**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 7327**

**Columns: BRIEF ARTICLE**

**Protective effects of intravenous anesthetics for the kidney tissue in obstructive jaundice**

Hatipoglu S *et al*. Protection of anesthetics for kidney in jaundice

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**Received:** November 11, 2013  **Revised:** January 14, 2014

**Accepted:** January 19, 2014

**Published online:**

**Abstract**

**AIM:** To evaluate the protective effects on kidney tissue of frequently used intravenous anesthetics (ketamine, propofol, thiopental, and fentanyl) in rats with obstructive jaundice.

**METHODS:** There is an increased incidence of postoperative acute renal failure in patients with obstructive jaundice. Thirty-two Wistar-albino rats were randomly divided into four equal groups. Laparatomy was performed on each animal in the four groups and common bile ducts were ligated and severance on day 0. Following 7 d, laparotomy was again performed using ketamine, propofol, thiopental, or fentanyl anesthesia whose antioxidative properties are well known in oxidative stress in a rat liver model of obstructive jaundice. After 2 h, the rats were sacrificed. Renal tissue specimens were analyzed for catalase, superoxide dismutase and malondialdehyde enzymes activities. All values are expressed as the mean ± standard deviation. *P* values less than 0.05 were considered statistically significant.

**RESULTS:** All animals survived without complications until the end of the study. Enlargement in the bile duct and obstructive jaundice were observed in all rats. Regarding the results of oxidative stress markers after in our experiment; Catalase was found to be significantly lower in the fentanyl group than in the ketamine (*P* = 0.039), propofol (*P* = 0.012), and thiopental (*P* = 0.001) groups. Superoxide dismutase activities were similar between the all groups (*P* > 0.05). Malondialdehyde was found to be significantly lower in the ketamine group than in the propofol (*P* = 0.028), thiopental (*P* = 0.002) and fentanyl (*P* = 0.005) groups. Malondialdehyde was also lower in the fentanyl group than in the thiopental group (*P* = 0.001). The results showed that the presence of obstructive jaundice sensitizes the renal tissue to damage under the different anesthetics.

**CONCLUSION:** Among the agents tested, ketamine and propofol generated the least amount of oxidative stres on renal tissues in this rat model of obstructive jaundice created by common bile duct ligation. The importance of free radical injury on renal tissue in obstructive jaundice under the difference intravenous anesthetics should be considered during the hepatobiliary and liver transplant surgery for prevention of postoperative acute renal failure.

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**Key words:** Obstructive jaundice; Postoperative acute renal failure; Oxidative stress; Intravenous anesthetics; Renal tissue damage

**Core tip:** There is an increased incidence of postoperative acute renal failure in patients with obstructive jaundice. Recent literature knowledge suggest that the free oxygen radicals produced in obstructive jaundice may play a major role in the etiopathogenesis of acute renal failure. We evaluated the protective effects on kidney tissue of frequently used intravenous anesthetics whose antioxidative properties are well known in oxidative stress in a rat liver model of obstructive jaundice. Among the agents tested, ketamine and propofol generated the least amount of oxidative stres on renal tissues in this rat model of obstructive jaundice created by common bile duct ligation.

Hatipoglu S, Yildiz H, Bulbuloglu E, Coskuner I, Kurutas EB, Hatipoglu F, Ciralik H, Berhuni MS. Protective effects of intravenous anesthetics for the kidney tissue in obstructive jaundice. *World J Gastroenterol* 2014;

**Available from:** URL: http://www.wjgnet.com/esps/

**DOI:** http://dx.doi.org/10.3748/wjg.v20.i0.0000

**INTRODUCTION**

Today, palliative and curative operations are performed to many patients with obstructive jaundice (OJ) under anesthesia. Especially in the last fifty-years as a result of improvements in liver transplant surgery, more complicated and prolonged operations are being held. Patients with severe OJ usually have a lot of metabolic disorders and one or multiple organ function failure. Renal dysfunction is one of serious complications in patients with OJ[1-3].

