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## LABORATORY STUDY

# Thiopental improves renal ischemia–reperfusion injury

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## ABSTRACT

Ischemia/reperfusion (I/R) occurs in a number of pathological conditions, including myocardial infarction, stroke, aortic surgery, cardiopulmonary bypass surgery, organ transplantation, resuscitation, and critical care. Massive and abrupt release of oxygen-free radicals after reperfusion triggers oxidative damage. Before critical operations or after resuscitation, it would be wise to find a suitable prophylactic treatment to avoid I/R damage. We aimed to determine whether several commonly used intravenous anesthetics protect against renal I/R injury. Methods: Animals were randomly divided into seven groups, each consisting of six animals: sham group, control group, thiopental group, propofol group, intralipid group, etomidate group, and ketamine group. At the end of the 60-min ischemic period, 60 min reperfusion was established and the materials administered 15 min before the reperfusion. At the end of the reperfusion period, the samples of blood and tissue were reaped for biochemical and serological evaluation. Results: I/R procedure significantly increased malondialdehyde (MDA) levels, decreased catalase (CAT) activities, and superoxide dismutase (SOD) levels. The lowest MDA mean level was in the thiopental group and the highest MDA mean level was in control group. The lowest CAT mean level was in the intralipid group and the highest CAT mean level was in the etomidate group. The lowest SOD mean level was in the control group and the highest SOD mean level was in the propofol group. Conclusion: Thiopental and propofol, especially thiopental, are more effective to protect renal I/R injury.

**Keywords:** renal ischemia–reperfusion injury; intravenous anesthetics; thiopental; propofol

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## INTRODUCTION

Ischemia/reperfusion (I/R) occurs in a number of pathological conditions, including myocardial infarction, stroke, aortic surgery, cardiopulmonary bypass surgery, organ transplantation, resuscitation, and critical care. According to the severity of the damage, many clinical occasions varying from prerenal azotemia without tissue damage to the acute kidney failure related to tubular and cortical necrosis can be encountered. Exposure to I/R causes tissue damage, which in turn may lead to organ failure and potentially death.<sup>1,2</sup> Acute tubular necrosis and renal failure developing related to I/R are the main reasons of morbidity and mortality.<sup>3</sup>

Massive and abrupt release of oxygen-free radicals after reperfusion, followed by endothelial dysfunction or neutrophil infiltration, triggers the oxidative damage.

The release of oxygen-free radicals disturbs the prooxidant–antioxidant balance and plays a central role in the pathophysiological sequelae of reperfusion injury. The cytotoxic effects of reactive oxygen species (ROS) are the initiation of peroxidation of polyunsaturated fatty acids in membrane or plasma lipoproteins and the direct inhibition of mitochondrial respiratory chain enzymes. Oxidative stress also results in cell injury involving DNA, protein, and lipid. Base-damage products (such as 8-hydroxydeoxyguanosine), carbonyls, and other amino acid modifications (such as methionine sulfoxide) were used to evaluate the oxidative damage on DNA, protein, and lipid. Malondialdehyde (MDA) is one of the toxic metabolites of lipid peroxidation after ROS production.<sup>4</sup> Superoxide dismutase (SOD) and catalase (CAT) protect reperfused organs from injury. Free radical formation in ischemic tissue and the increase of this formatting with reperfusion injury

imply the value in all surgical clinics. So before critical operations or after resuscitation, it would be wise to find a suitable prophylactic treatment to avoid I/R damage.

Thiopental is a highly lipid-soluble anesthetic, which has demonstrated antioxidant properties by inhibiting lipid peroxidation<sup>5</sup> or by depressing ROS production of neutrophils<sup>6</sup> and to a lesser degree anti-hemolytic activity by inhibiting free-radical-mediated hemolysis of red blood cell *in vitro*.<sup>7</sup>

Propofol (2,6-diisopropylphenol), an another highly lipid-soluble anesthetic, is often used in the induction of anesthesia and in the sedation of patients bound to mechanical ventilation in intensive care unit and has been reported to have a protective effect against I/R injury in several organs: for example, muscle,<sup>8</sup> heart,<sup>9</sup> and brain.<sup>10</sup> The mechanism underlying this protective effect reportedly involves either radical scavenging or inhibitory effects on calcium channels during I/R injury.<sup>11</sup>

Etomidate is commonly used for cardiac patients because of good induction properties.<sup>12</sup> Ketamine is commonly used as an intravenous or intramuscular anesthetic in patients with septicemia or trauma.<sup>13</sup> Intralipid is a lipid emulsion from which prepared etomidate and propofol are used in clinics.

