The effect of trimethazidine on mortality in an experimental acute pancreatitis model

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ABSTRACT

Background/Aims: *Acute pancreatitis has a high morbidty and mortality. Its physiopathogenesis has not been enlightened up to the present. This study aims to investigate trimethazidine (antiischemic, antioxidant and cardioprotective agent) 's effects on the acute pancreatitis.*

Materials-Methods: *In this study, four aqual groups are formed with 43 female Spraque-dawley type rats weighed between 230-300 gr (mean 265 gr). 0.9% NaCl is injected intraperitoneally after laparotomy to the Group 1 (n=6). Group 2 (n=6) is control group that without any intervention. Acute pancreatitis is formed in Group 3 (n=16) via injection of Na-taurocholate in the common bile duct. Group 4 (n=15) is being formed pancreatitis and treated with Trimetazidine. In group 4 Trimetazidine 10 mg/kg/day drugs were given, 30 minutes, 24 and 72 hours after formation of acute pancreatitis, in three equal doses by orogastric way. In all groups, the rats have been laparatomised 72 hours later under general anesthesia and pancreas tissues has been extracted and studied histopathologically. Amylase, lipase, lactate dehydrogenase, aspartate transaminase, alanine tranaminase levels in the rats serum and superoxide dismutase, catalase, glutathione, malondialdehyde, nitricoxide, protein carbonyl, glutathione peroxidase levels in the rats tissue also have been looked up.*

Results: *Serum and tissue findings and histopathologically examination of the pancreas tissues show significant decrease in the treatment group compare to study group.*

Conclusion: *Trimethazidine protects pancreas tissue and decreases the mortality by significantly lowering the biochemical and histopathological changes in the early stages of acute pancreatitis.*

Keywords: *Acute pancreatitis, na-taurocholate, trimethazidine*

INTRODUCTION

A number of factors play a role in the etiology of acute pancreatitis, which is a serious disease with a high morbidity and mortality rate and is associated with major complications (1, 2). Despite the accumulation of knowledge obtained from many years of experimental and clinical studies over the past century, the etiology, pathogenesis, and especially, the treatment of acute pancreatitis is still a matter of debate (3, 4). The pathogenesis of acute pancreatitis still remains to be elucidated, and there is usually a triggering factor such as excessive alcohol consumption or gallbladder stones. Trypsinogen acini, which is intracellularly mediated by lysosomal hydrolase cathepsin B, is the initial and most critical process. Early activation of the proteases caused by the reaction between the digestive and lysosomal enzymes leads to cellular injury. Activated proteases infiltrate the pancreatic interstitium, retroperitoneum, peritoneal cavity, and systemic circulation resulting in necrotizing injuries caused by autodigestion. After acinar cell injury, local control disappears and excessive uncontrollable activation of the inflammatory cells occurs. Activation of the monocytes/macrophages and polymorphonuclear granulocytes (PMN) increases the production of cytokines (i.e., TNF-α, IL-1, IL-6, and IL-8, PAF, ICAM-1) and other inflammatory mediators (i.e., prostaglandins leukotrienes, thromboxanes, platelet-activating factor, reactive oxygen species [ROS], nitric oxide [NO], and proteases). This results in clinical systemic inflammatory response syndrome (SIRS), followed by acute lung injury, shock, renal failure, and multiple organ dysfunction syndrome (MODS) with high mortality and morbidity rate (5, 6).

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Na-taurocholate acid is a bile acid thatis commonly used to induce acute pancreatitis in animal experiments. It is administered through the pancreaticobiliary duct to establish an experimental acute pancreatitis model. By adjusting the concentration and applying pressure of the material used in this model, mild-to-severe pancreatitis can be induced similar to that in humans.

Cellular ischemia is characterized by excessive free radical production leading to disrupted energy production, impaired hemostasis, acidosis, cytoplasmic sodiumion and calcium (Ca^{2+}) ion accumulation, and impaired cellular structure and function. Toxic effects of ROS depend on the oxidation of the membrane lipids, proteins, and nucleic acids.

