DOSE-DEPENDENT ANTI-INFLAMMATORY EFFECT OF KETAMINE IN LIVER ISCHEMIA-REPERFUSION INJURY

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Abstract

Introduction: Hepatic ischemia-reperfusion (I/R) injury is commonly observed in severe sepsis, hemorrhagic shock, liver transplantation, hepatic resection, and major trauma. Ketamine suppresses the production of cytokines, such as IL-6 and TNF-α, via NF-κB inhibition. We investigated the anti-inflammatory effects of ketamine in liver I/R injury.

Materials and Methods: Female Wistar-Albino rats (n = 18), weighing 150-200g, were divided into three groups (n = 6 each). Group I underwent reperfusion for 4h following 30 min of ischemia. Group II received 2.5 mg/kg ketamine IM following 30 min of ischemia and 4h of reperfusion and Group III received 10 mg/kg ketamine IM following 30 min of ischemia and 4h of reperfusion. Blood samples were obtained before and after ischemia and reperfusion. MDA, AST, ALT, TNF-α, IL-1β, IL-6, and NO levels were determined. Liver tissue samples were evaluated histologically.

Results: Increased TNF-α, IL-1β, and IL-6 levels were observed in all groups post-ischemia versus pre-ischemia (p <0.05). The TNF-α, IL-1β, and IL-6 levels in Group III increased less than they did in Groups I and II (p <0.05). Higher MDA, NO, AST, and ALT levels were found during the ischemia and reperfusion periods compared with during the pre-ischemia period in all groups (p <0.05). The MDA, NO, AST, and ALT levels of rats that received ketamine increased less than did those of Group I (p <0.05). Significantly less injury was observed in the histopathological analysis of livers of rats administered ketamine (p <0.05).

Conclusions: Ketamine showed a dose-dependent anti-inflammatory effect in I/R injury in the liver when administered after ischemia.

Key words: ketamine, liver, ischemia-reperfusion injury, TNF-α, IL-1β, IL-6

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Introduction

Ischemia-reperfusion (I/R) injury in patients who receive treatment in intensive care units and/or undergo surgical interventions is an crucial problem involving oxygen, free radicals, and cytokines. I/R injury in the liver is observed in clinical situations such as surgical interventions for hemorrhagic shock, the late period of sepsis, liver transplantation, significant trauma, and hepatic resection. In liver I/R injury, reactive oxygen metabolites secreted from Kupffer cells activate neutrophils by inducing a series of complex inflammatory processes.

Activated neutrophils cause the secretion of numerous enzymes, such as myeloperoxidase, elastase, and collagenase, and free radicals by adhering to endothelial cells, leading to a vicious cycle of increasing injury. As a result of I/R injury in the liver, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels increase. Tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6) have adhesion receptor-increasing effects on leukocyte activation, endothelial cells, and leukocytes. They coordinate the immune response by inducing the secretion of TNF-α and cytokines that play a key role in the inflammatory response. Increased TNF-α and IL-6 further increase the injury by causing the secretion of adhesion molecules and an influx of leukocytes in the perfused tissue.

Cytokines that appear after I/R (interferon-gamma IFN-γ, TNF-α, IL-1β) induce the inducible nitric oxide synthetase (iNOS) enzyme, expression of which occurs within a few hours. It then remains active for 4-24h and causes nitric oxide (NO) secretion independently of calcium/calmodulin. Through the mediation of iNOS, NO is liberated while L-arginine is transformed into L-citrulline. The cytotoxic effects of NO are non-specific, and its overproduction may be detrimental to the host.

Nuclear factor kappa B (NF-κB) is a transcription factor and is responsible for the expression of many genes in the inflammatory response. NF-κB is found in the cytoplasm, bound to its inhibitor (inhibitor kappa B, iκB). This becomes free NF-κB by separation from the inhibitor as a result of stimulation, such as by IL-1β, TNF-α, and lipopolysaccharide (LPS). Numerous binding sites exist for NF-κB in the upper region of the human iNOS gene promoter.

