Effects of ketamine, thiopental and their combination on the rat liver: A biochemical evaluation

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Abstract

Background. In the literature, it has been suggested that ketamine-related oxidative organ damage results from increased blood adrenaline level, and thiopental-related oxidative damage is caused by decreased adrenaline level, suggesting that ketamine-thiopental combination (KT) may be beneficial in reducing the hepatotoxic effect of ketamine.

Objectives. To biochemically investigate the effects of ketamine, thiopental and KT on the liver in rats.

Materials and methods. Male albino Wistar type rats received intraperitoneally (ip.) 30 mg/kg ketamine in the ketamine alone (KG) group (n = 6), 15 mg/kg thiopental in the thiopental alone (TG) group (n = 6), and 30 mg/kg ketamine + 15 mg/kg thiopental in the ketamine+thiopental (KTG) group (n = 6). The same volume of distilled water as solvent was given to the healthy (HG) animal group. This procedure was repeated once daily for 30 days. At the end of this period, the animals were killed by decapitation and their livers were removed. In liver tissue, malondialdehyde (MDA), total glutathione (tGSH), total oxidant status (TOS), total antioxidant status (TAS), tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and interleukin-6 (IL-6) levels were measured. The IL-1β, IL-6, TNF-α, adrenalin (ADR), noradrenalin (NDR), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels were determined in blood samples taken from the tail veins.

Results. In the group treated with ketamine and thiopental alone, MDA, TOS, IL-1β, IL-6, TNF-α, ADR, NDR, ALT, and AST levels were found to be high, and those of tGSH and TAS to be low. However, there was no significant change in the levels of these parameters in the KTG.

Conclusions. These results indicate that oxidative stress and inflammation developed in the liver tissue of the group that used ketamine and thiopental alone, suggesting that the KT form may be safer in terms of toxicity in the clinical usage.

Key words: hepatotoxicity, ketamine, thiopental, rat

Background

Ketamine is a dissociative anesthetic agent that has strong analgesic and mild hypnotic properties, and causes a rapid effect.[1] The efficacy of various routes of administration such as intravenous, intramuscular, oral, intranasal, rectal, and transdermal has been proven.[2] The high-dose intravenous form of ketamine is used clinically in short-term surgical procedures, and the low dose is used to create an analgesic effect.[3,4] It has been shown that ketamine at sub-anesthetic doses has rapid, strong antidepressant effects in patients with resistant depression.[5] Although there is not enough information on the long-term use of ketamine, its use in the treatment of chronic diseases is increasing.[6] In fact, it is known that ketamine infusions are used in the treatment of chronic pain.[7] In the literature, it has been reported that hepatotoxicity seen in patients treated with ketamine infusion causes the termination of ketamine treatment.[6] Additionally, repeated doses of ketamine over a long or short period increase the risk of developing liver damage.[8] Hepatotoxicity has been reported in the majority of people using ketamine for a recreational purpose.[9] The mechanism of liver damage caused by ketamine has not yet been fully elucidated. However, it has been suggested that one of the ketamine damage mechanisms is the blockade of N-methyl-D-aspartate (NMDA) receptors.[10] However, the formation of reactive oxygen species (ROS) and increased lipid peroxidation (LPO) have been implicated in the pathogenesis of ketamine hepatotoxicity.[9] Previous studies have also reported that pro-inflammatory cytokines such as ROS, interleukin 1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) play a role in the pathogenesis of ketamine-related cell damage.[11] In the study by Aksoy et al., it has been reported that ketamine increased the production of catecholamines such as endogenous adrenaline (ADR), noradrenaline (NDR) and dopamine in animals.[12] Another study established that oxidative damage has developed in the brain, heart and bronchial tissues of ketamine group rats with high blood adrenaline levels.[13]

Thiopental is a barbiturate-derivative anesthetic drug.[14] In a study in rats, oxidative damage occurred in the brain, heart and bronchial tissues of the thiopental group, whose blood adrenaline level was low.[13] It has been reported that thiopental, unlike ketamine, suppresses TNF-α production through inhibition of nuclear factor kappa-B (NF-κB).[15] This information indicates that keeping blood catecholamine levels within physiological limits may be beneficial in reducing oxidative stress. It also suggests that ketamine+thiopental combination (KT) will not have a toxic effect on the liver.

