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EXPERIMENTAL STUDY

The protective effects of ketamine and propofol in obstructive jaundice: an experimental study

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Abstract: *Objective:* In this study, we investigated the protective effects of frequently used intravenous anesthetics (ketamine, propofol, thiopental, and fentanyl) in oxidative stress in a rat liver model of obstructive jaundice.
Materials and methods: Thirty-two Wistar albino rats were divided into four groups in a randomized fashion. All rats were subjected to laparotomy, common bile duct ligation and severance on day 0. Following 7 days, laparotomy was again performed using ketamine, propofol, pentobarbital, or fentanyl anesthesia. After 2 hours, the animals were sacrificed and tissue specimens were acquired for histopathological scoring and determination of malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT) activities.
Results: All rats demonstrated enlargement in the bile duct, obstructive jaundice, and histopathologic ductal proliferation. MDA and SOD levels were significantly lower in the ketamine group compared with the thiopental and fentanyl groups. CAT was significantly increased in the ketamine group compared with the other groups. The best portal polymorphonuclear leukocyte and necrosis scores were in the ketamine group, but this difference was not statistically significant (p=0.07)
Conclusion: Ketamine and propofol were observed to cause the least amount of oxidative stress in this rat model of induced oxidative stress generated by ligation of the common bile duct. This experiment is the first study on this subject in the literature *(Tab. 3, Ref. 65)*. Full Text in PDF *www.elis.sk*.
Key words: ketamine, propofol, common bile duct, rat.

Obstructive jaundice can be induced in the rat by common bile duct ligation (CBDL), which causes parenchymal cell damage that may ultimately lead to liver cirrhosis and portal hypertension (1). Tissue injury induced by obstructive jaundice involves lipid peroxidation (2). Most CBDL animals have been shown to be deficient in fat-soluble vitamins, such as vitamins A and E (3). Because these vitamins are capable of ameliorating secondary tissue damage induced by lipid peroxidation, enhanced oxidative stress could possibly exacerbate secondary tissue damage. Moreover, obstructive jaundice could alter the activities of antioxidant enzymes resulting in increased production of superoxide (O_2•) and hydrogen peroxide (H_2O_2) (4). As a result, hydroxyl radicals (•OH) form through the interplay between O_2•, H_2O_2, and iron via the Haber-Weiss (1) or Fenton (2) reactions (2–5).

Patients with obstructive jaundice are often subjected to either general or sedation anesthesia, usually using drugs which are metabolized and/or eliminated by the liver. Intravenous agents commonly used have been shown to increase oxygen production and generate tissue damage in the liver (6–9). On the other hand, intravenous anesthetic drugs are also capable of reducing oxidative stress (10). In this study, we investigated the effects of frequently used intravenous anesthetics (ketamine, propofol, pentobarbital, and fentanyl), in a rat model of oxidative stress caused by obstructive jaundice through common bile duct ligation.

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Materials 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 were housed in individual cages in a temperature-controlled room with alternating 12-hour light–dark cycles, and acclimatized for one week before the study commenced. Animals were allowed free access to water and rat chow.

Experimental design

In this prospective experimental study, rats were divided randomly into four groups, each group containing eight animals. Food was witheld 12 hours before the operation, with water ad libitum during this period. Each rat was weighed 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 (11), following a midline incision, the common bile duct was exposed and a double-ligature was placed around the duct with a 5-0 silk suture. The bile duct was then transected between the ligatures and the abdominal wall was closed with 3-0 silk in two layers.

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

Sample collection

The animals were anaesthetized and a second laparotomy was performed. The liver was carefully dissected from its attachment and totally excised. The liver was flushed with physiological saline and then cut into two pieces, one of which was immediately frozen in liquid nitrogen and stored at –80 °C for later measurement of malondialdehyde (MDA), superoxide dismutase (SOT) and catalase (CAT) activities.

Histopathological evaluation

Liver fragments were kept in 10 % formaldehyde solution for 6-48 h. Following treatment with alcohol and xylene, specimens were embedded in paraffin blocks. After preparation, the sections were stained with hematoxylin and eosin. Pathological examination of portal mono- and polymorphonuclear leukocytes, ductal proliferation, and hepatic necrosis were made by a pathologist blinded to treatment group. Each of the histopathological parameters listed in Table 1 were evaluated and scored for each slide: 0 for no change, 1 for mild, 2 for moderate, and 3 for severe changes. The histopathological parameters were expressed as the minimum–median–maximum (Tab. 2).