Ketamine prevents liver injury due to LPS by increasing heme oxygenase-1 (HO-1) and decreasing iNOS levels. It has been demonstrated that ketamine has protective effects in liver injury caused by LPS; thus, ketamine may be an appropriate intravenous agent in patients with sepsis who require anesthesia. It has been shown that ketamine suppressed TNF-α levels due to endotoxins and reduced mortality in rats in endotoxemic shock. Through NF-κB inhibition, ketamine suppresses the production of such pro-inflammatory cytokines as IL-6 and TNF-α. Ketamine shows anti-inflammatory effects by inhibiting the reactivity of leukocytes.

The aim of this study was to investigate the effects of low and high doses of ketamine in rats who had experienced liver injury as a result of an experimental I/R injury.

Materials and Methods

After local ethics committee approval was obtained, 18 Wistar-Albino female rats weighing 150-200g were used. The study was conducted in accordance with the ethical provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, and care was taken to use the minimum number of rats. The rats were kept in a room that received sunlight for 12h and has an air conditioning system (22-24°C, 70-75% humidity) and were fed with standard laboratory food and water. Feeding was stopped 12h before the experiment, and the rats were allowed access to only water.

Rats were randomized into three groups (n = 6 each) using the sealed envelope method. Intraperitoneal xylazine (Rompun, Bayer-Istanbul, 5-10 mg/kg) and ether inhalation were used to anesthetize the rats. After draping and sterilization procedures, layers of the abdomen of the rats were opened, and the liver and arteria hepatica propria were reached. Rats in Group I (n = 6) underwent 30 min of ischemia by clamping the arteria hepatica propria, followed by reperfusion for 4 hours. Rats in Group II (n = 6) were administered...
intramuscular (IM) 2.5 mg/kg ketamine (Ketalar, 50 mg/mL Eczacibasi-Istanbul) following 30 min of ischemia and then underwent 4 hours of reperfusion. Rats in Group III (n = 6) were given 10 mg/kg ketamine IM following 30 min of ischemia and then underwent 4 hours of reperfusion. The isolated hepatic artery was clamped to cause ischemia. The portal vein was not clamped. No heparin was administered during the procedure.

Blood samples, obtained by vein puncture from the tail, avoiding hemolysis, were placed in plain tubes before and after ischemia and after 4 hours of reperfusion. Malondialdehyde (MDA), AST, ALT, TNF-α, IL-1β, IL-6, and NO levels were determined. Following centrifugation of blood samples (800g, 10 min), serum was separated and kept at -20°C until the biochemical analyses. At the end of the reperfusion period, hypovolemic shock was induced by incising the aorta abdominales of the rats, and they were sacrificed.

**Biochemical Analyses**

Plasma MDA levels of each animal were measured by high-performance liquid chromatography (HPLC; 515 nm excitation, 533 nm emission, C-18 column (125 nm × 4 mm) and flow rate 1 mL/min). TNF-α, IL-1β, and IL-6 levels were determined by ELISA (Invitrogen).

To assess nitric oxide levels, specimens were first deproteinized to prevent non-specific reactions, and the nitrite and nitrate concentrations were determined by the Griess reaction. Total nitrite (nitrite + nitrate) concentration was determined by a modified cadmium reduction method. Nitrate reduction was obtained by keeping copper-coated cadmium granules in pH 9.7 glycine buffer for a 90-min incubation with deproteinized sample supernatant. The rate of produced nitrite was assessed with spectrophotometer at 545 nm. Serum AST and ALT levels were measured with an autoanalyzer (results in U/L).

**Histology**

Liver tissue samples taken after reperfusion were fixed in 10% formaldehyde, and sections of 5 μm were obtained from paraffin wax-embedded samples and assessed under a light microscope (Olympus BX51, Japan) following staining with hematoxylin and eosin. Changes in cell histology were evaluated for congestion, necrosis, cytoplasmic vacuolization, eosinophilia, nuclear pyknosis, and inflammatory cell density by a pathologist who was blind to the details of the experiment. The histological scoring for liver injury (HSLD) was used for evaluation (HSLD 0: no injury or minimal injury, 1: mild injury, 2: moderate injury, 3: severe injury).

