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The Effects of Different Doses of Ketamine on Renal Ischemia/Reperfusion Injury in Rats

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ABSTRACT

In the patients who have perioperative renal failure risk, anesthetical substances should be choosen with caution to protect the function of kidneys. Ketamine, an anesthetic induction agent, is generally used in patients with severe hypotension or respiratory depression. We aimed to evaluate the different doses of ketamine's effects on ischemia/reperfusion (I/R) damage mediated by free radicals in rats.

Materials and methods: In this study, 42 Wistar albino male rats were splitted randomly into 7 different groups. In the ketamine group, ketamine was applied intraperitoneally (IP) in different doses (3 mg kg^{-1}, 10 mg kg^{-1}, 30 mg kg^{-1}, 60 mg kg^{-1}, 80 mg kg^{-1}) on the 45 th minutes. Clamps were opened at the end of 60 minutes ischemia period. At the end of the reperfusion period, renal tissue and blood samples were taken from the rats. In the plasma samples, pro-inflammatory biomarkers [Interleukin (IL)-1β, IL-6, tumour necrosis factor alpha (TNF-α)] were analysed. In renal tissue samples, antioxidating activities [Superoxide dismutase (SOD), glutathione peroxidase (GPx) and nitric oxide (NO)] and lipid peroxidation product "Malondialdehyde (MDA)" levels were studied biochemically. Renal tissue damage was evaluated histopathologically.

There were no differences among the beneficial effects of ketamine given groups (10-30-60-80 mg kg^{-1} doses) before reperfusion in the way of antioxidant activities, pro-inflammatory markers and lipid peroxidation product. When ketamin was applied in 3 mg kg^{-1} there were beneficial effects on tissues in the way of SOD, GPx, NO, MDA values and histopathologically ($p<0.05$).

Some studies have shown that ketamine has little anti-inflammatory properties. This animal study has shown that ketamine in low doses significantly reduces the I/R injury in rats ($p<0.05$).

Key Words: Ischemia/reperfusion injury, different doses of ketamine, urethane.

Introduction

Ischemia and reperfusion injury may occur in the kidneys during clinical conditions such as major trauma, systemic hypotension, hypovolemic shock, cardiac arrest, renovascular surgery, clamping of the aorta, and tissue injury. The severity of the damage increases with the duration of ischemia, and this damage has many different clinical manifestations ranging from prerenal azotemia to serious acute renal failure caused by tubular or cortical necrosis. Patients with perioperative renal failure risk who are undergoing surgical procedures (such as transplantation) should be given an anesthetic agent to protect kidney function; however, the ideal anesthetic agent to protect kidney function has not yet been discovered. These types of patients have a high risk of perioperative mortality and morbidity (1-2). After ischemia and reperfusion injury, organisms defend themselves against free oxygen radicals (FOR) with an antioxidant enzyme system. The

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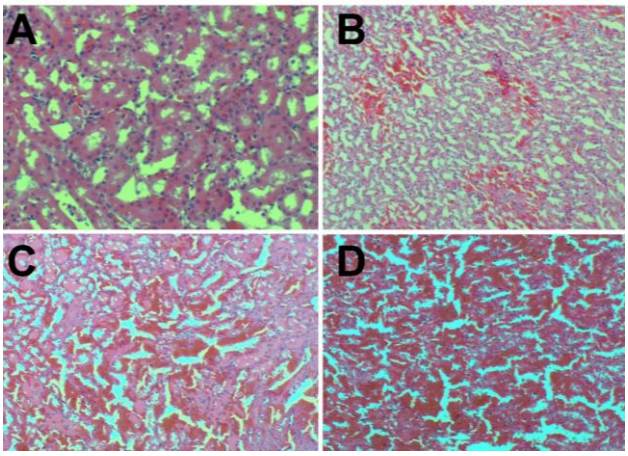

Fig. 1(A-D): Photomicrograph of kidney sections stained with Hematoxilen-Eocin dye. A and D. (A) Normal medullary structure. (B) Low level congestion. (C) Medium level congestion. (D) Severe congestion