Antioxidant study

In order to determine tissue antioxidant levels, 1x1 cm^2 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 14,000 rpm. SOD activity was measured by the method described by Fridovich (12). CAT activity was determined by measuring the decrease in hydrogen peroxide concentration at 230 nm by the method of Beutler (13). Lipid peroxidation was reflected by MDA levels, which were measured by the method described by Ohkawa et al (14). Protein concentrations were determined by the method of Lowry (15).

Statistical analysis

Histopathological data were expressed as the minimum–median–maximum. Tissue antioxidant levels were expressed as mean±standard deviation. 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 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

All animals survived without complications until the end of the experiment.

Although the mean histopathologic score was lower in the ketamine group , this was not significantly lower than the scores of the propofol , pentobarbital , and fentanyl groups (Tab. 1 and 2).

Regarding markers of oxidative stress, MDA was found to be significantly lower in the ketamine group than in the thiopental (p=0.005) and fentanyl (p=0.03) groups. Although MDA was lower in the ketamine group than in the propofol group, this difference was not statistically significant (p=0.3). MDA was also lower in the propofol group than in the thiopental group (p=0.007.) MDA was similar between the propofol and fentanyl groups and between the thiopental and fentanyl groups (Tab. 3).

Tab. 1. Numbers of rats (out of 8 in each group) receiving scores (0=none, 1=mild, 2=moderate, 3=severe) of histopathologic injury and necrosis in rats receiving ketamine, propofol, pentobarbital, or fentanyl one week after undergoing common bile duct ligation.

	Ketamine				Propofol				Thiopental				Fentanyl			
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Portal Polymorphonuclear Leukocytes	4	4	–	–	3	4	1	–	2	4	2	–	3	3	2	–
Portal Monomorphonuclear Leukocytes	5	3	–	–	4	4	–	–	3	3	2	–	4	3	1	–
Ductular proliferation	–	2	6	–	–	3	5	–	–	3	5	–	–	2	6	–
Necrosis	6	1	1	–	4	3	1		3	2	3		3	3	2	

Tab. 2. The histopathological parameters expressed as the minimum–median–maximum.

	Groups				
	Ketamine Min–M–Max	Propofol Min–M–Max	Thiopental Min–M–Max	Fentanyl Min–M–Max	P value
Portal Polymorphonuclear Leukocytes	0–0.5–1	0–1–2	0–1–2	0–1–2	0.574
Portal Monomorphonuclear Leukocytes	0–0–1	0–0.5–1	0–1–2	0–0.5–2	0.601
Ductular proliferation	1–2–2	1–2–2	1–2–2	1–2–2	0.905
Necrosis	0–0–2	0–0.5–2	0–1–2	0–1–2	0.409

Tab. 3. Mean malondialdehyde (MDA), superoxide dismutase (SOD) levels and catalase (CAT) levels in rats (8 rats in each group) receiving ketamine, propofol, pentobarbital, or fentanyl one week after undergoing common bile duct ligation.

	Groups			
	Ketamine Mean±SD	Propofol Mean±SD	Pentobarbital Mean±SD	Fentanyl Mean±SD
MDA	0.44±0.16[a,b]	0.51±0.12[c]	0.79±0.19	0.74±0.28
SOD	5.58±1.06 [a]	7.23±1.69	7.18±2.76	8.05±3.57
CAT	201.4±28.0 [a,b,c]	166.5±22.0	144.6±32.5	152.75±61.51

MDA: Malondialdehyde, [a], p=0.005 in ketamine vs pentobarbital, [b] p=0.03 in ketamine vs. fentanyl, [c], p=0.007 in Propofol vs pentobarbital comparisons, SOD: Superoxide dismutase, [a] p=0.03 in ketamine vs propofol, CAT: Catalase, [a] p=0.02 in ketamine vs propofol, [b] p=0.007 in ketamine vs pentobarbital, [c] p=0.06 ketamine vs pentobarbital

SOD activity was significantly lower in the ketamine group compared to the propofol group (p=0.03). No other significant intergroup difference was found (Tab. 3).

CAT was significantly higher in the ketamine group compared to the propofol (p=0.02), thiopental (p=0.007), and fentanyl (p=0.06) groups. No other significant intergroup difference was found (Tab. 3).