Trimetazidine is a cytoprotective drug that prevents a decrease in intracellular adenosine triphosphate (ATP) levels and preserves the energy metabolism in hypoxic or ischemic cells. It ensures the proper functioning of ionic pumps and transmembranal sodium–potassium flow. It exerts its effect through the inhibition of the long-chain 3-ketoacyl-CoA thiolase and β-oxidation of fatty acids, increasing glucose oxidation. In an ischemic cell, energy produced during glucose oxidation requires less oxygen consumption than in the β-oxidation process. Enhanced glucose oxidation optimizes cellular energy processes and provides proper energy metabolism during ischemia. In addition, this process inhibits the production of ROS and decreases lipid peroxidation with cytoprotection. That is to say, trimetazidine decreases intracellular acidosis, prevents high-energy phosphate depletion, reduces myocardial Ca^{2+} accumulation, and inhibits neutrophil accumulation, exerting a cytoprotective effect against the harmful effects of ROS during reperfusion (7, 8).

Hypothetically, trimetazidine can protect the pancreas from cellular injury owing to its anti-oxidant, free radical scavenging, and anti-ischemic effects by considerably reducing the biochemical and histopathological changes in hypoxic and ischemic cells with the regulation of the mitochondrial permeability transition pore (mPTP) located in the mitochondrial inner membrane (9, 10).In this study, we aimed to experimentally investigate whether trimetazidine can prevent or reduce necrosis during acute severe pancreatitis and favorably affect mortality rate.

MATERIALS AND METHODS

This study was carried at the İnönü University School of Medicine Experimental Animal Laboratory after obtaining approval from the İnönü University School of Medicine Ethics Committee for Animal Experiments (02.05.2012/225). In the study, a total of 43 Sprague-Dawley female rats weighing 230–300 g (mean 265 g) were used. The animals were fed with standard feed for 10 days before the experiment without water restriction in individual cages and were allowed to adapt to ambient conditions. The rats were housed at a constant temperature for 12 hours in darkness and 12 hours in light. The rats were randomly assigned to 4 groups: Group 1 (n=6),sham group (laparotomy only): Group 2 (n=6),control group (untreated group); Group 3 (n=16),pancreatitis group (acute pancreatitis induced with Na-taurocholate);and Group 4 (n=15),treatment group (acute pancreatitis induced with Na-taurocholate and exposed to trimethazidine).

The rats were fasted for 8hours before the experiment without water restriction. Subjects in Groups 1, 3, and 4 were anesthetized by the administration of 20 mg/kg ketamine hydrochloride (Ketalar®, Eczacibasi, Istanbul, Turkey) and 5 mg/kg xylazine HCl (Alfazyne® 2%, 20 mg/mL, 30 mL, Alfasan int.B.V., Woerden, Netherlands) intraperitoneally. Following the appropriate ambient temperature and site clearance (10% povidone iodine, Batticon® solution, Adeka, Istanbul, Turkey) and sterile draping, the abdomen was entered through a midline incision of 3 cm. Through random selection, the abdominal wall and skin of the rats in the sham group (Group 1, n=6) were sutured with 3/0 silk (Mersilk®, Ethicon, Sommerville, NJ, USA) suture.

In the rats included in the acute pancreatitis induction model (Groups 3 and 4, n=31), the biliopancreatic duct (BPD) was explored after laparotomy to perform the duct injection model. The duodenal wall was punctured with a 24-gauge catheter (Introcan-w, Braun, inner diameter 7 mm) at the anti-mesenteric region and cannulated advancing the catheter to the common BPD. To prevent reflux of the agent into the intrahepatic biliary tracts, the choledoch was temporarily clamped with a plastic bulldog (World precision instruments, Micro Bulldog Clamp, Friedberg, Germany) near the liver hilus. To prevent reflux of duodenal content into the BPD, micro-aneurysm clips (Aesculap Yasargil aneurysm clips, Aesculap, MO, USA) were placed onto the BPD near the duodenum. Na-taurocholate (5%) (Sigma, St. Louis, MO, USA) was infused into the common BPD through the catheter for 3minuteswith a total dose of 0.15 mL/kg. The plastic bulldog clamp (World precision instruments, Micro Bulldog Clamp, Friedberg, Germany) in the proximal BPD was removed once the infusion was completed (Figure 1). The puncture hole on the duodenum wall was sutured with a single prima-