We aimed to determine whether several commonly used intravenous anesthetics protect against renal I/R injury to a similar extent using an *in vivo* rat model with plasma MDA levels, and the activities of CAT and SOD.

## METHODS

All assays were performed by an investigator blinded to study group assignment.

### Animals

The experimental protocol used for this study was approved by the Animal Ethics Review Committee of the Faculty of Medicine, and adhered to National Institutes of Health guidelines for the use of experimental animals. Forty-two Wistar rats were housed in individual cages in a temperature-controlled room with alternating 12-hr light–dark cycles and acclimatized for a week before the study. Food was removed 8 hr prior to the study, but all animals were allowed free access to water and rat chow diet.

### Experimental design

Rats were anesthetized with thiopental sodium 40 mg/kg, intraperitoneally (i.p.), and the abdominal region was shaved with a safety razor and sterilized with povidone iodine solution (Pental, I.E. Ulagay Türk İlaç Sanayii

A.Ş. Topkapı, İstanbul, Türkiye). The abdominal region was shaved and sterilized with povidone iodine solution. A midline incision was made and the abdominal viscera were retracted to the right side. The left renal hilus was dissected, the renal artery was occluded using a microvascular clamp (REDA Instrument, 13111-06, Tuttlingen, Germany), and the intestine was replaced into the abdominal cavity. At the end of the 60-min ischemic period, 60 min reperfusion was established by removal of the clamp and left nephrectomy was performed. Animals were randomly divided into seven groups, each consisting of six animals:

- Group 1 (sham group,  $n = 6$ ) rats were subjected to identical surgical procedures described above, except for renal I/R;
- Group 2 (control group,  $n = 6$ ) rats received 60 min of left renal ischemia followed by 60 min of reperfusion;
- Group 3 (I/R + thiopental group,  $n = 6$ ) animals were administered thiopental sodium (20 mg/kg, i.p.) 15 min before the reperfusion phase;
- Group 4 (I/R + propofol group,  $n = 6$ ) animals were administered propofol (25 mg/kg, i.p.; Propofol 1% Fresenius, Fresenius Kabi AB, Uppsala, Sweden) 15 min before the reperfusion phase;
- Group 5 (I/R + intralipid group,  $n = 6$ ) animals were administered intralipid [250 mg/kg (according to the phosphatide ratio), i.p.; intralipid 10% 500 mL Fresenius, Fresenius Kabi AB, Uppsala, Sweden] 15 minutes before the reperfusion phase;
- Group 6 (I/R + etomidate group,  $n = 6$ ) animals were administered etomidate (10 mg/kg, i.p.; Etomidate-Lipura, B. Braun Melsungen AG, Germany) 15 minutes before the reperfusion phase; and
- Group 7 (I/R + ketamine group,  $n = 6$ ) animals were administered ketamine hydrochloride (20 mg/kg, i.p.; Ketalar, Eczacıbaşı, Türkiye) 15 minutes before the reperfusion phase.

At the end of the reperfusion period, tissue was harvested for biochemical evaluation.

### Antioxidant study

To determine tissue antioxidant levels,  $1 \times 1 \text{ cm}^2$  tissue samples were taken from the left kidney. The samples were preserved in a deep freezer until examination. The tissues were homogenized with three volumes of ice-cold 1.15% KCl. The activities of antioxidant enzymes and the levels of lipid peroxidation were measured in the supernatant obtained from centrifugation at 14,000 rpm ( $18,400 \times g$ ). SOD activity was measured according to the method described by Fridovich.<sup>14</sup> CAT activities were determined by measuring the decrease in hydrogen peroxide concentration at 230 nm by the method of Beutler.<sup>15</sup> Lipid peroxidation

level in the tissue samples was expressed in MDA and measured according to the procedure of Ohkawa et al.<sup>16</sup> Protein concentration was determined according to the method of Lowry.<sup>17</sup>

### Statistical analysis

All variables were expressed as mean and standard deviation. Differences between groups were evaluated by Kruskal–Wallis variance analysis followed by a post hoc Mann–Whitney *U*-test. *p*-Values < 0.05 were considered statistically significant. All data were entered and processed by SPSS 11.0 (SPSS Inc., Chicago, IL, USA) for Windows statistical package.