Discussion

Biliary obstruction is associated with an intense state of oxidative stress. Antioxidant defenses (as demonstrated by SOD and CAT activities) are decreased and lipid peroxidation (as demonstrated by MDA levels) are increased in the liver during extrahepatic BDL in rat models (16). Liver damage associated with obstructive jaundice in BDL may be caused by accelerated generation of hydroxyl radicals (17).

Some intravenous anesthetic agents have been shown to increase production of reactive oxygen species and cause tissue damage (6–9). Intravenous anesthetic agents generate free radicals by altering intracellular cytochrome p450, peroxisomes, and enzymatic systems in the mitochondria (6). 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 may lead to alterations in cellular functions such as reduced gap junction-mediated transmission, activation of transcription factors (AP-1, NF-kB), intracellular calcium and pH changes, and/or cell death (6–9, 18). Intravenous anesthetic agents have also been shown to cause a decrease in hepatic blood flow (19, 20), up to a 30 % decrease in the absence of any surgery in healthy individuals (21, 22). In addition, these agents may lead to hypercapnia or global hypoxia for various reasons during anesthesia. In all the ways listed above, these agents increase oxidative damage (23).

To date, no one has reported the effects of anesthetic agents on oxidative stress in rats with obstructive jaundice. In this study therefore, we used intravenous anesthetics (ketamine, propofol, pentobarbital, and fentanyl) whose antioxidative properties are well known.

Ketamine is an N-Methyl-D-aspartate (NMDA) receptor antagonist that has been extensively studied as a safe and reliable dissociative sedative/anesthetic agent in various clinical situations. It possesses novel analgesic and anti-inflammatory properties (24) and has protective properties on ischemic/reperfusion injury of the brain, kidney, skeletal muscle, heart, and intestine (25–29). In the present study, MDA levels were lower and CAT activities higher in the ketamine group compared to the other groups, confirming ketamine's properties as an agent which protects against oxidative stress. SOD activities were also significantly lower in the ketamine group than in the propofol group. The lower SOD activity in the ketamine group was thought to be due to an adequate reduction of superoxide radicals, whereas the increase in CAT activity was associated with higher peroxide concentration. Since ketamine lowered MDA levels more than the other agents, we can surmise that it has an influence over the antioxidant defense system, while reducing lipid peroxidation. SOD catalyzes the produced superoxide radicals into H_2O_2, whereas CAT prevents oxidative damage by dissociating H_2O_2 and inhibiting lipid peroxidation.

Ketamine may influence the concentrations of superoxide radicals by various mechanisms: neutralization via directly reducing the concentration of superoxide radicals, reduction of the superoxide synthesis by stimulating the glutathion peroxidase enzyme (30), and suppression of the neutrophils. Weiss et al. believe that ketamine cannot have an important influence on the first mechanism above due to its chemical structure, which includes a phenol component (30). Regarding the third mechanism above, ketamine has been shown to inhibit neutrophils and reduce neutrophil-derived superoxide radicals in coronary bypass grafting under *in vivo* and *in vitro* conditions (30–32). Similarly, ketamine has been found to reduce the adhesion of exogenously delivered human neutrophils in the guinea pig heart during ischemia-reperfusion (33). Moreover, ketamine has been observed to inhibit neutrophil adhesion in the rat mesentery, possibly due to suppression of E-selectine which is known to be an adhesion molecule activated by cytokines (34). In summary, based on our results and those of others, ketamine probably reduces lipid peroxidation by neutrophil suppression in rats with obstructive jaundice. Regarding histopathologic damage in this model, although portal polymorphonuclear leukocytes and necrosis scores were lower in the ketamine group, the scores were not significantly different from the other groups.

In this study, both ketamine and propofol provided better control over oxidative stress in rats with obstructive jaundice compared to pentobarbital and fentanyl.

Propofol (2, 6-diisopropylphenol) and thiopental are highly lipid-soluble anaesthetics and have antioxidant activities, protecting against lipid peroxidation (35). Both are often used to reduce cerebral edema during liver transplantation in fulminant hepatic failure patients (36–37). To date, the question of whether

the antioxidant activities of propofol and thiopental were able to protect the liver from oxidative stress in the setting of biliary obstruction had not been asked.

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 (38), lungs (39), brain (40), and kidney (41).

Although a few cases of acute hepatic failure linked to propofol have been reported (42), propofol has been found to limit oxidative injury in the liver and other tissues (43). Its effects on hepatic injury due to obstructive jaundice had not been examined until the current study.