Objectives

The aim of the study was to biochemically investigate the effect of ketamine, thiopental and KT on rat livers.

Materials and methods

Animals

In total, 24 male albino Wistar rats weighing 255–268 g were used in the experiment. The animals were housed and fed under appropriate conditions in a suitable laboratory environment at normal room temperature (22°C). The study was approved by the Local Animal Experimentation Ethics Committee (date: 21.05.2021, meeting No. E-77040475-641.04-2100132117).

Chemicals

Ketamine used in the experiment was obtained from Pfizer Ltd. Sti. (Istanbul, Turkey), and thiopental sodium from I.E Ulagay (Istanbul, Turkey).

Animal groups

The animals used in the experiment were divided into 4 groups: ketamine alone group (KG), thiopental alone group (TG), ketamine+thiopental group (KTG), and healthy control (HG) group.

Experimental procedure

In this study, 30 mg/kg ketamine was administered intraperitoneally (ip.) to the KG (n = 6), 10 mg/kg thiopental to the TG (n = 6) and 30 mg/kg ketamine + 15 mg/kg thiopental to the KTG (n = 6). The same volume of distilled water as solvent was given to the HG. This procedure was repeated once daily for 30 days. On the 31st day, blood samples were taken from the tail veins of the animals, and immediately afterwards all of the rats were euthanized using an overdose of a general anesthetic (thiopental sodium, 50 mg/kg), their livers were removed. The IL-1β, IL-6, TNF-α, adrenaline (ADR), noradrenaline (NDR), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels were measured in the samples. Malondialdehyde (MDA), total glutathione (tGSH), total oxidant status (TOS), total antioxidant status (TAS), tumor necrosis factor alpha (TNF-α), IL-1β, and IL-6 levels were measured in a part of the liver tissue.

Biochemical analysis

Protein analysis in tissue

Protein measurement in tissue was performed according to the Bradford method.[16] The principle of this method is based on measuring the absorbance at 595 nm of the colored complex, formed as a result of the interaction of the Coomassie Brilliant Blue G-250 dye (C.I. 42655, Sigma-Aldrich, St. Louis, USA) with the acidic and basic

groups of the proteins. All measurements made in tissue were standardized by dividing to protein.

MDA and tGSH analyses in tissues

The MDA measurements were based on the method used by Ohkawa et al., which includes the spectrophotometric measurement of the absorbance of the pink-colored complex formed by thiobarbituric acid (TBA) and malondialdehyde (MDA; μmol/g protein).[17] Total glutathione (tGSH; nmol/g protein) measurement was made according to the method described by Sedlak and Lindsay.[18]

Measurements of TOS and TAS

The total oxidant status (TOS; μmol H_2O_2 equivalent/mg protein) and total antioxidant status (TAS; mmol Trolox equivalent/mg protein) levels of tissue homogenates were determined using a novel automated measurement method and commercially available kits (Rel Assay Diagnostics, Gaziantep, Turkey), both developed by Erel.[19,20]

TNF-α, IL-1β and IL-6 analyses in serum and tissues

Samples kept at –80°C on the working day were removed from the deep freezer and thawed at 4°C. Then, 0.1 g of each tissue was taken and 2 mL of phosphate buffer was added, and homogenate was obtained with the help of homosenier. Next, the samples were centrifuged 20 min at 10,000 × g and the supernatants were carefully collected. The levels of TNF-α (ng/mg protein), IL-1β (ng/mg protein) and IL-6 (ng/mg protein) were measured using an enzyme-linked immunosorbent assay (ELISA) kit supplied by Eastbiopharm Co. Ltd. (Hangzhou, China).