**Statistical Analysis**

The SPSS software (ver. 15.0) was used. Data are shown as means ± SD. Variance comparison analyses between the groups were conducted with a post hoc Tukey HSD test. The Wilcoxon test was used to assess in-group repeated measurements. P-values <0.05 were considered to indicate statistical significance.

**Results**

The MDA levels in all groups were higher in the post-ischemia and reperfusion periods than in the pre-ischemia period (p <0.05). The MDA levels of the groups given ketamine increased more than did those of the Group I during the same periods of time (Table 1).

The group that received low-dose ketamine showed a significantly smaller increase in ALT levels in the post-reperfusion period (p <0.005). However, the ALT levels in the group that was given high-dose ketamine increased more than did those in the other groups.

The total nitrite levels increased in all groups during the ischemia and reperfusion periods compared with during the pre-ischemia period (p <0.005). The post-reperfusion total nitrite levels in Groups II and III increased less than did those in Group I; however, the difference was not statistically significant.

AST and ALT levels were higher in all groups during the ischemia and reperfusion periods than during the pre-ischemia period (p <0.05). The group that received low-dose ketamine showed a significantly smaller increase in ALT levels in the post-reperfusion period (p <0.005). However, the ALT levels in the group that was given high-dose ketamine increased more than did those in the other groups (Table 1).
Table 1
Serum MDA, AST, ALT, TNF-α, IL-6, IL-1β and NO levels pre-ischemia, post-ischemia and reperfusion injury in groups

<table>
<thead>
<tr>
<th></th>
<th>Pre-ischemia</th>
<th>post-ischemia</th>
<th>post-reperfusion</th>
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<tbody>
<tr>
<td><strong>MDA (mmol/l)</strong></td>
<td></td>
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</tr>
<tr>
<td>Group I</td>
<td>12 ± 0.78</td>
<td>22.83 ± 1.07*</td>
<td>27.47 ± 2.07*</td>
</tr>
<tr>
<td>Group II</td>
<td>17.00 ± 2.31</td>
<td>28.94 ± 5.20*</td>
<td>36.25 ± 4.43*</td>
</tr>
<tr>
<td>Group III</td>
<td>18.18 ± 0.98</td>
<td>28.12 ± 0.98*</td>
<td>38.75 ± 1.74*</td>
</tr>
<tr>
<td><strong>AST (U/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>135 ± 28.31</td>
<td>338.16 ± 71.99*</td>
<td>466.17 ± 138.92*</td>
</tr>
<tr>
<td>Group II</td>
<td>119.66 ± 48.88</td>
<td>233.66 ± 22.30*</td>
<td>274.17 ± 45.97*</td>
</tr>
<tr>
<td>Group III</td>
<td>114 ± 38.87</td>
<td>266.66 ± 28.40*</td>
<td>262.67 ± 121.06*</td>
</tr>
<tr>
<td><strong>ALT (U/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>47 ± 9.09</td>
<td>105.83 ± 42.62*</td>
<td>246.33 ± 86.37*</td>
</tr>
<tr>
<td>Group II</td>
<td>56 ± 10.56</td>
<td>90.16 ± 9.04*</td>
<td>145 ± 31.57**</td>
</tr>
<tr>
<td>Group III</td>
<td>52.66 ± 21.01</td>
<td>143.33 ± 29.82*</td>
<td>262 ± 57.11*</td>
</tr>
<tr>
<td><strong>TNF-α (pg/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>12.57 ± 1.83</td>
<td>2665.52 ± 38.76*</td>
<td>1300.04±57.87*</td>
</tr>
<tr>
<td>Group II</td>
<td>12.79 ± 2.66</td>
<td>1922.37 ± 64.76*</td>
<td>1156.96 ± 42.89*</td>
</tr>
<tr>
<td>Group III</td>
<td>13.27 ± 2.95</td>
<td>1435.36 ± 50.86*</td>
<td>689.83 ± 66.84*</td>
</tr>
<tr>
<td><strong>IL-6 (pg/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>107.61 ± 7.58</td>
<td>3374.51 ± 68.78*</td>
<td>3738.02 ± 48.29*</td>
</tr>
<tr>
<td>Group II</td>
<td>107.48 ± 0.79</td>
<td>2679.24 ± 203.69*</td>
<td>3085.96 ± 246.00*</td>
</tr>
<tr>
<td>Group III</td>
<td>111.42 ± 5.97</td>
<td>2180.70 ± 48.96*</td>
<td>2500.14 ± 57.60*</td>
</tr>
<tr>
<td><strong>IL-1β (pg/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>19.39 ± 3.33</td>
<td>3120.98 ± 80.64*</td>
<td>3815.03 ± 60.18*</td>
</tr>
<tr>
<td>Group II</td>
<td>23.02 ± 2.74</td>
<td>2715.19 ± 175.10*</td>
<td>3121.33 ± 64.54*</td>
</tr>
<tr>
<td>Group III</td>
<td>19.29 ± 3.198</td>
<td>2279.80 ± 89.69*</td>
<td>2755.16 ± 86.22*</td>
</tr>
<tr>
<td><strong>NO (U/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>0.2 ± 0.31</td>
<td>0.09 ± 0.09**</td>
<td>0.32 ± 0.30**</td>
</tr>
<tr>
<td>Group II</td>
<td>0.18 ± 0.19</td>
<td>0.05 ± 0.07**</td>
<td>0.09 ± 0.12**</td>
</tr>
<tr>
<td>Group III</td>
<td>0.02 ± 0.01</td>
<td>0.07 ± 0.07**</td>
<td>0.10 ± 0.14**</td>
</tr>
</tbody>
</table>