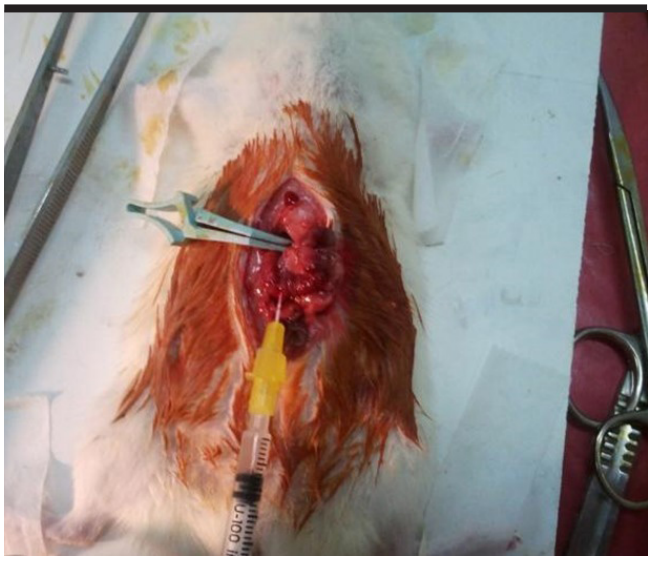

Figure 1. Transient choledochal clamping and transduodenal biliopancreatic duct cannulation in a rat.

ry suture with 6/0 polypropylene (Prolene®, Ethicon). The abdominal wall and the skin were closed with 3/0 silk (Mersilk®, Ethicon) suture. Daily trimetazidine was administered through the orogastric catheter to 15 rats (Group 4) randomly selected from 31 pancreatitis-induced rats afterthe operation. Postoperatively, the rats were fed with water and standard feed (11). In Group 4, trimetazidine 10 mg/kg/day was given 30 minutes, 24 hours, and 72 hours after the formation of acute pancreatitis in 3equal doses through the orogastric way. Trimetazidine is eliminated primarily in the urine, mainly in the unchanged form. The elimination half-life is about 6 hours. In experimental studies, no toxicity has been found even in higher doses compared withtherapeutic doses. The time for reaching steady state of trimetazidine after multiple dose administration is between 24 and 36 hours (12-15).

After 72 hours, all subjects were anesthetized by intraperitoneal administration of 20 mg/kg ketamine HCl and 5 mg/kg xylazine HCl. All subjects were sacrificed by intracardiac blood withdrawal. The blood samples were placed into biochemistry tubes immediately after cardiac puncture, stored at 18°C-22°C, and transported to the biochemical laboratories under appropriate conditions for analyses of serum aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), amylase, and lipase. The pancreas and tissue specimens of each rat obtained for histopathological and biochemical examination were sent to the pathology (embedded into 10% formalin solution) and biochemistry lab. Histopathological and biochemical examinations were carried out in a double-blind manner.