Analysis of serum ALT and AST

Venous blood samples were collected into tubes without an anticoagulant. After clotting, the serum was separated with centrifugation and stored at –80°C until assay. Using a Cobas 8000 autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany) with commercially available kits (Roche Diagnostics), serum AST [U/L] and ALT [U/L] activities were measured spectrophotometrically for the liver function tests.

Measurement of ADR and NDR levels

Blood samples were collected from the hearts of rats in 2 mL of ethylenediamine tetraacetic acid (EDTA) vacuum tubes to determine the adrenaline and noradrenaline levels. Within 15 min of venesection, the EDTA samples for the adrenaline and noradrenaline measurements were placed on ice and centrifuged at 3500 × g for 5 min. After centrifugation, the plasma adrenaline and noradrenaline concentrations were measured with an isocratic system using a high-performance liquid chromatography (HPLC) pump (Hewlett Packard Agilent 1100; Hewlett Packard Enterprise, Spring, USA; flow rate: 1 mL/min; injection volume: 40 μL; analytical run time: 20 min) and an electrochemical detector. We used a reagent kit for HPLC analysis of the catecholamines in the plasma serum (Chromsystems, Munich, Germany).

Statistical analyses

For statistical analyses, IBM SPSS v. 22 (IBM Corp., Armonk, USA) was used. Biochemical findings were presented with boxplot and p-values for all comparisons were reported in the Table 1. Normality assumption of biochemical variables was checked using Shapiro–Wilk test, and homogeneity of variances assumption was evaluated with Levene's test. The differences between groups were obtained using one-way analysis of variance (ANOVA) for normally distributed variables. The Tukey's honestly significant difference (HSD) test or Games–Howell test was used as post hoc test, according to homogeneity of variances assumption being met or not. Kruskal–Wallis test was used to determine the differences for TAS, OSI, TNF-α, and IL-1β. Post hoc Dunn's test was applied after Kruskal–Wallis test. The value of $p < 0.05$ was considered statistically significant.

Results

Biochemical findings

Tissue MDA and tGSH analysis

As shown in Fig. 1, the amount of MDA in the liver tissue of animals treated with ketamine and thiopental alone was higher than in the HG and KTG ($p < 0.001$). The amount of MDA in the liver tissue of the KTG animals was close to that in the HG ($p > 0.05$). In addition, ketamine and thiopental caused a decrease in tGSH in the liver tissue of the animals. While the amount of tGSH in the KG and TG was lower than the healthy and KTG ($p < 0.001$), the amount of tGSH in the HG and KTG was almost the same ($p > 0.05$). All p-values for post hoc comparisons are reported in Table 1.

Tissue TOS, TAS and OSI analysis

As presented in Fig. 2, while TOS level was higher in liver tissue of animals from the KTG compared to HG and KTG ($p < 0.001$), TAS level was lower ($p < 0.001$). Statistical analysis showed that the difference between TOS and TAS levels in the liver tissue of the HG and KTG was insignificant ($p > 0.05$). In addition, the Oxidative Stress Index (OSI) value in the KG and TG was higher than that of the HG and KTG ($p < 0.001$). The OSI values between the HG and KTG were close to each other and

Table 1. Analysis of variance (ANOVA) test results and post hoc p-values for group comparisons