*p < 0.05 pre-ischemia period vs other periods in all groups

** p < 0.005
The TNF-α, IL-6, and IL-1β levels increased significantly in the post-ischemia period in all groups compared with their pre-ischemia values (p <0.05). During the reperfusion period, the TNF-α, IL-6, and IL-1β levels in Group III increased significantly less than they did in Groups I and II (p <0.05; Table 1).

The total nitrite levels increased in all groups during the ischemia and reperfusion periods compared with during the pre-ischemia period (p <0.005). The post-reperfusion total nitrite levels in Groups II and III increased less than did those in Group I; however, the difference was not statistically significant (Table 1).

According to the histopathological analysis, necrosis, inflammation, and congestion in the liver were significantly less common in Groups II and III than in Group I (p <0.05; Table 2) (Figs. 1, 2, 3).

<table>
<thead>
<tr>
<th>Histologic changes staging of liver in groups</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestion</td>
<td>1.83</td>
<td>1.17</td>
<td>1.17</td>
</tr>
<tr>
<td>Necrosis</td>
<td>1.83</td>
<td>1.83</td>
<td>1.67</td>
</tr>
<tr>
<td>Stoplasmic vacuolisation</td>
<td>2.00</td>
<td>1.25</td>
<td>1.67</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>1.83</td>
<td>1.08</td>
<td>1.00</td>
</tr>
<tr>
<td>Nuclear picnosis</td>
<td>1.00</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>Inflammatory cell accumulation</td>
<td>2.00</td>
<td>1.67</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Fig. 1
Liver histology in group I; Congestion, inflammation and necrosis is significant.
(Heamatoxilen eosin x200)

Fig. 2
Liver histology in group II; Necrosis, inflammation and congestion is fewer than group I
(Heamatoxilen eosin x200)

Fig. 3
Liver histology in group III Necrosis, inflammation and congestion is significantly decreased groups;
(Heamatoxilen eosin x200)
Discussion

In current study reveals that ischemia and reperfusion injury can cause increased tissue inflammation in liver and high levels inflammatory cytokines in plasma. Ketamine can ameliorate this inflammatory process as dose dependent.