Assessment of Results

The pancreatic tissue of the rats was assessed histopathologically according to the scoring system defined by Schmidt et al. (16). Pancreatic tissue samples obtained for histopathological examination were fixed with 10% formaldehyde solution for 48 hours. After fixation, the pancreatic tissue specimens were treated with a number of routine histological tissue tracing procedures and embedded in paraffin blocks. Sections of 6 µm thickness were prepared from the paraffin blocks using a microtome. The sections on the slides were stained with hematoxylin and eosin, examined with a Leica DFC 280 light microscope (Leica Microsystems, Mannheim, Germany), and captured by a Leica Q Win Image Analysis System (Leica Microsystems Imaging Solutions, Cambridge, UK). The pancreatic tissue sections were examined for leukocyte infiltration (mononuclear and polymorphonuclear), acinar necrosis, interstitial edema, and hemorrhage and were scored for a maximum total score of 12 points (none=0 point, mild=1 point, moderate=2 points, and severe and widespread=3 points). The caspase-3 level was measured using the flowcytometry method in the medical genetic laboratory. Serum amylase, lipase, LDH, AST, and ALT levels were measured in the blood samples of rats, whereas superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), malondialdehyde (MDA), NO, protein carbonyl (PC), and glutathione peroxidase (GSH-Px) levels were measured in the tissue samples using the commercial kit of the Olympus-600 autoanalyzer (Olympus Optical Co. Ltd. Shizuoka-ken, Japan)

Statistical Analysis

Statistical analysis was performed using the Statistical Packages for the Social Sciences (SPSS) for Windows version 23 (IBM Corp., Armonk, NY, USA). Descriptive data were expressed asmean±standard deviation. The data were analyzed using one-way Analysis of Variance because the number of study groups were more than 2. The Mann–Whitney U test was used for pair-wise comparison of the groups. Comparison of the histological data between the groups was carried out with the Kruskal–Wallis H test. In case of statistically significant differences, multiple comparisons of the groups were carried out using the Conover test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 8 of the 16 rats (50%) with Na-taurocholate-induced pancreatitis died within72 hours, 4 (25%) of which

Table 1. Biochemical results of blood samples of the groups.

	Sham group (Group 1) (mean±SD(range))	Control group (Group 2) (mean±SD(range))	Pancreatitis group (Group 3) (mean±SD(range))	Pancreatitis + Treatment group (Group 4) ((mean±SD(range))	p	Group 1 vs 2 p	Group 1 vs 3 p	Group 3 vs 4 p
AST	50 ±31.2(36-115)	66±19.8 (54-106)	87±33.2 (33-167)	61±18 (38-94)	0.013	0.93	0.165	0.034
ALT	18.5±5.1 (11-26)	29±7.4 (21-43)	30±9.7(7-42)	19±6.9 (9-34)	0.002	0.11	0.014	0.006
LDH	227±106(113-431)	379±209(223-799)	415±432 (55-1557)	266±100.3 (117-539)	0.249	0.64	0.583	0.843
Amylase	442±278 (312-1011)	495±94(397-677)	882±324 (309-1685)	460±314 (199-1176)	0.002	0.99	0.048	0.006
Lipase	9±5.4(6-20)	5±1.5(4-8)	53±35.9 (10-159)	18.4±29.1 (7-123)	<0.001	0.58	0.01	0.017

AST: Aspartate Transaminase; ALT: Alanine Transaminase; LDH: Lactate Dehydrogenase; SD: Standart Deviation

occurred within the first 24 hours. Of 15 rats treated with trimetazidine, 2rats (13.3%) died within 24 hours, and 4 rats (26.6%) died at 72 hours. The subjects thatdied were excluded from the biochemical and pathological analyses of the study.

Biochemical Findings

The biochemical histopathological findings of our study were significantly different between the groups. The serum AST, ALT, amylase, and lipase levels were significantly lower in the treatment group than in the pancreatitis group (Table 1). The serum LDH level also tended to be lower in the treatment group, although it did not reach statistical significance. The serum AST, ALT, amylase, and lipase levels were lower in the treatment group than in the control and sham groups, although it did not reach statistical significance (p>0.05 for all). When the treatment group and the pancreatitis group were compared in terms of biochemical tissue parameters, there was a significant difference between the treatment group and the pancreatitis group in terms of CAT, SOD, GSH-Px, NO (protein), NO (fresh tissue), MDA, GSH (fresh tissue), and PC levels (p<0.01). There was no statistically significant difference between the other groups in terms of the aforementioned parameters (Table 2).