Biochemical parameters	ANOVA or KW results		Post hoc test p-values					
	(3;20) or -W	p-value	HG vs KG	HG vs TG	HG vs KTG	KG vs TG	KG vs KTG	TG vs KTG
MDA*	89.1	0.0001	0.0001	0.0001	0.0296	0.0001	0.0001	0.0001
tGSH**	62.2	0.0001	0.0001	0.0001	0.0639	0.0001	0.0001	0.0001
TOS*	97.4	0.0001	0.0001	0.0001	0.0516	0.0001	0.0001	0.0001
TAS^{+}	0.576	0.0001	0.0001	0.0059	0.2880	0.1416	0.0019	0.0936
OSI^{+}	1.360	0.0001	0.0001	0.0039	0.1890	0.1401	0.0021	0.0190
TNF-α^{+}	9.980	0.0001	0.0001	0.0099	0.4620	0.1420	0.0009	0.0459
IL-1β^{+}	9.867	0.0001	0.0001	0.0110	0.5141	0.1422	0.0011	0.0403
IL-6^{+}	0.400	0.0001	0.0001	0.0072	0.3270	0.1421	0.0099	0.0461
ALT**	43.6	0.0001	0.0001	0.0001	0.2104	0.1643	0.0001	0.0001
AST**	87.4	0.0001	0.0001	0.0001	0.2165	0.0040	0.0001	0.0001
ADR**	7379.6	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
NDR**	7893.9	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

MDA – malondialdehyde; tGSH – total glutathione; TOS – total oxidant status; TAS – total antioxidant status; TNF-α – tumor necrosis factor alpha; IL-1β – interleukin 1 beta; ALT – alanine aminotransferase; AST – aspartate aminotransferase; ADR – adrenaline; NDR – noradrenaline; KW – Kruskal–Wallis test; OSI – oxidative stress index; HG – healthy group; KG – ketamine group; TG – thiopental group; KTG – ketamine+thiopental group. *Games–Howell test was performed as the post hoc test after ANOVA (F(3;20)); **Tukey HSD test was performed as the post hoc test after ANOVA (F(3;20)); $^{+}$ Kruskal–Wallis test was used and Dunn's test was performed as post hoc test.

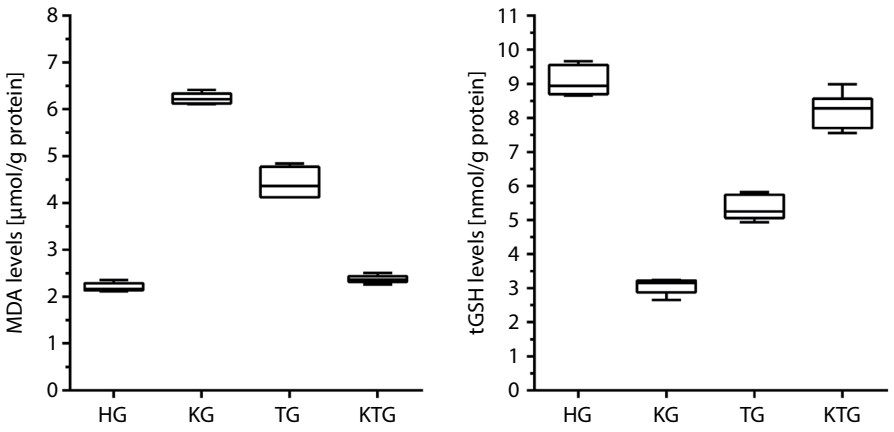

Fig. 1. Malondialdehyde (MDA) and total glutathione (tGSH) levels in the liver tissue of the study groups

HG – healthy group; KG – ketamine group; TG – thiopental group; KTG – ketamine+thiopental group; horizontal line – median; bottom line of the box – 1st quartile (Q1, 25th); topline of the box – 3rd quartile (Q3, 75th); whiskers – minimum and maximum observation (excluding outlier).