Although various techniques can be used in order to evaluate liver functions after I/R injury, the most widely accepted and frequently used currently is to evaluate the level of AST and ALT. The activity of those enzymes are known to increase in liver damage. Ischemia-reperfusion has been suggested to increase ALT and AST levels and this was attributed to the damage of the tissues that was developed by free radicals that are produced following ischemia-reperfusion.

In this present study, plasma AST and ALT levels were found to be increased after I/R injury. Increase in AST levels following reperfusion in the groups that were administered ketamine was found to be lesser compared to the control group, though statistically not significant. ALT levels following reperfusion in the groups that were administered ketamine was found to be lesser compared to the group I.

On the other hand the MDA, NO, AST, and ALT levels of rats that received ketamine increased less than did those of Group I (p <0.05) and significantly less injury was observed in the histopathological analysis of livers of rats administered ketamine (p <0.05).

During the reperfusion period, the TNF-α, IL-6, and IL-1β levels in high dose ketamine (group III) increased significantly less than they did in Groups I and II (p <0.05).

IL-1β and TNF-α stimulate a group of changes in the endothelium. These changes are increased expression of adhesion molecules, secretion of some cytokines and growth factors, synthesis of eicosanoids and nitric oxide (NO) and increased endothelial thrombogenicity. Leukocytes secrete toxic oxygen products and proteolytic enzymes and may produce endothelial damage.

Antiinflammatory effect of ketamine investigated some researcher, Suliburk et al. reported in a study where rats were given saline (no anesthesia), underwent isoflurane inhalation, and received intraperitoneal ketamine (70 mg/kg); 1h later, saline or LPS (20 mg/kg) was given for 5h intraperitoneally. They analyzed liver inducible nitric oxide synthase (iNOS) protein and heme oxygenase-1 (HO-1) by Western blotting, and NF-κB (LPS) significantly elevated AST levels, hepatic iNOS, and heme oxygenase-1 (HO-1) immunoreactivity. They reported that ketamine had protective effects on the liver in LPS-induced hepatic injury via regulation of oxidative stress proteins, such as iNOS and HO-1. The use of ketamine as anesthesia has been suggested for septic patients.

Two different doses of ketamine were used in this study to investigate its role in preventing liver I/R injury. No significant difference was found in the NO levels of rats administered low and high doses of ketamine following I/R; however, the NO levels of these rats increased more than the levels of the controls that were not administered ketamine.

Lipids are an important target structure damaged by free radicals as a result of I/R. Indeed, lipid peroxidation is key in I/R injury. Free radicals induce lipid peroxidation by abstracting a hydrogen atom from polyunsaturated fatty acids, creating hydroperoxides. As a result of these reactions, cell membranes lose viscosity, and membrane integrity is damaged. This leads to the release of cell fractions into the environment and cell death. These released subcellular components trigger inflammatory events and further exacerbate the injury. Various methods have been used to produce indicators of lipid peroxidation in tissues. Among the most frequently used is the assessment of MDA. Studies conducted with an experimental I/R model demonstrated that gadolinium chloride (GdCl3) suppressed AST and ALT release and decreased mitochondrial MDA formation. Li et al. reported that inhibition of liver Kupffer cells by GdCl3 can protect against hepatic reperfusion injury. They randomly divided Wistar rats into two groups, a GdCl3 group and a control group, and collected blood samples from each group at 0.5, 1, 6, 12, and 24h following reperfusion. They analyzed ALT, AST, TNF-α, and MDA levels in hepatic mitochondria. They showed that GdCl3 depressed ALT, AST, and TNF-α levels and reduced the accumulation of mitochondrial MDA.
In our study, we showed that ketamine suppressed AST release dose-dependently; however, that it did not prevent the MDA increase in reperfusion injury and did not suppress ALT levels in the group given high-dose ketamine after reperfusion. We also investigated in our study the hepatoprotective effect of ketamine which demonstrated this effect by suppressing the release of proinflammatory cytokines such as TNF-α. Inflammatory cytokines, namely, TNF-α, IL-1β, and IL-6 levels were observed in all groups post-ischemia versus pre-ischemia (p <0.05). Administration of ketamine in subanesthetic doses inhibited the release of TNF-α and other pro-inflammatory cytokines. TNF-α has an important role in inflammatory reaction and regulation of inflammation in addition to its cytotoxic effect.

