

In the literature, intravenous ibuprofen has been studied for clinical prospective studies aimed at preemptive analgesia. Experimental studies with intravenous ibuprofen are very rare; in fact, intravenous ibuprofen has never been studied in experimental renal ischemia-reperfusion injury. Therefore, our study is the first one in the literature in experimental renal ischemia-reperfusion injury.

In a clinical study by Balestracci et al., they reported that ibuprofen increased kidney damage independent of dehydration in pediatric patients. In a study including 105 pediatric patients (according to the pediatric RIFLE criteria), they reported that acute kidney injury was observed to be developing twice as much in children given ibuprofen (15). Our results are not consistent with the results of Balestracci A. et al. In our experimental study, we observed that intravenous ibuprofen was protective against renal ischemia-reperfusion injury.

In another study by Raaijmakers et al., they reported that ibuprofen exposure in low birth-weight newborns did not impair renal function in the long term. Cystatin C and glomerular filtration rates were observed in 93 low birth-weight infants up to the age of 11 years. In this long term study, it was stated that ibuprofen exposed during the newborn period did not change renal functions in the later periods (16). The results of the study by Raaijmakers et al. support our hypothesis.

In their clinical study, Lahiri et al. have obtained results that support our results. Ibuprofen was used to treat cystic fibrosis. High dose ibuprofen may slow the decrease in lung functions in patients with cystic fibrosis, but its use is restricted owing to take care of about renal and gastrointestinal toxicity. Lahiri et al., used high-dose ibuprofen in children with cystic fibrosis and monitored potential renal damage with urinary biomarkers, that are kidney injury molecule 1 (KIM-1) and Nacetyl βglucosaminidase (NAG). These urinary biomarkers are more sensitive than serum creatinine, showing kidney damage. They reported no difference in urinary biomarkers with urinary excretion between the high dose ibuprofen group and the group that did not receive ibuprofen treatment. The authors stated that ibuprofen does not cause renal toxicity and is a safe molecule for renal functions (17). Our results are partially concordance to those of Lahiri et al, because our study doses are experimental study doses.

CONCLUSION

In conclusion, the biochemical and pathological results we obtained in our experimental study suggest that intravenous low dose ibuprofen, has a protective effect against renal injury. More clinical studies are needed to prove whether the intravenous form of ibuprofen causes renal toxicity. We believe that our study will shed light on future clinical prospective studies.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

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