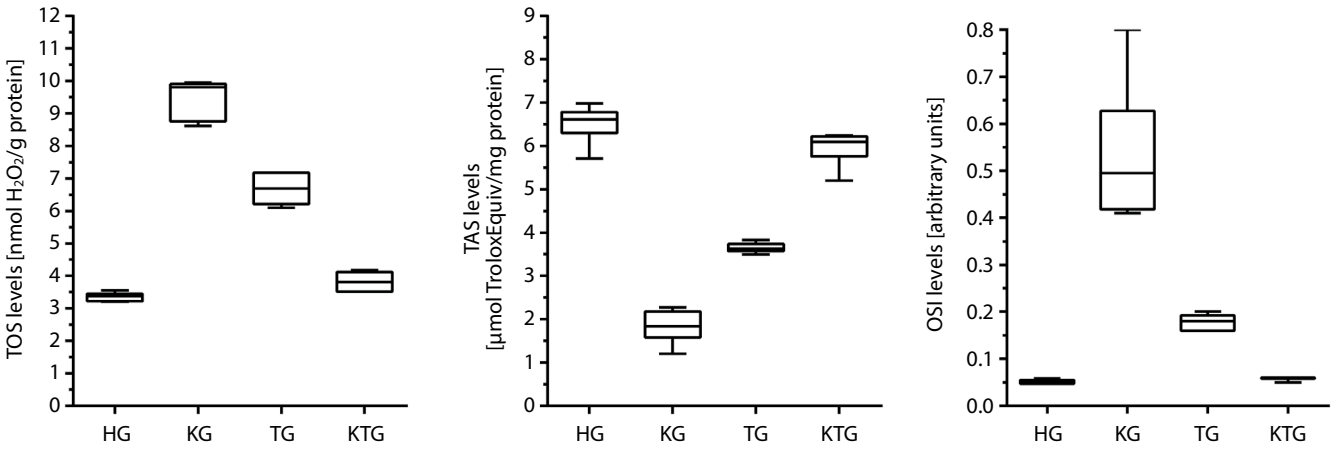

Fig. 2. Total oxidant status (TOS) and total antioxidant status (TAS) levels and the Oxidative Stress Index (OSI) values in the liver tissue of the study groups

HG – healthy group; KG – ketamine group; TG – thiopental group; KTG – ketamine+thiopental group; horizontal line – median; bottom line of the box – 1st quartile (Q1, 25th); topline of the box – 3rd quartile (Q3, 75th); whiskers – minimum and maximum observation (excluding outlier).

were statistically insignificant ($p > 0.05$). All p-values for post hoc comparisons are reported in Table 1.

Serum and tissue TNF-α, IL-1β and IL-6 analysis

As presented in Fig. 3, TNF-α, IL-1β and IL-6 levels in the liver tissue of the KG and TG were higher than those of the HG and KTG ($p < 0.001$). There was no significant difference between TNF-α, IL-1β and IL-6 levels in the HG and KTG ($p > 0.05$). In addition, TNF-α, IL-1β and IL-6 levels in the blood serum of the KG and TG were higher than in the HG and KTG ($p < 0.001$). The TNF-α, IL-1β and IL-6 levels in the KTG were found to be similar to those obtained in the HG ($p > 0.05$) (Fig. 5). All p-values for post hoc comparisons are reported in Table 1.

Serum ALT and AST analysis

Serum ALT and AST activities in the KG and TG were higher than those of the HG and KTG ($p < 0.001$). However, the difference between ALT and AST activities in the HG and KTG was found to be insignificant ($p > 0.05$; Fig. 4). All p-values for post hoc comparisons are reported in Table 1.

Blood serum ADR and NDR analysis

As can be seen in Table 2, ADR and NDR levels in the KG were significantly higher compared to the HG and KTG ($p < 0.001$), while they were decreased in TG ($p < 0.001$). In addition, ADR and NDR levels in the KTG were closely related to the HG ($p > 0.05$).

Discussion

In this study, oxidant, antioxidant and pro-inflammatory parameters and ADR and NDR levels were investigated in rats treated with ketamine, thiopental and KT. From our biochemical test results, it can be concluded that oxidative and inflammatory damage in the liver tissue of rats treated with repeated subanesthetic doses of ketamine alone. In addition, the systemic oxidative stress and inflammation was observed. In the literature supporting our biochemical findings, the role of oxidant and pro-inflammatory cytokines such as ROS, IL-1β, IL-6, and TNF-α in the pathogenesis of ketamine-related cell damage has been shown.[11]