## RESULTS

I/R procedure significantly increased MDA levels and decreased CAT activities and SOD levels (*p* < 0.05). MDA levels were lower in thiopental, propofol, and intralipid groups compared to sham group and in all groups compared to control group (*p* < 0.05). The lowest MDA mean level was in the thiopental group and the highest MDA mean level was in control group (Table 1). Mean MDA level obtained in the thiopental group was significantly lower when compared to the other groups (*p* < 0.05) except propofol – lower but not statistically different. MDA levels accepted 100% in control group were decreased 52.6% in sham group, 79.7% in thiopental group, 76.0% in propofol group, 62.5% in intralipid group, 49.7% in etomidate group, and 61.2% in ketamine group.

Our findings showed that CAT levels increased in sham, thiopental, propofol, and etomidate groups compared to the control group. The lowest CAT mean level was in the intralipid group and the highest CAT mean level was in the etomidate group (Table 1).

CAT levels accepted 100% in control group were increased 55.3% in sham group, 40.9% in thiopental group, 41.6% in propofol group, 113.7% in etomidate group, and 25.8% in ketamine group, and decreased 1.3% in intralipid group.

When mean SOD levels were evaluated, SOD levels were increased in all groups compared to control group. At the same time, SOD level in sham group was decreased when compared the other groups except control group. The lowest SOD mean level was in the control group, the highest SOD mean level was in the propofol group (Table 1). SOD levels accepted 100% in control group were increased 61.2% in sham group, 161.8% in thiopental group, 359.2% in propofol group, 190.3% in intralipid group, 107.6% in etomidate group, and 119.8% in ketamine group.

## DISCUSSION

Reperfusion damage is the chain of events related to free oxygen radicals produced during tissue ischemia and reperfusion. These chain of events continue with the activation of endothelial cells and the inflammation developed by the circulating leukocyte migration to the area. Cellular defense against free radical injury is provided by enzymatic (CAT, SOD, and glutathione peroxidase) and nonenzymatic (alpha tocopherol, vitamin C, carotene, urate, etc.) free radical scavenging systems. The protection provided by these free radical scavengers against ROS produced during injury further supports the hypothesis that free radical species are involved in the cellular pathogenesis of I/R injury.<sup>18</sup> In fact ROS such as superoxide anions (O<sub>2</sub><sup>-</sup>), hydrogen peroxides (H<sub>2</sub>O<sub>2</sub>) and the extremely toxic hydroxyl radical (°OH) are difficult to detect in patient because of their short half-life. As oxygen radicals are short lived and hard to detect, and the kidney tissue has a complex structure, bio-products of lipid peroxidation (MDA) or depletion of endogenous antioxidants (CAT and SOD) have been used as indirect markers for free radical generation in the kidney tissue to show the damage and compare the anesthetics' effects in decreasing the damage.<sup>8</sup>

The kidney I/R damage, which is a critical clinical problem, has been the subject of many clinical and experimental studies in the development of transplantation and cardiac surgeries and of critical care. The early phase of reperfusion – the first hour when the damage is at its maximum – was expected to benefit from the maximum effects. For this reason, these active materials were applied 15 min before the reperfusion.

TABLE 1. Levels of MDA, SOD, and CAT.

	MDA (nmol/mg protein)	SOD (U/mg protein)	CAT (U/mg protein)
Group 1 (Sham)	0.7	5.03	60.05
Group 2 (Control)	1.33*	3.12*	38.65*
Group 3 (Thiopental)	0.27***	8.17***	54.48**
Group 4 (Propofol)	0.32***	13.43***	54.76
Group 5 (Intralipid)	0.52***	9.06***	38.16*
Group 6 (Etomidate)	0.67**	6.48***	82.63**
Group 7 (Ketamine)	0.53**	6.86***	42.64

Notes: \**p* < 0.05, significant difference from sham group;  
\*\**p* < 0.05, significant difference from control group.