For the association between OJ and acute renal failure (ARF) has been recognized for well over a century. The renal damage is due to biliary disorders either present on admission to hospital or develops postoperatively. One third of the patients with OJ have deterioration of renal function before surgical intervention[4]. On the other hand, surgery on patients with OJ is known to be associated with increased risk of post-operative renal failure[5-8]. Early diagnosis and prevention of spontaneous evolution of the disease can improve prognosis, otherwise very poor in many cases.

Patients with intra- or extrahepatic bile-duct obstruction are susceptible to ARF especially when undergoing major surgery[9]. Surgical treatment for the relief of OJ is still complicated by postoperative ARF in almost 10 percent of patients[3]. Patients with OJ are often subjected to either general or sedation anesthesia, usually using drugs which are metabolized by the liver and/or eliminated by the kidney and the liver. Some intravenous anesthetic agents have been shown to increase production of reactive oxygen species and cause tissue damage[9-13]. In addition to, some intravenous anesthetic drugs are also capable of reducing oxidative stres[13,14].

To date, no one has reported the effects on renal tissues of intravenous anesthetic agents on oxidative stress in rats with OJ. Biliary obstruction is associated with an intense state of oxidative stress. Antioxidant defenses [as demonstrated by superoxide dismutase (SOD) and catalase (CAT) activities] are decreased and lipid peroxidation [as demonstrated by malondialdehyde (MDA) levels] are increased in rat models with OJ[13,15]. So that, in this study, we investigated the effects on renal tissues of frequently used intravenous anesthetics (ketamine, propofol, thiopental, and fentanyl), in a rat model of oxidative stress caused by OJ through common bile duct ligation. We used these intravenous anesthetics whose antioxidative properties are well known.

**MATERİALS AND METHODS**

***Animals***

The experimental protocol was approved by the Animal Ethics Review Committee of the Faculty of Medicine, University of Kahramanmaras and adhered to the National Institutes of Health Guidelines for the Use of Experimental Animals. Thirty-two male Wistar rats (300-375 g) were subjected to controlled conditions of temperature (about 22 ºC) and illumination (12 h light:12 h dark cycle), and were provided with food and water ad libitum. They were fed a commercial diet. Rats were put in individual metabolic cages and acclimatized for one week before the study commenced.

***Experimental design***

In this prospective experimental study, rats were divided randomly into four groups, each group containing eight animals. Food was interrupted 12 h before the operation, with water ad libitum during this period. Each rat was weighed during each anaesthetic and anaesthetized with ketamine (50 mg/kg) intramuscularly. As described by Lee in their model of experimental jaundice created by ligation of the common bile duct [13, 15, 16]. The abdominal cavity was opened with a midline incision after desinfecting the skin. The common bile duct was located and OJ induced by a double ligation with 5/0 silk and transsection of the common bile duct in the supraduodenal part between the lowermost tributary of the bile duct and the uppermost tributary of the pancreatic duct. And then the abdominal wall was closed with 3-0 silk in two layers. Cages were examined daily.

Seven days later, Group I received intramuscular single-dose ketamine (50 mg/kg), Group II received intramuscular single-dose propofol (10 mg/kg), Group III received intramuscular single-dose thiopental (20 mg/kg), and Group IV received intramuscular single-dose fentanyl (50 mcg/kg). Two hours later, the rats were sacrificed.

***Sample collection***

The animals were anaesthetized and a second laparotomy was performed through a similar incision. The left and right kidneys of each rat were carefully removed in all groups and kept with iced 0,9% NaCl solution for short time. A portion of dimension 0.5 cm × 0.5 cm of kidneys (left or right) which contain both renal cortical and medullar tissue were washed with physiological salineto remove hematoma and blotted on filter paper. The renal tissue was immediately frozen in liquid nitrogen and stored at –80 °C for later measurement of MDA, SOD and CAT activities.