While ketamine caused the most remarkable reduction in MDA levels, propofol's effect was not significantly different from that of ketamine. The propofol group had significantly higher SOD levels than the ketamine group. Propofol group had significantly lower CAT activities compared to the ketamine group. However,there was no significant difference between the propofol and other anesthetic groups. Regarding the histopathologic score, the propofol gorup had the second best score after the ketamine group, demonstrating that propofol stimulated oxidative stress in this rat model of obstructive jaundice to a lesser degree than thiopental and fentanyl. This may be due to inhibition of neutrophil migration.

Since *in vitro* studies have shown that propofol has antioxidant effects, reacts with toxic oxygen radicals and is transformed into phenoxyl radical, propofol may be showing its above mentioned impact over MDA by reducing the amount of toxic oxygen radicals (44), because the chemical structure of propofol is close to that of the vitamin E, an antioxidant (45). In view of the current data, the lower MDA levels in the propofol group may be explained by its antioxidant effect. In other studies, propofol has been specifically shown to increase antioxidant capacity in rat erythrocytes, lungs, liver, and heart by *in vivo* studies (46). The increase in the antioxidant capacity with propofol is believed to be secondary to the acquisition of an electron by propofol from SOR and its transformation into a more stable by-product (46, 47). Erythrocytes demonstrate elevated antioxidant capacity when exposed to propofol in *in vivo* and *in vitro* studies, which indicates that its antioxidant effect arises from the direct influence of the drug without any need of mediators. In addition, propofol has been shown to modify glutathion-related antioxidant systems in several studies (48). The positive effects of propofol, as shown in our study, can not be attributed to its intralipid carrier, because its carrier was found to have no antioxidant capacity in several studies (49, 50).

Thiopental is a highly lipid soluble anaesthetic which has demonstrated antioxidant properties by inhibiting lipid peroxidation (51, 52) and to a lesser degree, antihemolytic activity by inhibiting free-radical-mediated hemolysis of red blood cell in vitro (53,54). In one study, at clinically relevant concentrations, thiopental significantly reduced reactive oxygen species production of neutrophils (54). Thiopental has been shown to act as an antioxidant by inhibiting MDA formation *in vitro* (52,55). In a study by Almaas et al., thiopental inhibited iron-stimulated, but not the peroxynitrite-stimulated, MDA formation *in vitro* (52). The effect of thiopental on lipid peroxidation and free radicals *in vivo* may thus be a result of additional mechanisms than those suggested by *in vitro* experiments.

Previous studies have shown that thiopental alters hepatic function (56); for example, low- and single-dose thiopental are known to have no effect on the liver enzymes, but influence liver enzymes when applied at high and continuous doses (57,58). As noted in various studies, high-dose intravenous anesthetics can lead to serious hepatic dysfunction (59). In our study, MDA was observed to reach its highest levels in the thiopental group, levels significantly higher than those of the ketamine and propofol groups. CAT activities were lowest in the thiopental group. Although not statistically significant, thiopental had the worst histopathologic score in terms of polymorphonuclear leukocytes and necrosis than any of the groups.

Protection by opioid receptor agonists against ischemia-reperfusion injury has been demonstrated during the last several years (60). Fentanyl is one of many opioid receptor agonists and has effects on the brain, heart, and liver (61, 62). Regarding its effects in obstructive jaundice however, little is known. In our study, the fentanyl group had significantly higher MDA levels compared to the ketamine group. CAT activities were significantly higher in the fentanyl group compared to the ketamine group only, however, SOD activities were similar between the groups.

Hepatocyte injury during cholestasis is due partly to the release of proinflammatory mediators that cause polymorphonuclear leukocytes to accumulate in the liver and become activated to damage hepatocytes (63). Infiltration by polymorphonuclear leukocytes may represent a source of liver injury during acute biliary obstruction in rats with bile duct ligation. In addition to sinusoids, neutrophils adhere in portal and postsinusoidal venules and extravasate from these locations (64, 65). In our study, although the ketamine group had the best score regarding portal polymorphonuclear leukocytes and necrosis, its scores were not significantly better than the other drugs.

Among the agents tested, ketamine and propofol generated the least amount of oxidative stress in this rat model of hepatic jaundice created by common bile duct ligation. They also demonstrated the strongest protective effect as measured by portal polymorphonuclear leukocytes and necrosis. Ketamine exhibited a stronger effect than propofol, as demonstrated by the lower levels of MDA in the ketamine-treated animals.

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