FOR causes the oxidation of polyunsaturated fatty acids, leading to malondialdehyde (MDA) accumulation in the cell organelles. Early reperfusion damage increases activation of both neutrophils and macrophages and triggers proinflammatory cytokine release from macrophages. These cytokines lead to neutrophil and T-lymphocyte activation in the late stages (3-5). Ketamine is a derivative of aminocyclohexanone whose chemical structure is related to phencyclidine. Ketamine, an anesthetic induction agent, is generally used in patients with severe hypotension or respiratory depression. Ketamine suppresses this proinflammatory cytokine release, especially when used in the induction of patients with sepsis (6). In vitro studies have shown that neutrophils can inhibit FOR production and can prevent cell damage by suppressing the production of TNF-α (7). Several drugs and antioxidant substances have been examined for the treatment of ischemia and reperfusion injury. In recent years, different approaches to preventing ischemia and reperfusion injury have been researched in the clinical setting (8). Our current study aimed to investigate the effects of the anaesthetic agent ketamine at different doses against the free oxygen radicals and proinflammatory components occurring due to renal ischemia and reperfusion.

Materials and Methods

Materials: Anesthetic drugs [Urtehane (Urethane 99%, Sigma-Aldrich, Germany) and Ketamine (Ketalar, Eczacıbası, Turkey)] and other chemical were bought from INTERLAB Laboratuar Ürünleri Sanayi ve Ticaret Incorporated Company, Istanbul, Turkey.

Experimental Animals: A total of 42 healthy adult male rats weighing 250±10 g of Wistar albino strain were maintained from Kahramanmaras Sutcu Imam University experimental animals center (Turkey). The rats were kept in wire cages, in constant temperature (22±2°C) and humidity (50-60%) and were exposed to 12 h dark/light cycle. The rats were allowed to access to water and standard animal food for rats (*ad libitum*). This study was performed after approval from the local ethics committee for animal experiments in the University of Kahramanmaras, Medical Faculty (No: 2009/9/3).

Ischemia/Reperfusion Injury Model: After intraperitoneal (IP) Urethane (1 g kg^{-1}) anesthesia, 3 cm midline incision was performed. Renal ischemia was obtained by putting small atraumatic vascular clamp to left renal artery and vein. On the 45th minute of ischemia, ketamine hydrochloride (Ketalar, Eczacıbası, Turkey) was used intraperitoneally (IP). The clamps were opened on the 60th minute of ischemia. The blood stream in the renal artery and vein were observed. After 1 hour of reperfusion time, left nephrectomy was performed than decapsulated, halved longitudinally in two for histopathological and biochemical analysis. One of the pieces was immersed in formaldehyde solution for histopathological analysis. The other part was preserved in -70°C for biochemical analysis. Intracardiac 5 ml blood samples were taken and were put in the heparin coated tubes then the animals were eutanised with high doses of anesthetic drugs. Blood samples were preserved in -70°C soon after centrifuging them in the rate of 3000xg for 10 minutes in heparin coated tubes until they were analyzed. The experimental model in this study was designed suitable to the methods described by previous experimenters (9).

Experimental Design: The study carried out in the histopathology and chemistry laboratory of Medical school of Kahramanmaras Sutcu Imam University, 42 male rats were separated randomly into 7 experiment groups in equal numbers (n=6) as follows:

Group 1 (Sham): Tissue and blood samples were taken 120 minutes after laparotomy by left nephrectomy. No drugs.

Group 2 (Control): Laparotomy, 60 minutes ischemia, 60 minutes reperfusion, tissue and blood samples were taken by left nephrectomy. No drugs.