***Antioxidant study***

In order to determine tissue antioxidant levels, 0.5 cm × 0.5 cm renal tissue samples were removed from the freezer, brought to room temperature, then homogenized with three volumes of ice-cold 1.15% KCl. Activities of antioxidant enzymes and levels of lipid peroxidation were measured in the supernatant after centrifugation at 14000 rpm. SOD activity was measured by the method described by Fridovich[17]. CAT activity was determined by measuring the decrease in hydrogen peroxide concentration at 230 nm by the method of Beutler[18]. Lipid peroxidation was reflected by MDA levels, which were measured by the method described by Ohkawa *et al*[19]. All enzyme activities are expressed as units per milligram protein (U/mg protein).

***Statistical analysis***

All values are expressed as the mean ± SD. The Kolmogorov–Smirnov statistic was used to test the normality of distributions. Differences between SOD groups were evaluated by Kruskal–Wallis variance analysis followed by a *post-hoc* (Bonferroni correction ) Mann–Whitney *U* test. Differences between MDA and CAT groups were evaluated by one way analysis of variance (ANOVA) for continuous variables with *post-hoc* procedures (Bonferroni correction). *P* values less than 0.05 were considered statistically significant. Data were analyzed using the SPSS 9.05 for Windows® statistical package.

**RESULTS**

This prospective analysis was undertaken to assess amount of oxidative stress function of renal tissue in rats with OJ under the different anesthetics. All animals survived without complications until the end of the study. Enlargement in the bile duct and OJ were observed in all rats. The mean values of the parameters studied are found in table I. The results showed that the presence of OJ sensitizes the renal tissue to damage under the different anesthetics.

Regarding the results of oxidative stress markers after in our study, CAT was found to be significantly lower in the fentanyl group than in the ketamine (*P* = 0.039), propofol (*P* = 0.012), and thiopental (*P* = 0.001) groups. Although CAT was higher in the thiopental group than in the ketamine and propofol groups, this difference was not statistically significant (Table1), ( Figure 1A).

SOD activity was similar between the all groups and intergroup difference was not found (*P* > 0.05), (Table1), (Figure 1B).

MDA was found to be significantly lower in the ketamine group than in the propofol (*P* = 0.028), thiopental (*P* = 0.002) and fentanyl (*P* = 0.005) groups. MDA was also lower in the fentanyl group than in the thiopental group (*P* = 0.001). MDA was similar between the propofol and thiopental groups and no other significant intergroup difference was found (Table 1), (Figure 1C).

**DİSCUSSİON**

Many clinical observations and experimental studies point to the frequent occurence of different organ complications in patients with OJ. One of the main consequences of biliary obstruction is its effect on renal function, which markedly increases patient morbidity and mortality. Acute renal failure is a life-threatening complication of OJ which continues to be a significant challenge, involving 6%-18% of patients and associated with high mortality (20%-100%)[20-23]. Patients with intra- or extra-hepatic bile-duct obstruction are susceptible to ARF especially when undergoing major surgery and postoperative ARF in patients with OJ remains a clinically significant complication[9,24]. Acute renal failure occurs in approximately 9 percent of patients requiring surgery for relief of OJ, and contributes to eventual mortality in 76 percent of those who develop it. Postoperative mortality has been directly attributed to ARF in approximately 5%-16% of patients after surgery for OJ[25,26].

When mechanical biliary obstruction is diagnosed, surgical, endoscopic or radiologic intervention is usually recommended. On the other hand, despite advances in preoperative evaluation and postoperative care, especially surgical intervention, for relief of obstructive jaundice still carries high morbidity and mortality rates, mainly due to sepsis and renal dysfunction[25,27-30]. The presence of OJ (total bilirubin less than 8 mg/dL) is an independent risk factor for the development of postoperative renal dysfunction[31].