Pathological Findings

When the groups were assessed in terms of edema, there was a significant decrease in the level of edema in the treatment group compared with that in the pancreatitis group (p<0.05). When the groups were compared in terms of acinar necrosis, the necrosis degree was significantly lower in the treatment group than in the pancreatitis group (p<0.05), whereas necrosis was not observed in the control group or the sham group. When the groups were compared pathologically in terms of hemorrhage, the degree of hemorrhage in the treatment group was significantly lower than that in the pancreatitis group (p<0.05). When the groups were compared in terms of the degree of leukocyte inflammation, inflammation was not observed in the control group or the sham group, whereas the degree of inflammation was significantly lower in the treatment group than in the pancreatitis group (p<0.05) (Figure 2). When the pancreatitis group and the treatment group were compared for caspase-3, the levels were significantly higher in the pancreatitis group than in the treatment group (p=0.002). Histopathological results are shown in Figure 3.

DISCUSSION

Acute pancreatitis has a high morbidity and mortality rate, and its physiopathogenesis has not been fully elucidated yet. The treatment of acute pancreatitis is mainly conservative, and to date, the precise benefit of any drug administration has not been shown. In 80% of patients with acute pancreatitis, the disease is self-limited; however, severe acute pancreatitis develops in 20% of patients with a mortality rate of up to 15% in this patient group (17). Most of these patients have high mortality because of severe complications such as SIRS and MODS. The main cause of pancreatitis development is thought to be the intrinsic pancreatic tissue digestion owing to the early activation of trypsinogen to active trypsin in the acinar cells, thereby, resulting in a widespread inflammation. The current treatment modalities attempt to suppress the pancreatic exocrine secretion. Establishing an experimental acute pancreatitis model gives us an insight into the mechanism of this complex disease and develop new approaches to treatment.

The reason for choosing the ductus injection model for setting an experimental acute pancreatitis model is that

Table 2. Biochemical tissue results of the groups.

	Sham group (Group 1) (mean±SD(range))	Control group (Group 2) (mean±SD(range))	Pancreatitis group (Group 3) (mean±SD(range))	Pancreatitis + treatment group (Group 4) (mean±SD(range))	p	Group 1 vs 2 p	Group 1 vs 3 p	Group 3 vs 4 p
Catalase	0.16±0.058 (0.09-0.23)	0.08±0.034 (0.07-0.16)	0.25±0.32 (0.1-1.2)	0.18±0.27 (0.05-0.9)	0.02	0.84	0.03	0.048
SOD	0.17±0.13 (0.25-0.49)	0.12±0.022 (0.06-0.15)	0.33±0.042 (0.08-0.59)	0.24±0.09 (0.2-0.38)	0.03	0.58	0.02	0.046
GSH-Px	1.7 ±0.96 (1.88-8.28)	1.6±1.05 (1.43-4.88)	3±1.95 (2.23-5.30)	2.1±1.03 (1.44-3.27)	0.006	0.844	0.026	0.038
NO (protein)	0.005±0.0036 (0-0.01)	0.005±0.0032 (0-003)	0.007±0.003 (0.001-0.01)	0.003±0.0028 (0-0.01)	0.006	0.92	0.054	0.02
NO (tissue)	0.017±0.009 (0.02-0.03)	0.018±0.009 (0.02-0.11)	0.025±0.006 (0.02-0.04)	0.02±0.0026 (0.01-0.04)	0.002	0.766	0.033	0.041
MDA	3.5±12.96 (3.9-31.5)	4 ±10.5 (0.65-29.1)	6.2±14.1 (2.49-41.8)	3±11.5 (1.76-33.5)	0.006	0.07	0.038	0.031
GSH	185±32.4 (152-244)	174±48.1 (140-274)	219±64.9 (131-334)	126±74 (126-324)	0.027	0.81	0.3	0.002
PC	1.43±0.52 (0.96-2.43)	1.33±0.66 (0.71-2.62)	1.83±0.64 (0.97-2.98)	0.89±0.84 (0.44-2.98)	0.027	0.83	0.068	0.018
Caspase-3	10.1±1.44 (9.6-24.1)	8.6±0.9 (7,7-10.4)	21.2±2.16 (19-25.4)	8.2±1.76 (7.4-12.8)	0.004	0.86	0.034	0.002

