

## Original Article

# Antioxidative Effects of Propofol vs. Ketamin in Individuals Undergoing Surgery

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## Abstract

Propofol (2, 6-diisopropylphenol) is a widely used intravenous sedative-hypnotic agent for both induction/maintenance of anesthesia and sedation of critically ill patients. The present study aimed to evaluate oxidative stress biomarkers in individuals undergoing surgery with propofol and ketamine at doses used to induce anesthesia. The plasma oxidative stress biomarkers such as total antioxidant capacity (TAC), lipid peroxidation (LPO), total thiol molecules (TTM) and antioxidant enzymes activity such as glutathione peroxidase (GPx), superoxid-dismutase (SOD) and catalase (CAT) were studied in blood samples obtained from 40 patients with propofol, and compared to samples from 40 patients with ketamine aged 11 – 50 years. The results showed that the ketamine group had significantly higher blood LPO level, GPx and SOD activity while having lower blood TAC and TTM concentrations in comparison to the propofol group. In conclusion, our findings showed that propofol has antioxidant effects in human. Further studies need to be conducted to demonstrate the exact mechanism of oxidative stress caused by anesthesia in surgery patients.

**Keywords:** Blood, ketamine, oxidative stress, propofol

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## Introduction

Oxidative stress occurs as a result of an imbalance between generation of reactive oxygen species (ROS) and inadequate antioxidant defence systems leading to cell damage either directly or through altering signaling pathways. The consequence of oxidative stress may be oxidative damage of lipids, proteins, and DNA, with subsequent development of diseases such as chronic lung disease, diabetes and Alzheimer's disease.<sup>1,2</sup> ROS production may result from exogenous factors such as radiation, air pollution and drug exposure or endogenous factors such as increased mitochondrial respiration and oxidative enzymes in infections and inflammation.<sup>3</sup> However, oxidants and free radicals are permanently formed in the organism.<sup>4</sup> The major sources of oxidants in the ICU patient are mitochondria and drug metabolism among others.<sup>5</sup> Propofol was the first of a new class of intravenous anesthetic agents; the alkylphenols. It is indicated for induction and maintenance of general anesthesia as well as for sedation of intubated, mechanically ventilated adults in ICU.<sup>6,7</sup> Propofol is characterized by a phenolic structure similar to that of  $\alpha$ -tocopherol, and presents antioxidant properties that have been demonstrated both *in vitro* and *in vivo*.<sup>8</sup> Recently, *in vitro* studies showed that propofol could effectively suppress apoptotic signaling and prevent apoptotic death of myocardial cells exposed to fatal stimuli.<sup>9,10</sup> *In vivo* studies demonstrated that propofol reduced cell apoptosis in rats.<sup>11,12</sup>

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To complete the previous surveys, this study was conducted to evaluate the existence of oxidative stress, balance between total antioxidant capacity and ROS, in patients with acute propofol exposure compared with ketamine.

## Materials and Methods

### Chemicals

Tetraethoxypropane (MDA), 2-thiobarbituric acid (TBA), trichloroacetic acid (TCA), n-butanol, 5,5-Dithiobis-2-nitrobenzoic acid (DTNB), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), Tris base, Propofol, Ketamine, ethylenediamine tetraacetic acid (EDTA), 2, 4, 6-tripyridyl-S-triazine (TPTZ), GPx and SOD (Ransel kit, Randox Laboratories Ltd, Crumlin, UK), were used in this study. All other chemicals were obtained from Sigma company, USA.

### Study subjects

#### Anesthesia

80 (40 per each group) patients undergoing general surgeries were randomized into two groups, the propofol group and the ketamine group, after signing the consent form. The study protocol was approved by the Ethics Committee of the Hamadan University of Medical Sciences, and was conducted according to the Declaration of Helsinki, and Good Clinical Practice Guidelines. The participants were informed about the nature of the study.

In the operating room, all patients were given fentanyl (1.5  $\mu$ g/Kg) and atropine (0.01 mg/Kg) and midazolam (70  $\mu$ g/Kg) by intravenous injection. In the propofol group, anesthesia was induced by intravenous injection of propofol (1.5 mg/Kg), and atracurium (0.15 mg/Kg), and maintained by isoflurane and O<sub>2</sub>+N<sub>2</sub>O (50%). In the ketamine group, anesthesia was induced by intravenous injection of ketamine (1.5 mg/Kg), atracurium (0.15 mg/Kg), and maintained by isoflurane and O<sub>2</sub>+N<sub>2</sub>O (50%). All patients under-

went tracheal intubation and mechanical ventilation.

#### *Post-operative management*

After the operation, all patients were admitted to the recovery room and monitored. Before discharging from the recovery, patients should have the following criteria: 1) consciousness; 2) spontaneous breathing; 3) stable hemodynamics.

#### *Biochemical analysis*

Venous blood samples were obtained 15 minute after induction, for the purpose of measuring serum superoxide dismutase (SOD) activity, glutathione peroxidase (GPx), catalase activity (CAT) and levels of lipid peroxidation (LPO), total antioxidant capacity (TAC) and total thiol molecules (TTM). The blood samples were centrifuged at 1,000 g for 15 minutes and the serum samples were stored at -80°C until analyzed.