The association between OJ and ARF has been recognized since 1910 when Clairmont and Von Haberer first postulated that jaundice might predispose to post-operative renal failure, surprisingly few reports or series have appeared in the literature[20,32]. Antifibrinolytic agents, OJ, prostaglandin inhibitors, cyclosporine A, radiocontrast dyes and volatile anesthetic agents contribute to ARF[31,33,34]. There isn’t any knowledge about the oxidative effects of intravenous anesthetic agents for renal tissue during the surgery for OJ patients in the literature.

Postoperarative ARF may be precipitated in patients with OJ either by operation or septicaemia or a combination of both. The effective plasma volume depletion, systemic endotoxemia, and myocardial dysfunction affects haemodynamic and renal disturbance in patients with acute OJ[32]. Intrarenal vasoconstriction, attributable to a decrease in effective arterial blood volume, induced by peripheral arterial vasodilation, is proposed to play a causative role in OJ[35]. The concentration clearances of creatinine and urine osmolality are the parameters which point to the probability of renal dysfunction occurrence in OJ[4]. Although the aetiology of renal dysfunction is multifactorial, it is strongly associated with haemodynamic and body fluid disturbances. However, the ethiology of this clinical status is still unclear.

Oxidative stress occurs during many pathological processes in an organism. Free oxygen radicals are neutralized by the antioxidant system and a balance is maintained. A major protective mechanism against reactive oxygen metabolites is also the antioxidant enzyme cascade [36-38]. Antioxidant defenses (as demonstrated by CAT and SOD activities) are decreased and lipid peroxidation (as demonstrated by MDA levels) are increased during extrahepatic OJ in rat models[13,15]. When this balance is impaired, however, tissue damage may result. Oxydant injury is considered to be an important mechanism in the pathophysiology of ARF[36-40] and severe oxidative stress has been implicated in the renal dysfunction associated to experimental OJ[41]. Ischemia and nephrotoxicity are important factors in the pathogenesis of ARF and their effects on renal cells can be loss of superoxide dismutase and superoxide radical accumulation[36]. Oxygen free radicals produce damage to the renal arteriolar endothelial cells, glomerular cells, and renal tubular epithelial cells[36-38].

Renal tissues in OJ appear to be susceptible to ischemia-reperfusion injury[42]. Tissue injury induced by OJ involves lipid peroxidation[43]. Most experiments of animals with OJ have been shown to be deficient in fat-soluble vitamins, such as vitamins A and E[13,43]. Because these vitamins are potential of ameliorating secondary tissue damage induced by lipid peroxidation, enhanced oxidative stress could possibly exacerbate secondary tissue damage. Moreover, OJ could alter the activities of antioxidant enzymes resulting in increased production of superoxide and hydrogen peroxide[44]. Tissue damage associated with OJ may be caused by accelerated generation of hydroxyl radicals[43-46]. Oxidative stress seems to be a cardinal feature of cholestasis, implicated in the pathophysiology of organ injury not only in the liver, but also in renal tissues[47]. Superoxide radical may play an important role in the pathophysiology of cholestatic liver injury, intestinal barrier failure and ARF[47].

Commonly used intravenous agents have been shown to increase oxygen production and generate tissue damage[9-13,48]. Intravenous anesthetic agents generate free radicals by altering intracellular cytochrome p450, peroxisomes, and enzymatic systems in the mitochondria[9]. Moreover, they consume and inhibit enzymatic and non-enzymatic systems that protect the cells via scavenging free radicals. They cause lipid peroxidation, DNA damage and changes in proteins by inducing oxidative damage, which eventually may lead to alterations in cellular functions such as reduced gap junction-mediated transmission, activation of transcription factors, intracellular calcium and pH changes, and/or cell death[9-13,49].

Transient functional impairment of renal cation and water transport in the proximal convoluted tubule occur 3 to 4 d following bile duct ligation in rats[6]. Maximum plasma concentrations and renal clearance of bile acids occurred between the third or fourth postoperative day following common bile duct ligation. This peak coincided with maximal disruption of proximal convoluted tubule architecture and postoperative changes in renal function-increased urine flow rate and decreases in urine osmolality and sodium excretion[6]. Because of these evidence in our experiment, we chose to sacrifice rats on 7th postoperative day and specimens of renal tissues were resected.