Table 1. IL-1, IL-6, TNF-α, MDA, SOD, NO, and GPx values of the experimental groups (Values expressed as mean ± SD)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
	Sham	Control	I/R+3 mg.kg-1 Ketamine	I/R+10 mg.kg-1 Ketamine	I/R+30 mg.kg-1 Ketamine	I/R+60 mg.kg-1 Ketamine	I/R+80 mg.kg-1 Ketamine
IL-1β	8.42±0.26	19.85±8.79 *	12.85±6.02**	14.70±5.59	14.92±4.93	15.62±4.70	15.58±4.94
pg.ml-1	8.10-8.80	14.20-37.20	8.10-22.40	8.20-22.00	9.10-22.50	9.60-23.10	10.40-24.20
IL-6	27.90±5.08	45.80±14.00 *	32.65±5.51**	34.85±10.36	34.60±7.03	36.25±7.52	35.37±6.05
pg.ml-1	19.6-33.40	31.30-64.70	26.10-40.20	23.50-48.20	28.10-46.50	29.20-46.20	30.30-46.20
TNF-α	29.52±11.98	45.60±18.35	32.82±7.38	32.07±6.13	38.78±9.52	35.93±8.88	35.73±8.00
pg.ml-1	18.50-46.40	29.00-77.20	24.50-45.70	22.50-37.50	32.10-56.50	22.10-45.70	26.10-49.50
MDA	3.11±1.19	9.61±4.37 *	3.34±0.80 **	3.46±0.61**	3.26±0.75 **	3.10±0.89 **	3.10±0.53 **
nmol.mg-1	2.03-4.75	5.85-17.26	2.01-4.48	2.74-4.42	2.58-4.61	2.11-4.17	2.38-3.70
SOD	24.21±6.90	8.18±3.64 *	16.36±4.90**	14.27±3.95 **	14.90±3.63 **	17.04±4.05 **	13.43±2.65 **
U.mg-1 pr.	17.15-35.82	3.99-13.90	11.14-24.12	10.74-19.55	10.04-19.52	10.63-22.40	10.86-17.53
NO	0.50±0.08	1.95±0.45 *	0.68±0.09 **	0.68±0.16 **	1.03±0.45 **	0.97±0.28 **	0.90±0.32 **
μmol.mg-1 pr.	0.38-0.61	1.10-2.39	0.58-0.80	0.44-0.87	0.64-1.78	0.75-1.53	0.42-1.27
GPx	0.68±0.15	0.02±0.01*	0.26±0.04 **	0.41±0.12 **	0.48±0.16 **	0.43±0.11**	0.44±0.20 **
U.mg-1 pr.	0.49-0.86	0.01-0.03	0.20-0.32	0.21-0.51	0.35-0.77	0.34-0.64	0.29-0.81

*Significantly different from the sham group ($p<0.05$)
**Significantly different from the control group ($p<0.05$)

Group 3 (I/R + Ketamine hydrochloride 3 mg kg^{-1}): Laparotomy, 60 minutes ischemia, 3 mg kg^{-1} ketamine hydrochloride was used IP 15 minutes before reperfusion, 60 minutes reperfusion, left nephrectomy.

Group 4 (I/R + Ketamine hydrochloride 10 mg kg^{-1}): Laparotomy, 60 minutes ischemia, 10 mg kg^{-1} ketamine hydrochloride IP 15 minutes before reperfusion. 60 minutes reperfusion, left nephrectomy.

Group 5 (I/R + Ketamine hydochloride 30 mg kg^{-1}): Laparotomy, 60 minutes ischemia, 30 mg kg^{-1} ketamine hydrochloride IP 15 minutes before reperfusion. 60 minutes reperfusion, left nephrectomy.

Group 6 (I/R + Ketamine hydrochloride 60 mg kg^{-1}): Laparotomy, 60 minutes ischemia, 60 mg kg^{-1} ketamine hydrochloride IP 15 minutes before reperfusion. 60 minutes reperfusion, left nephrectomy.

Group 7 (I/R + Ketamine hydrochloride 80 mg kg^{-1}): Laparotomy, 60 minutes ischemia, 80 mg kg^{-1} ketamine hydrochloride IP 15 minutes before reperfusion. 60 minutes reperfusion, left nephrectomy.