#### *Measurement of Cu/Zn- SOD activity*

The activity of Cu/Zn- SOD was measured using a commercial kit (Ransod kit, Randox Laboratories Ltd, Crumlin, UK). Measurement of the enzyme was based on the generation of superoxide radicals produced by xanthine and xanthine oxidase and reacted with 2-(4-iodophenyl)-3-(4-nitrophenol) 5-phenyltetrazolium chloride (INT) to form a red formazan dye. The formazan was read at 505 nm. One unit of Cu/Zn- SOD was defined as the amount of enzyme necessary to produce 50% inhibition in the INT reduction rate.

#### *Measurement of GPx activity*

The amount of GPx was determined using a commercially available kit (Ransel kit, Randox Laboratories Ltd, Crumlin, UK) by measuring the rate of oxidation of NADPH at 340 nm. A unit of enzyme was expressed as the amount of enzyme needed to oxidize 1 nmol of NADPH oxidase/minute.

#### *Measurement of CAT activity*

Catalase activity was assayed in the samples by measuring the absorbance decrease at 240 nm in a reaction medium containing H<sub>2</sub>O<sub>2</sub> (10 mM), sodium phosphate buffer (50 mM, pH = 7.0). One unit of the enzyme is defined as 1 mol H<sub>2</sub>O<sub>2</sub> as substrate consumed/min, and the specific activity is reported as units/mL plasma.<sup>13</sup>

#### *Measurement of Total Thiol Molecules (TTM)*

Total sulfhydryl content was determined in plasma by the method of Hu (24). A volume of plasma (0.20 mL) was mixed in a 10 mL test tube with 0.6 mL of Tris-EDTA buffer (Tris base 0.25 M, EDTA 20 mM, pH 8.2) followed by the addition of 40 mL of 10 mM of DTNB in methanol. The final volume of the reaction mixture was made up to 4.0 mL by adding 3.16 mL of methanol. The test tube was capped, and the color was developed for 15–20 min, followed by centrifugation at 3000 g for 10 min at ambient temperature. The absorbance of the supernatant was measured at 412 nm.<sup>14</sup>

#### *Measurement of lipid peroxidation (LPO)*

The LPO product in tissues was determined by TBARS expressed as the extent of malondialdehyde (MDA) production during an acid heating reaction. Briefly, the samples were diluted by 1.5 mL TCA (20% w/v) was added to 250 µL of this samples and

centrifuged in 3000 g for 10 min. Then, the precipitation was dissolved in sulfuric acid and 1.5 mL of the mixture was added to 1.5 mL of TBA (0.2% w/v). The mixture was then incubated for 1 h in boiling water bath. Following incubation, 2 mL of n-butanol was added, the solution centrifuged, cooled and the absorption of the supernatant was recorded in 532 nm. The calibration curve of tetraethoxypropane standard solutions was used to determine the concentrations of TBA+MDA adducts in samples.<sup>15</sup>

#### *Measurement of Plasma TAC*

The antioxidant capacity of plasma was determined by measuring the ability of plasma to reduce Fe<sup>3+</sup> to Fe<sup>2+</sup>. The complex between Fe<sup>2+</sup> and TPTZ gives a blue color with absorbance at 593 nm.<sup>16</sup>

#### *Statistical analysis*

Mean and standard error values were determined for all the parameters and the results were expressed as mean ± SEM. All data were analyzed with SPSS Version 18. Tje Student's t-test was used to analyze the differences between variables in case and control groups. Pearson correlation test was used to determine the significant correlations between variables. P-values of 0.05 or less were considered statistically significant.

## **Results**

Eighty randomized patients (40 per each group) successfully completed the study. None refused to participate in the study. Three patients were excluded, one due to loss of the cold chain for the blood samples (ketamine group). Adequacy of randomization was confirmed by comparison of general characteristics in both groups, as shown in Table 1.

Table 2 shows the mean ± SE (95% confidence interval) of variables related to either oxidative stress or exposure to propofol and ketamine measured in samples from the two groups. The TAC was significantly higher (P = 0.003) in patients exposed to propofol than that of the ketamine group. The TAC values for propofol and ketamine groups were 0.61 ± 0.049 and 0.44 ± 0.019 µmol /mL respectively.

Total thiol molecules of the group exposed to ketamine were significantly (p = 0.001) lower than those of the propofol group 0.28 ± 0.015 vs 0.43 ± 0.02 mM.

The LPO of patients exposed to ketamine was significantly (p = 0.014) higher than that of the propofol group 0.27 ± 0.018 vs. 0.21 ± 0.014 nmol/ mL.

The GPX activity of the group exposed to propofol was significantly (p = 0.037) lower than that of the ketamine group 661 ± 31 vs. 799 ± 58 U/mL. However, the SOD activity of the group exposed to propofol was significantly (p = 0.047) lower than that of the ketamine group: 9.2 ± 1.1 vs. 14.3 ± 2.4 U/mL. No significant difference was observed between the CAT activity of the propofol and ketamine groups.