Hepatic NF-κB activation and plasma TNF-α and IL-6 concentrations increased in rats subjected to experimentally induced inflammation. Ketamine has been demonstrated to reduce hepatic NF-κB activation in many studies. It is believed that TNF-α plays a key role in the pathogenesis of inflammatory events. In our study, we analyzed IL-6 and IL-1β levels in addition to TNF-α levels. In vivo experimental studies have found that ketamine suppressed TNF-α and IL-6 formation in shock induced with an endotoxin and reported that it had dose-dependent anti-inflammatory effects. Additionally, many in vitro studies have reported that ketamine suppressed the production of pro-inflammatory cytokines and the expression of TNF-α. In our study, TNF-α, IL-1β, and IL-6 levels were decreased in the groups that were administered ketamine.

Sun et al. reported that ketamine reduced the activity of TNF-α and IL-6 in the intestine and that this effect may have been achieved through the inhibition of NF-κB. Their experimental study included six groups of rats: saline controls, rats challenged with an endotoxin (5 mg/kg) and administered saline, rats challenged with an endotoxin (5 mg/kg) and treated with three different doses of ketamine (0.5, 5, and 50 mg/kg), and rats injected with saline and treated with ketamine (50 mg/kg). They measured TNF-α, IL-6, and NF-κB levels in jejunal tissue after 1, 4, and 6h. Ketamine 0.5 mg/kg depressed endotoxin-induced TNF-α elevation and inhibited NF-κB activity. IL-6 can be inhibited by a 5-mg/kg ketamine dose. Ketamine also suppressed serum levels of endotoxin-induced TNF-α and reduced mortality in mice in endotoxin shock. Ketamine inhibits neutrophil activation and neutrophil-endothelial association. TNF-α causes release of adhesion molecules in endothelial cells (ELAM-1 ve ICAM-1) and IL-6 and IL-8. Ketamine inhibits adhesion of leukocytes to the endothelium. It is debatable that ketamine suppresses the phagocytic function of neutrophils.

Peralta et al. reported that preventing high-level TNF-α release from Kupffer cells in the liver via NO by preconditioning decreased both liver and lung injury related to hepatic I/R. Preconditioning has preventative effects through reducing liver TNF-α levels after I/R. NF-κB is an inducible nuclear transcription factor that plays a role in the expression of pro-inflammatory cytokines. Many researchers have reported that the major source of pro-inflammatory cytokines in the acute phase of inflammatory events was hepatic Kupffer cells. Few studies have examined the effects of ketamine on NF-κB. In vivo and in vitro experiments have shown that ketamine inhibits NF-κB in brain cells. It was also demonstrated that ketamine depressed TNF-α and NF-κB activation in the liver, lungs, and intestines. Additionally, high-dose ketamine (50 mg/kg) induced LPS injury and inhibited acute lung injury in rats. In this study, ketamine was used at two doses, 2.5 and 10 mg/kg, and was found to suppress TNF-α, IL-6, and IL-1β levels compared with the control group.

Cytokines play important roles in endotoxin-induced shock, and some studies have claimed that ketamine reduces the production of some cytokines under endotoxemic conditions. Taniguchi et al. studied 40 rats in four groups: a group given Escherichia coli endotoxin (15 mg/kg, administered intravenously), a saline control group, a group administered ketamine (10 mg/kg per h) before the endotoxin challenge, and another group administered ketamine 2h after the endotoxin challenge. After a 5-h period of endotoxin exposure, the hemodynamic parameters and acid-base status and plasma TNF-α and IL-6 levels were measured in each group. They demonstrated that ketamine administration inhibited hypotension, metabolic acidosis, and cytokine responses in rats.
injected with an endotoxin. The results suggested that judicious use of ketamine as an anesthetic agent may offer advantages in endotoxemia.