SOD: Superoxide dismutase; GSH-Px: Glutathione peroxidase; NO: Nitric oxide; MDA: Malondialdehyde; GSH: Glutathione; PC: Protein carbonyl

it can provide the opportunity to establish mild and severe forms of acute pancreatitis similar to that in humans by adjusting the concentration of the substance used and the administration pressure. Furthermore, because this model is reproducible, it provides important data for examining the systemic effects of acute pancreatitis. Laukkarinen et al. (18) conducted an experimental model to assess the relationship between the Na-taurocholate concentrations and severity of pancreatitis. Experimental pancreatitis models were established with 1%–5% Na-taurocholate concentrations, and the severity of pancreatitis induced was evaluated. In another study, Wettel et al. (19) created an experimental pancreatitis model using 2% and 5% Na-taurocholate concentrations and found a relationship between severe necrotizing pancreatitis with 5% concentration and severity of pancreatitis. In another experimental study, Paran et al. (20) induced an experimental pancreatitis model using 5% and 10% Na-taurocholate concentrations and reported that this method was feasible in inducing pancreatitis. In addition, these authors showed that the severity of pancreatitis and mortality was correlated with the increased concentration of Na-taurocholate, with a mortality rate of 30% at5% concentration and 80% at10% concentration on Day 10. In our study, we used Na-taurocholate at a concentration of 5% to induce severe acute pancreatitis in rats. The effect of trimetazidine on mortality reduction can be clearly seen in the mortality rates within the first 24 and 72 hours, and this reduction was significantly lower in the treatment group than in the pancreatitis group (13.3% versus 25% at 24 hours and 26.6% versus 50% at 72hours).

In the experimental acute pancreatitis induced by Na-taurocholate in rats, apoptosis was observed in the acinar cells. Apoptosis was calculated through the objective caspase-3 activity measurement and was observed using a microscope at ×40 magnification by counting the apoptotic bodies in the nuclei in 10 adjacent sites. The acinar cell apoptosis rate was found to be higher in acute edematous pancreatitis than seen in acute necrotizing pancreatitis. As the severity of the disease increased, the rate of apoptosis increased. This suggests that apoptosis is a positive response to resistance against pancreatic cell damage (21). In our study, the histological structures deteriorated owing to the significant histopathologi-