Ketamine has been extensively studied as a safe and reliable dissociative sedative/anesthetic agent in various clinical situations. Ketamine’s properties as a protective agent against oxidative stress and ischemia/reperfusion injury of the brain, kidney, skeletal muscle, heart, and intestine were reported[50-54]. In our experiment, MDA levels were lower in the ketamine group compared to the other groups, confirming ketamine’s properties as an agent which protects against oxidative stress. MDA is one of the fairly reactive metabolic products resulting from the effect of free oxygen radicals on tissues and from a series of reactions during lipid peroxidation. The tissue MDA level is a sensitive indicator of lipid peroxidation and thus of oxidative stress[55]. Since ketamine lowered MDA levels more than other agents used, we can conclude that it has an influence over the antioxidant defense system, while reducing lipid peroxidation.

Propofol and thiopental are another type of highly lipid-soluble anaesthetics which have demonstrated antioxidant properties by inhibiting lipid peroxidation[56-58]. Both are often used to reduce cerebral edema during liver transplantation in fulminant hepatic failure patients[13]. Propofol is widely used for the induction and maintenance of general anesthesia, as well as for sedation of intubated postoperative patients on mechanical ventilation. Propofol has been proven to ameliorate ischemic/reperfusion injury in several organs, including the heart[59], lungs[60], brain[61], and kidney[62]. Propofol has been found to limit oxidative injury in the liver and other tissues[63]. According to our literature searches, oxidative effects of propofol and thiopental on renal tissue injury due to OJ have not been studied before our experimental design. Regarding the markers of oxidative stress, MDA was the highest among thiopental group, and was significantly higher than those of the ketamine or fentanyl groups. Although CAT was higher in the thiopental group than in the ketamine and propofol groups, this difference was not statistically significant. SOD catalyzes the produced superoxide radicals into H2O2, whereas CAT prevents oxidative damage by dissociating H2O2 and inhibiting lipid peroxidation [64]. In our experiment, SOD activity was similar between all groups and no significant intergroup difference was found.

Fentanyl is one of many opioid receptor agonists and has effects on the brain, heart, and liver[65]. Regarding its oxidative effects on renal tissue in OJ however, little is known. In our experiment, CAT was found to be significantly lower in the fentanyl group than in the ketamine, propofol, and thiopental groups.

The association between ARF and OJ is well established. However, despite the substantial number of clinical reviews, prospective animal studies, various pathogenic mechanisms and therapeutic strategies proposed, main pathophysiological mechanisms are still obscure. Therefore post-operative ARF remains a major challenge in hepatobiliary and liver transplant surgery. It is important to recognize ARF early and take adequate measures to prevent its occurrence. One option is, since free oxygen radicals seem to play a significant role in the etiopathogenesis, pre-operative and post-operative antioxidant treatment may prevent ARF in OJ. According to our experiment, ketamine and propofol generated the least amount of oxidative stres on renal tissues in this rat model of obstructive jaundice created by common bile duct ligation. In addition, close collaboration of clinicians, especially hepatobiliary and liver transplant surgeons and anesthesiologists, is very important during pre-operative, per-operative, and post-operative process to prevent of ARF.

**COMMENTS**

***Background***

The association between acute renal failure and obstructive jaundice is well established and there is an increased incidence of postoperative acute renal failure in patients with obstructive jaundice. Recent literature knowledge suggest that the free oxygen radicals produced in obstructive jaundice may play a major role in the etiopathogenesis of acute renal failure. Authors evaluated the protective effects on kidney tissue of frequently used intravenous anesthetics whose antioxidative properties are well known in oxidative stress in a rat liver model of obstructive jaundice.