Taniguchi et al. reported that ketamine administration depressed hypotension, metabolic acidosis, and cytokine responses in endotoxemia. In their study, 65 rats were divided into five equal groups: after exposure to an endotoxin, Group C was given saline alone, Group E was given an endotoxin alone (E. coli endotoxin, 10 mg/kg, IV), Group L received low-dose ketamine (5 mg/kg/h, IV), Group M received a medium dose of ketamine (10 mg/kg/h, IV), and Group H received a high dose of ketamine (20 mg/kg/h, IV). After endotoxin injection, hemodynamics, acid-base status, mortality, and plasma concentrations of TNF-α and IL-6 were assessed. Hypotension, metabolic acidosis, and increased plasma cytokine concentrations were observed. They found that ketamine administration dose-independently inhibited hypotension, metabolic acidosis, and cytokine responses in rats injected with an endotoxin. On the contrary to that study, this present study suggests that the antiinflammatory effect of ketamine might be dose dependent. In our study, IL-6 levels in subjects that were applied high dose ketamine during reperfusion period were found to increase lesser compared to the Groups 1 and 2.

The limitation of current study is that there might be an additional study group in which the dose of ketamine would be 5 mg/kg. However, since a significant difference in the applied doses suggests a different effect, we kept the dose range high. We did not administer the dose of 20 mg/kg either since this dose may be toxic for the rats and might have put the study in a challenge.

In conclusion, ketamine administration might be effected anti-inflammatory process in experimental liver I/R injury in to rats as dose-dependent but this topic may confirm more studies.
References


BRIDION---for **optimal neuromuscular blockade management** and improved recovery

**Predictable and complete reversal**

- 98% of BRIDION patients recovered to a TOF ratio of 0.9 from reappearance of T1 within 5 minutes
- 97% of BRIDION patients recovered to a TOF ratio of 0.9 from 1 to 2 PTCs within 5 minutes

**Rapid reversal**

- BRIDION rapidly reversed patients from reappearance of T2 in 1.4 minutes
- BRIDION rapidly reversed patients from 1 to 2 PTCs in 2.7 minutes

BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. In children and adolescents (aged 2-17 years), BRIDION is only recommended for routine reversal of moderate rocuronium-induced neuromuscular blockade.

**Important safety information**

BRIDION is not recommended in patients with severe renal impairment. Studies in patients with hepatic impairment have not been conducted and, therefore, patients with severe hepatic impairment should be treated with great caution. Caution should be exercised when administering BRIDION to pregnant women as no clinical data on exposed pregnancies are available.

Bridion has not been investigated in patients receiving rocuronium or vecuronium in the intensive care unit (ICU) setting.

The neuromuscular blockade is required within 24 hours of BRIDION administration, a nonsteroidal neuromuscular blocking agent should be used instead of rocuronium or vecuronium. The most commonly reported adverse reactions were dysgeusia (metal or bitter taste) and anesthetic complications (movement, coughing, pinnating, or straining on the endotracheal tube). In patients treated with BRIDION, a few cases of awareness were reported. The relation to BRIDION is uncertain. In a few individuals, allergic-like reactions (e.g., flushing, erythematous rash) following BRIDION were reported. Conclusions should be prepared for the possibility of allergic reactions and take the necessary precautions. In a trial of patients with a history of pulmonary complications, bromethapram was reported in 2 patients and a causal relationship could be not be fully excluded.

Volunteer studies have demonstrated a slight (11%-22%) and transient (<3 minutes) prolongation of the prothrombin time/activated partial thromboplastin time (PT/aPTT) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on peri- or postoperative bleeding complications with BRIDION alone or in combination with anticoagulants. As BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants, caution should be exercised in patients on anticoagulation for a pre-existing or concomitant condition. This pharmacodynamic interaction is not clinically relevant for patients receiving routine postoperative prophylactic anticoagulation. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are unlikely with the possible exception of terfenadine, fusidic acid, and hormonal contraceptives.

† First of four
‡ Second twitch


Please see summary of product characteristics for full prescribing information.

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