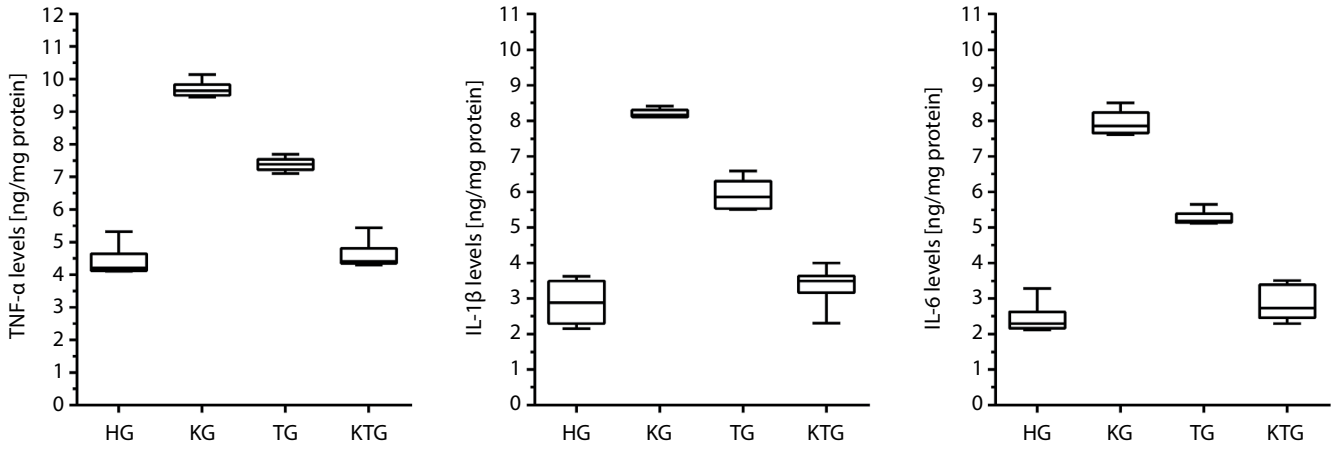

Fig. 3. Tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin-6 (IL-6) levels in the liver tissue of the study groups

HG – healthy group; KG – ketamine group; TG – thiopental group; KTG – ketamine+thiopental group; horizontal line – median; bottom line of the box – 1st quartile (Q1, 25th); topline of the box – 3rd quartile (Q3, 75th); whiskers – minimum and maximum observation (excluding outlier).

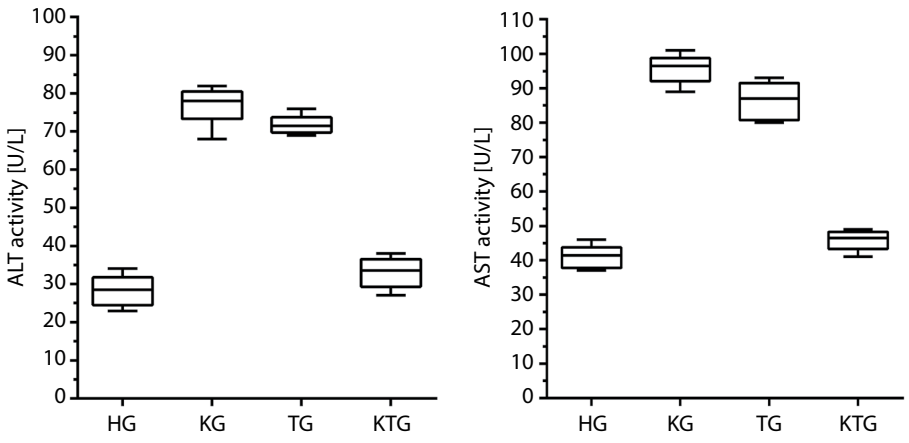

Fig. 4. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity in blood of the study groups

HG – healthy group; KG – ketamine group; TG – thiopental group; KTG – ketamine+thiopental group; horizontal line – median; bottom line of the box – 1st quartile (Q1, 25th); topline of the box – 3rd quartile (Q3, 75th); whiskers – minimum and maximum observation (excluding outlier).