***Research frontiers***

The importance of free radical injury on renal tissue in obstructive jaundice under the difference intravenous anesthetics should be considered during the hepatobiliary surgery for prevention of post-operative acute renal failure.

***Innovations and breakthroughs***

To date, no one has reported the effects on renal tissues of intravenous anesthetic agents on oxidative stress in rats with obstructive jaundice. Biliary obstruction is associated with an intense state of oxidative stress. Antioxidant defenses (as demonstrated by superoxide dismutase and catalase activities) are decreased and lipid peroxidation (as demonstrated by malondialdehyde levels) are increased in rat models with obstructive jaundice. Ketamine and propofol generated the least amount of oxidative stres on renal tissues in this rat model of obstructive jaundice created by common bile duct ligation.

***Peer review***

The paper describes how different anesthetics could potentially reduce the risk of acute renal failure in patients with obstructive jaundice by reducing the oxidative stress inflicted by jaundice in combination with acute surgery. So that, it is of interest and should be of interest to the readers of World Journal of Gastroenterology.

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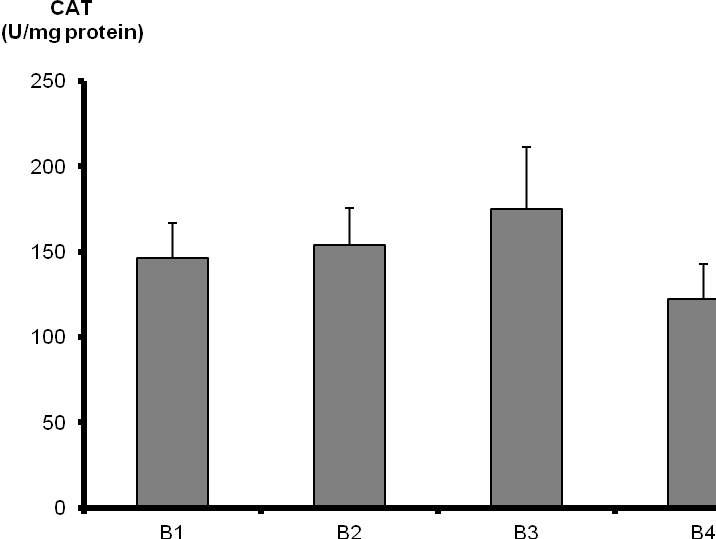
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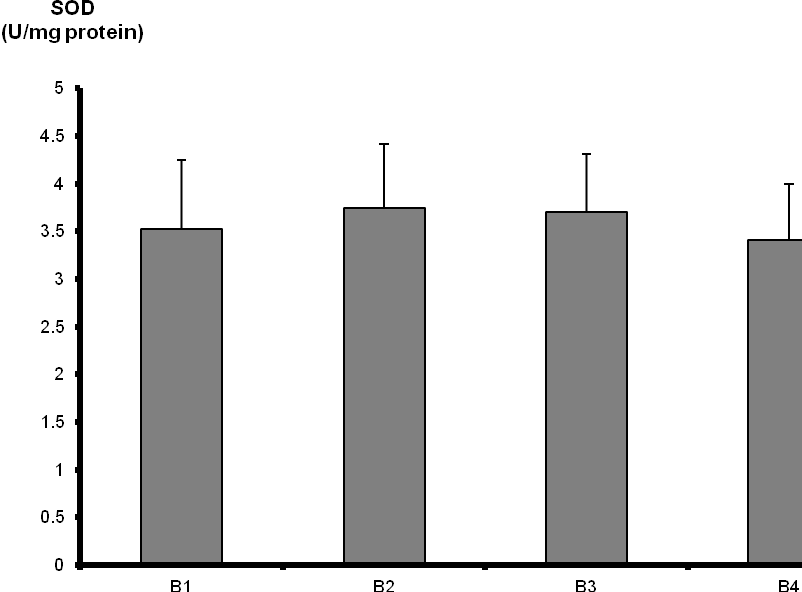
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**P-Reviewers:** Boyuk A, Coelho AMM, Sandblom G **S-Editor:** Gou SX