Preparation of Kidney Homogenates and Oxidative Response Estimation: Tissue samples obtained from the left nephrectomy were weighed and homogenized with a 1/5 ratio of cold 1.15% M KCL, at a rate of 14,000xg for 30 minutes. Then, the supernatants were isolated by centrifugating at 10,000 cycles/minute rate for 30 minutes in +4°C. Measurement of antioxidating activities of the enzymes and the lipid peroxidation levels were made in the supernatants. The enzyme activities of superoxide dismutase (SOD) according to the method described by Fridovich (10), glutathione peroxidase (GPx) according to the method described by Beutler (11) and MDA according to the method described by Okhawa (12). NO according to the method described by Cortas et al. (13) previously and protein levels were also measured in the kidney tissue (Shidmadzu-UV 1601 Spectrophotometer (Japan)). Protein determination was performed via the Lowry method (14). Antioxidant enzyme activity results were shown as U mg protein^{-1}, MDA levels as nmol mg^{-1} protein, and NO levels as μmol mg^{-1} protein.

The Pro-Inflammatory Component Levels Evaluation: IL-1β, IL-6 and TNF-α in the serum were measured by using standard kits for each test (eBioscience, Inc. San Diego, CA 92121, USA). The minimum calculable values for IL-1β, IL-6 and TNF-α 16 pg.ml^{-1}, 31 pg.ml^{-1} and 39.1 pg.ml^{-1} respectively.

Histopathologic Study: Tissue samples for histopathological examination were fixed in 10% buffered neutral formaldehyde solution about 24 hours, and paraffin blocks were prepared. 5 μm thick serial sections were dyed with hematoxylin and eosin (H&E) staining and analyzed with light microscopy. Tubular cell swelling, interstitial edema, tubular dilatation, medullary congestion, hyaline cast formation and epithelial necrosis were evaluated; all of these parameters were graded as

Table 2. Results of histopathological analysis of renal tissue

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
	Sham	control	I/R+3 mg.kg-1 Ketamine	I/R+10 mg.kg-1 Ketamine	I/R+30 mg.kg-1 Ketamine	I/R+60 mg.kg-1 Ketamine	I/R+80 mg.kg-1 Ketamine
Mean±SD	0±0	2,17±0,41*	1,50±0,55**	2,33±0,52	2,17±0,75	1,83±0,75	1,33±1,03
(Min. Max. Values)	(0-0)	(0-3)	(0-2)	(0-3)	(0-3)	(0-3)	(0-3)

Renal tissues were dyed with hematoxilen-eocin dye and evaluated with light microscopy. Mean values were expressed as Mean±SD, n = 6 for each treated group. Congestion was observed in the medium level in the control group. In the group ketamine (3 mg kg^{-1}) congestion were statistically lower than the control group ($p<0.05$)

*Different from the sham group meaningfully ($p<0.05$)
** Different from the control group meaningfully ($p<0.05$)

either positive or negative (Figure 1). Positive findings were graded "+", "++", "+++" and negative findings were graded "no (−)" findings as were described by Yuzer et al. (15) previously.

Data Analysis: Results were expressed as a Mean±Standard Deviation in each group. SPSS Inc. Chicago, IL; USA analysis program was used. In the biochemical data statistical analysis, Kruskal-Wallis method was used in the evaluation of the differences between the groups and Mann-Whitney U test was used in the evaluation of the double check, $p<0.05$ values were accepted as statistically significant.

Results

All the biochemical parameters including ketamine's effect on the proinflammatory cytokines and antioxidants were presented in Table 1. The control group's IL-1β levels were significantly higher than the sham group ($p<0.05$, Table 1). The IL-1β and IL-6 levels of Group 3 (I/R + Ketamine 3 mg kg^{-1}) were 12,85 (±6.02) pg ml^{-1} and 32,65 (±5,51) pg ml^{-1}, lower than those of the control group ($p <0.05$, Table 1). While the other ketamine receiving groups (10 mg kg^{-1}, 30 mg kg^{-1}, 60 mg kg^{-1}, 80 mg kg^{-1}) had also lower IL-1β and IL-6 levels than the control group, however the differences were not statistically significant (Table 1). The TNF-α values of the control group were higher than those of the sham group ($p<0.05$, Table 1). All of the ketamine given groups (3 mg kg^{-1}, 10 mg kg^{-1}, 30 mg kg^{-1}, 60 mg kg^{-1}, 80 mg kg^{-1}) had lower TNF-α levels than the control group, however the differences among the ketamine given groups weren't statistically significant (Table 1). The MDA, SOD, NO, and GPx levels of the control group were higher than those of the sham group ($p<0.05$, Table 1). The MDA levels of all the ketamine groups (3 mg kg^{-1}, 10 mg kg^{-1}, 30 mg kg^{-1}, 60 mg kg^{-1}, 80 mg kg^{-1}) were lower than those of the control group ($p<0.05$, Table 1). However, the differences in MDA values between the ketamine given groups were not statistically significant (Table 1). Renal tissues were dyed with hematoxilen-eocin dye and evaluated with light microscopy. Mean values were expressed as Mean±SD, n = 6 for each treated group. Congestion was observed in the medium level in the control group. In the group ketamine (3 mg kg^{-1}) congestion were lower than the control group ($p<0.05$). Mean scores having after evaluation of renal tissue samples' stained with H&E; 0 in the Sham group, 2,17 in the Control Group, 1,50 in the Group 3. In the Group 3 (I/R+Ketamine 3 mg kg^{-1}), congestion were lower than the Control Group ($p<0.05$). The difference found in the tissue damage levels among the other ketamine applied groups (10 mg kg^{-1}, 30 mg kg^{-1}, 60 mg kg^{-1}, 80 mg kg^{-1}) weren't significant according to the control group statistically (Table 2).