## **Discussion**

The present results demonstrated that propofol increased TTM and TAC, decreased LPO, SOD and GPx activity compared to the ketamine group after surgery. There was no significant change in the level of CAT activity. These findings well indicate that propofol decreases significant changes in body antioxidant defense

**Table 1.** Basic characteristics of the patients

Characteristics	Groups	
	Propofol (N=40)	Ketamine (N=40)
Age (Years, Mean )	29.1	26.9
Sex		
Male	58.5%	64%
Female	41.5%	36%
Smoking		
Yes	15%	15.4%
No	85%	84.6%
History of disease		
Yes	2.4%	2.6%
No	97.6%	97.4%
WBC (Mean ± SD)	7321.42 ± 258	8163.63 ± 268
RBC (Mean ± SD)	4.54 ± 0.57	4.63 ± 0.53
Hemoglobin gr (Mean ± SD)	12.96 ± 1.5	13.36 ± 1.98
FBS mg/dL (Mean ± SD)	103.53 ± 15.4	108.00 ± 37.8
Sodium mEq/L (Mean ± SD)	1421 ± 3.21	1417 ± 2.66
Potassium mEq/L (Mean ± SD)	4.29 ± 0.19	4.49 ± 0.24

**Table 2.** Oxidative stress parameters in plasma of propofol and ketamine patients

Biomarker	Propofol	Ketamin	p-value
μTAC (mol mL <sup>-1</sup> )	0.61 ± 0.049	0.44 ± 0.029	0.003
LPO (nmol mL <sup>-1</sup> )	0.21 ± 0.014	0.27 ± 0.018	0.014
TTM (nmol mL <sup>-1</sup> )	0.43 ± 0.02	0.28 ± 0.015	0.001
GPx (U mL <sup>-1</sup> )	661 ± 31	799 ± 58	0.037
SOD (U mL <sup>-1</sup> )	9.2 ± 1.1	14.3 ± 2.4	0.047
CAT (U mL <sup>-1</sup> )	31.02 ± 1.97	34.2 ± 1.8	0.240

**Note:** Data are Mean ± SE of 40 propofol & 40 ketamine patients

and this can lead to further consequences, supporting the previous findings about antioxidant properties of propofol in human,<sup>17,18</sup> and rat,<sup>19,20</sup> there is evidence that total antioxidant level induce with this drug.<sup>21,22</sup>

Trauma and surgical injury are associated with increased production of ROS,<sup>23,24</sup> and the use of antioxidant system, in particular when associated with injury, may inhibit ROS production.<sup>25,26</sup> The results in these patients showed reduced ROS in the propofol group compared to the ketamine group. Previous study results indicated that thiopental decreases lipid peroxidation and improves ultra structure, whereas propofol decreases lipid peroxidation without improving ultra structure 1 hour after spinal cord injury in rats.<sup>27</sup> Numerous studies have clearly demonstrated the antioxidant effects of propofol in last decades.<sup>17,28,29</sup> The low level of LPO in the group receiving propofol in our study suggests that propofol prevents lipid peroxidation, and similar to previous studies, the TAC level and, TTM, concentration in the propofol group were significantly higher than those in the ketamine group. Also, other investigations showed that propofol pretreatment greatly attenuated the impairment in comparison with midazolam, which agrees with the concept of antioxidant activity of propofol in the present study.<sup>30</sup>

Propofol has been reported to inhibit lipid peroxidation in various experimental models to protect cells against oxidative stress and to increase the antioxidant capacity of plasma in humans.<sup>17,31,32</sup> The results of previous studies reported that propofol reacts with peroxynitrite, leading to the formation of a propofol-derived phenoxyl radical and has therefore been hypothesized to be a peroxynitrite scavenger.<sup>33,34</sup> The results of the present study suggest that propofol has a greater potential to reduce oxidative stress than does ketamine.

Apoptosis is an important process in many pathological conditions. There are two major pathways for apoptosis: mitochondria-

dependent caspase-9 pathway and the mitochondria-independent caspase-8 pathway. The mitochondria-dependent pathway is activated by agents such as ROS which trigger the release of cytochrome c from mitochondria.<sup>35,36</sup> Propofol was also shown to promote mitochondrial function by stabilizing the transmembrane electrical potential and inhibiting mitochondrial permeability transition pore opening, both contributing to suppression of mitochondrion-dependent apoptotic signaling.<sup>37-40</sup> Although the antiapoptotic effect of propofol in various cells has been widely studied, the underlying mechanism is far from clear.

In conclusion, our results show that propofol has antioxidant effects and reduced oxidative biomarkers in humans. The effects may be beneficial for patients in whom free radicals play an important role, such as those with ischemic processes in various tissues.<sup>17,41</sup> Further studies need to be conducted to demonstrate the exact mechanism of oxidative stress due to anesthesia and surgery in humans.

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