Table 2. The effect of ketamine, thiopental and ketamine+thiopental combination on adrenaline and noradrenaline levels in rats

Groups	ADR	p-value	NDR	p-value
HG	1435.3	0.001	813.8	0.0001
KG	2388.2	0.001	1364	0.0001
TG	779	0.001	291	0.0001
KTG	1513	0.001	710.6	0.0001

HG – healthy group; KG – ketamine group; TG – thiopental group; KTG – ketamine+thiopental group; ADR – adrenaline; NDR – noradrenaline. The analysis of variance (ANOVA) test was used. A value of $p < 0.05$ was considered statistically significant.

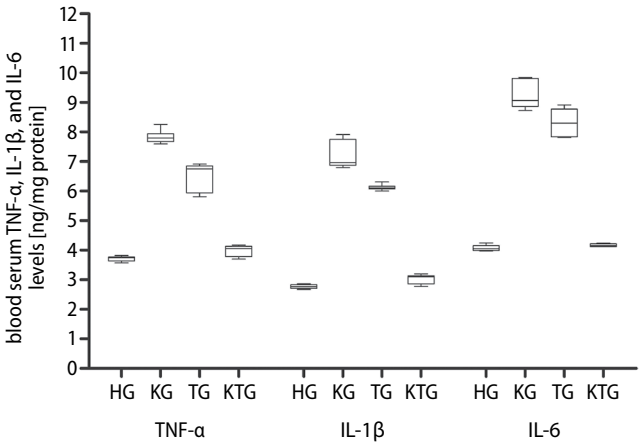

Fig. 5. Tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin-6 (IL-6) levels in the blood serum of the study groups

HG – healthy group; KG – ketamine group; TG – thiopental group; KTG – ketamine+thiopental group; horizontal line – median; bottom line of the box – 1st quartile (Q1, 25th); topline of the box – 3rd quartile (Q3, 75th); whiskers – minimum and maximum observation (excluding outlier).

In a previous study, excessive ROS formation and increased lipid peroxidation (LPO) were perceived as the cause of ketamine hepatotoxicity.[9] In our study, the amount of MDA in the blood serum and liver tissue of animals treated with ketamine alone was found to be higher than in the HG and KTG. These findings indicate that ROS and LPO increased in the ketamine group. MDA is widely used oxidant parameter in oxidative stress-induced LPO. The MDA reacts with nucleic acids and proteins, allowing the damage caused by LPO to continue exacerbated.[22] In the studies of Ahiskalioglu et al., it was reported that the subanesthetic dose of ketamine increased the amount of MDA in the brain, heart and bronchi. However, it was emphasized that the amount of MDA in the ketamine+thiopental group was close to that in the control group.[13]

In recent studies, it has been reported that an increase in ROS-related MDA is accompanied by a decrease in GSH stores.[23] Glutathione is an endogenous antioxidant with a low molecular weight, composed of c-L-glutamyl-L-cysteinyl-glycine. The sulfhydryl group (–SH) of cysteine is involved in reduction and conjugation reactions, which are generally considered to be the most important functions of GSH.[24] Glutathione protects cells from ROS damage by reacting with or detoxifying hydrogen peroxide (H_2O_2) and organic peroxides.[25] It was determined that the amount of tGSH decreased in animal organs given ketamine alone.[13] In our study, TOS and TAS levels were determined to evaluate oxidative stress in liver tissue in more detail. Total oxidant status and total antioxidant status reflect the total effects of all oxidants and antioxidants in tissues.[19,20] The fact that MDA and TOS levels are higher in the KG compared to the HG and KTG, and that tGSH and TAS levels are lower compared to KG, indicate that oxidative stress has developed in the liver tissue.