Discussion

Many factors such as microvascular injury, inflammatory cytokines, cell death by release of free oxygen radicals and subsequent peroxidation of lipids play a role in the formation of I/R injury. Malondialdehyde (MDA) and nitric oxide (NO) forming by lipid peroxidation in the cellular membrane, which are metabolites that are used to measure I/R injury, accumulates. Cellular enzymatic defense against free radical damage is provided by free radical scavenging systems (CAT, SOD and GPx) (16-17). Tissue damage caused by ischemia in the reperfusion period results in catastrophic outcomes. Therefore therapeutic approaches to protect kidney tissue include

inhibition of inflammatory responses (18-21). Saricaoglu et al. (21) showed reduced MDA levels in synovial membrane samples of patients having arthroscopic knee surgery under tourniquet with sedative doses of ketamine (0,5 mg kg^{-1} h^{-1}). In that study, MDA levels in kidney tissues were significantly higher in the control group. Ozmen et al. (22) in the study investigating the effects of increased intra-abdominal pressure on cytokines, CRP, SOR and tissue histology in rats, they found that serum NO, MDA and IL-6 levels were significantly elevated in the ischemic group in comparison to the control group. In that study, control group's NO levels were significantly higher than the sham group. While the NO values determined in all groups of ketamine were lower than the control group, the difference between the ketamine given groups was not significantly different. Ergun et al. (23) reported that they observed the most prominent effects of ketamine in the groups which are given subanesthetic doses of ketamine (3 mg kg^{-1}) in their extremity I/R injury study. Chang et al. (24) has shown that ketamine (100 and 250 μM) inhibited lipopolysaccharide (LPS)-induced NO and IL-1β release in primary cultured microglia in a concentration dependent manner. However, ketamine (100 and 250 μM) did not significantly inhibit the LPS-induced TNF-*a* production in microglia, except at the higher concentration (500 μM). Yuzer et al. (15) used ketamine (60 mg kg^{-1} IM) anesthesia in the renal I/R injury model in rats, then they administered ketamine (20 mg kg^{-1}) intraperitoneally before reperfusion and examined anti-inflammatory effects. They suggested that the anti-inflammatory effects of ketamine are few like in many other studies. However due to in this study ketamine is high because anesthesia provided with ketamine. In this present study; there was a statistically significant increase in SOD and GPx levels, decrease in MDA and NO levels, decrease in plasma pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in kidney tissue ketamine 3 mg kg^{-1} applied group according to the control group.

In conclusion, our findings showed that ketamine has antioxidating properties in different doses however the prominent antioxidating properties occur in lower doses. We are also of the opinion that higher doses may be harmful in relation to elevated blood catecholamine concentrations because of ketamine's sympathomimetic effect, therefore ketamine 3 mg kg^{-1} may be used in the kidney with I/R injury, the higher doses of it aren't necessary.

Significance Statement: This animal study has shown that lower doses of ketamine can protect against oxidative damage induced by I/R.

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