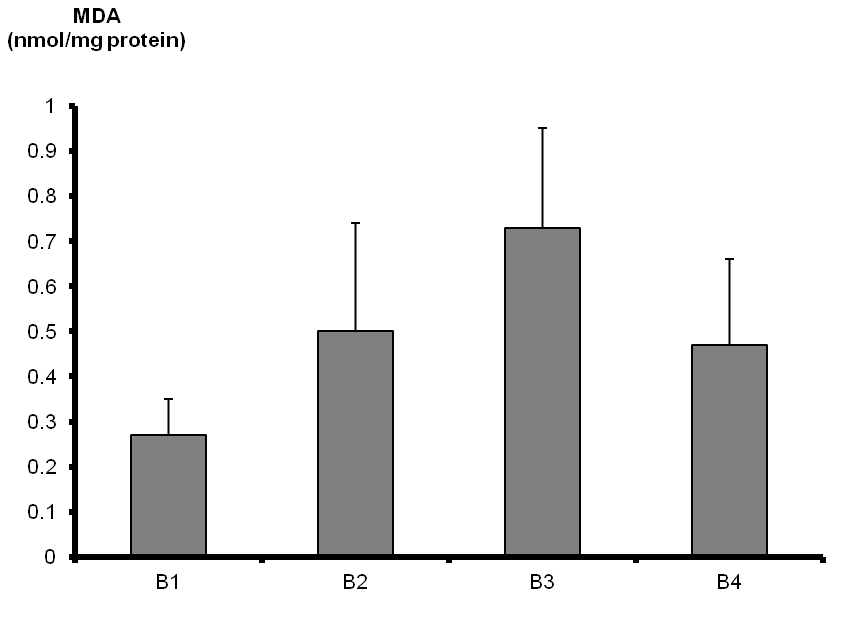
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A



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C

**Figure 1 Mean malondialdehyde, superoxide dismutase levels and catalase** **activity in our groups [B1 (ketamine), B2 (propofol), B3 (thiopental) and B4 (fentanyl)].** A: Catalase (CAT); B: Superoxide dismutase (SOD); C: Malondialdehyde (MDA).

**Table 1 Mean malondialdehyde, superoxide dismutase levels and catalase levels in renal tissue of rats**

|  |  |  |  |
| --- | --- | --- | --- |
| **Groups** | **Catalase** | **Superoxide dismutase** | **Malondialdehyde** |
| B1 (ketamine) | 146.11 ± 20.911 | 3.52 ± 0.73 | 0.27 ± 0.0804,5,6 |
| B2 (propofol) | 154.11 ± 21.462 | 3.74 ± 0.67 | 0.50 ± 0.244 |
| B3 (thiopental) | 174.8 ± 36.63 | 3.70 ± 0.61 | 0.73 ± 0.225,7 |
| B4 (fentanyl) | 122.48 ± 20.541,2,3 | 3.41 ± 0.59 | 0.47 ± 0.196,7 |

Data are expressed as mean ± SD. Mean malondialdehyde (MDA), superoxide dismutase (SOD) levels and catalase (CAT) levels in renal tissue of rats (8 rats in each group). CAT and SOD activities are expressed as units per miligram protein (U/mg protein). MDA enzyme activities are expressed as nmol/mg protein. *P* values less than 0.05 were considered statistically significant. In CAT group: 1*P* = 0.039 in ketamine *vs* fentanyl comparisons; 2*P* = 0.012 in propofol *vs* fentanyl comparisons; 3*P* = 0.001 in thiopental *vs* fentanyl comparisons; In MDA group: 4*P* = 0.028 in ketamine *vs* propofol comparisons; 5*P* = 0.002 in ketamine *vs* thiopental comparisons; 6*P* = 0.005 in ketamine *vs* fentanyl comparisons; 7*P* = 0.001 in thiopental *vs* fentanyl comparisons.