Increased MDA level in control group means that increased I/R damage. In this regard, all anesthetic agents and intralipid could be said to decrease lipid peroxidation, especially thiopental and propofol. Runzer et al.<sup>19</sup> detected that MDA levels decreased significantly when high-dose propofol was mixed with halothane in all tissues and had a significant protective effect primarily in liver and then kidney, heart, and lungs. They explained the tissues' different responses as each tissue has different lipid peroxidation sensitivity.

In our study thiopental had better antioxidant activity than propofol. Thiopental-based anesthesia induction could be the reason of this situation. Thus, high dose of thiopental was used. This means that in this study higher thiopental dose had a better antioxidant activity. In Yuzer's study,<sup>18</sup> MDA levels were lower in ketamine, propofol, and thiopental groups. As ketamine was an anesthetic induction agent for that study, it means that ketamine was used at high dose. It was stated that higher doses of ketamine had a better effect than the low doses of ketamine in that study. Runzer et al.<sup>19</sup> reported that more positive results were observed in high dose of propofol.

Yagmurdur's research<sup>5</sup> has shown increased MDA levels in etomidate groups in laparoscopic surgery. Our study showed that MDA level was higher in etomidate groups than in thiopental, propofol, and intralipid groups. But thiopental was not as effective as propofol in that study; clinical usage of low dose might be a reason of this.

The positive effects of propofol in many organs such as skeletal muscle,<sup>8</sup> heart,<sup>20</sup> lungs,<sup>21</sup> brain,<sup>22</sup> liver,<sup>23</sup> and testis<sup>24</sup> were observed. Propofol may limit the oxidative damage in various tissues, including kidney.<sup>18</sup> Theoretically propofol, which contains phenol groups, could be active as an antioxidant on the basis of this mechanism of action even if a different role played by this anesthetic agent in the oxyradical generating process is feasible.<sup>8</sup> In the study of Wang et al.,<sup>25</sup> propofol's antioxidant activity might be via heme oxygenase-1 induction. Otherwise Ebel et al.<sup>26</sup> concluded that propofol provided no protective effect against reperfusion injury in rat heart at a clinically relevant concentration and likewise Shimono et al.<sup>27</sup> concluded that propofol provided no protective effect against reperfusion injury in rat liver at all concentrations.

The forms of etomidate and propofol used in clinics are preparations prepared as 10% lipid emulsion. As intralipid was expected to be an antioxidant and how those components affect I/R damage, we also used intralipid solution, including 10% lipid contents as another group. Szekely et al.<sup>28</sup> reported intralipid explosion reaction redoubling the effect of neutrophils. Kamikawa and Yamazaki showed that intralipid administration decreased free radical formation in

mitochondria isolated from normal and ischemic dog hearts.<sup>29</sup> On the other hand, some studies<sup>30,31</sup> found that intralipid had an effect in a low level. In our study, we confirmed that intralipid in rats may reduce kidney I/R damage at a low level, supported by the results of those studies; however, propofol lowers kidney I/R damage at a significant level. If intralipid itself reduced the amount of free oxygen radicals, propofol did not have any additional renal effect of in our study. However, our study was not designed to investigate the influence of intralipid's effects on free oxygen radicals in reperfused renal tissue.

CAT levels were not decrease in sham, thiopental, propofol, and etomidate groups. This means that, because of antioxidant activity of these agents, CAT consumption was lowered. With respect to CAT levels, thiopental and propofol had better antioxidant activity. Ketamine had a low-level antioxidant activity and was not different statistically. One of interesting finding of this study, CAT level in etomidate group was very high. This is an inadaptable finding to MDA and SOD levels. According the CAT level, intralipid did not have antioxidant property.

In examining the SOD levels, the lowest level was in the control group but the highest level was in the propofol group. SOD levels in this study were adaptable to MDA levels nearly.

In conclusion, in researching the effects of these anesthetic materials on kidney I/R damage, it was found that thiopental was the anesthetic material in this study with the most positive effects. Thiopental and propofol, especially thiopental, are more effective to protect renal I/R injury. After myocardial infarction, stroke, resuscitation, or hypotensive attack in critical care, or during aortic surgery, cardiopulmonary bypass surgery, or organ transplantation, additional thiopental therapy improves renal I/R injury. However, experimental studies for a wide range of clinical research and the antioxidant effect mechanism of anesthetics are required.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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