In the previous research, it has been reported that ROS increase pro-inflammatory cytokine production.[26] As can be seen from our experimental results, the production of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 increased in the KG with high oxidant parameters and low antioxidants. These cytokines are shown as the response of the immune system in acute and chronic liver damage.[27] As is known, if the overproduction of cytokines is not controlled, it can cause serious consequences.[28] Previous studies have also reported that pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α play a role in the pathogenesis of ketamine-related cell damage.[11] In a mouse model of fulminant hepatitis, TNF-α produced by inflammatory cells caused fatal necroinflammatory liver damage.[29] There was no information in the literature on the effects of ketamine on hepatic cytokines. However, it has been reported that ketamine increases the expression of IL-1β and IL-6 in rat spleen.[30] In another study, it was emphasized that ketamine induced the production of ROS, IL-1β, IL-6, and TNF-α in bladder cells.[11] In addition, it has been assumed that the toxic effects of ketamine on the central nervous system are related to inflammatory cytokines (such as IL-1β and IL-6).[31]

Serum ALT and AST activities were found to be high in animals administered with ketamine, whose blood serum and liver tissue oxidant as well as pro-inflammatory cytokine levels were high. These aminotransferases are accepted in literature as sensitive indicators of liver cell damage.[32] It has been reported that elevated hepatic oxidant and pro-inflammatory cytokine levels are accompanied by increased blood serum ALT and AST activity.[33] Intravenous ketamine infusion with 16-day intervals in the clinics caused an increase in serum ALT and AST activity in patients.[8]

In our study, MDA, TOS, OSI, IL-1β, IL-6, TNF-α, ALT, and AST levels were higher in the TG, and their tGSH and TAS levels were lower than those of the HG and KTG. There are studies supporting that thiopental alone increases oxidant levels and decreases antioxidant levels in organ tissues.[13] It has been reported in the literature that human lymphocytes treated with thiopental exhibit excessive ROS production.[34] In another study, it was reported that thiopental did not change MDA and antioxidant levels in the platelets of patients.[35] There are data in the literature showing that thiopental suppresses TNF-α production by inhibiting NF-κB, which does not overlap with our biochemical test results.[15] However, the information stating that ROS increase pro-inflammatory cytokine production supports our biochemical findings.[26] In addition, repeated doses of thiopental have been shown to increase the levels of liver enzymes.[36]

In our study, the use of ketamine and thiopental alone led to an increase in oxidant and pro-inflammatory cytokines in the liver tissue. However, the use of KT did not change the MDA, tGSH, TOS, TAS, IL-6, TNF-α, and IL-1β levels in the liver tissue. The reason for this can be shown as an increase in catecholamine level of ketamine and a decrease in thiopental. In previous studies, it was observed that oxidative stress increased in the brain, heart and bronchi, in the ketamine group with high blood ADR levels and in the thiopental group with low blood ADR levels. In addition, the damage to these organ tissues of animals administered KT was minimal or nonexistent.[13] In addition, histopathological damage was observed at a minimum level in the KTG animals whose MDA and tGSH levels were similar to those in the HG. As can be understood from our experimental results, pro-inflammatory cytokine levels in the KTG animals whose oxidant and antioxidant levels were close to the HG were similar to those in the HG. Recently, it has been suggested that thiopental reduces the level of ADR and subsequently induces hyperalgesia in rats. It is assumed that ketamine increases the level of ADR, and that – in the case of suppression of ADR – adrenaline has an important role in controlling the duration of anesthesia. Reducing the amount of endogenous ADR has resulted in prolonged anesthesia time of ketamine.[37]

Limitations

In further studies, the mechanism of action of ketamine, thiopental and KT on the liver should be clarifed – it was not investigated in the present paper. Moreover, effects of long-term use of ketamine in other organs should be elucidated.

Conclusions

The use of ketamine and thiopental alone caused oxidative and pro-inflammatory changes in the liver. However, when these drugs were used as KT, no changes were observed in oxidative stress and inflammation markers. These results indicate that the KT form may be useful in reducing the risk of toxicity of ketamine and thiopental on the liver in clinical setting. In order to clarify the mechanisms of action of ketamine, thiopental and KT on the liver, it is necessary to measure blood serum catecholamine levels. Further studies on the subject are needed in the future.

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