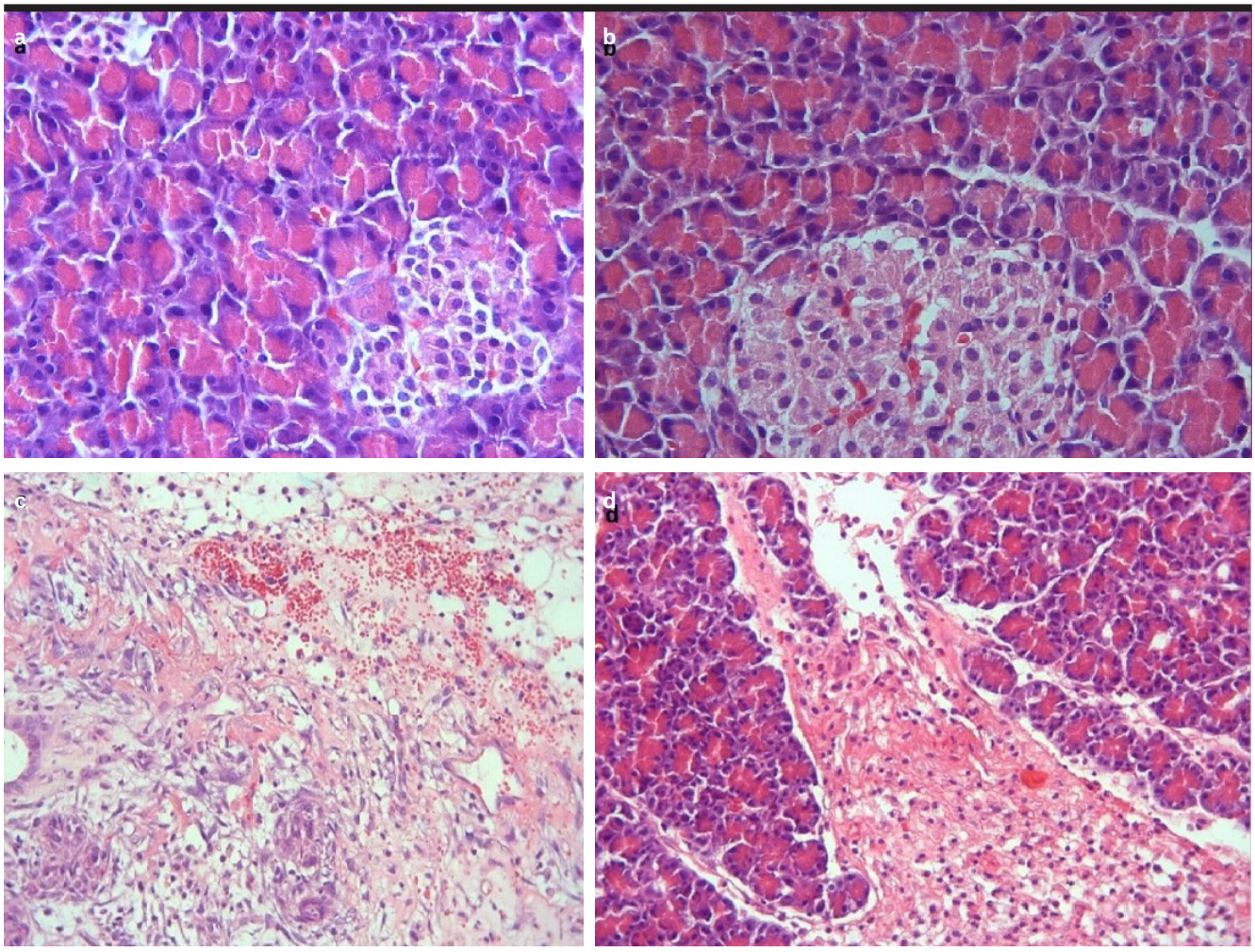

Figure 2. a-d. Hystological appearances of all groups (Group 1-4).

cal changes in the exocrine pancreas, and the level of caspase-3 increased because of apoptotic bodies in the rats that received Na-taurocholate to induce pancreatitis (pancreatitis group and treatment group). However, the histological structures were smooth in the pancreatic tissue sections of the rats in the sham and control groups. As a biochemical indicator of the tissue injury, CAT, SOD, GSH-Px, NO (protein), NO (fresh tissue), MDA, GSH (fresh tissue), and PC levels increased in the rats in Group 3 along with serum AST, ALT, LDH, amylase, and lipase levels.

In another experimental pancreatitis model, Yenicerioglu et al. (22) reported that trimetazidine had a protective effect in a pancreatitis-induced model with L-arginine. In this study, L-arginine (20 mg/100 mg) was administered with 20% 0.15 M NaCl intraperitoneally at 2 doses (1 hour apart). Different from our study, the levels of AST, ALT, LDH, amylase, IL-1β, IL-6, and TNF-α were analyzed. The authors showed that trimetazidine decreased the histopathological and biochemical levels with a pancreatic protective effect.

The effect of free radicals arising from normal metabolism or pathological pathways iscalled oxidative stress. In pathological conditions, ROS emerge in relatively large amounts and alter the oxidation balance. As a result, cellular damage and impairment of tissue functions occur. Oxidative stress is thought to contribute to the pathogenesis of acute pancreatitis as is the case in many other diseases. The ROS have been also shown to be released in the early stages of acute pancreatitis. ROS are highly reactive molecules that damage the cell membrane, causing peroxidative reactions in the membrane and leading

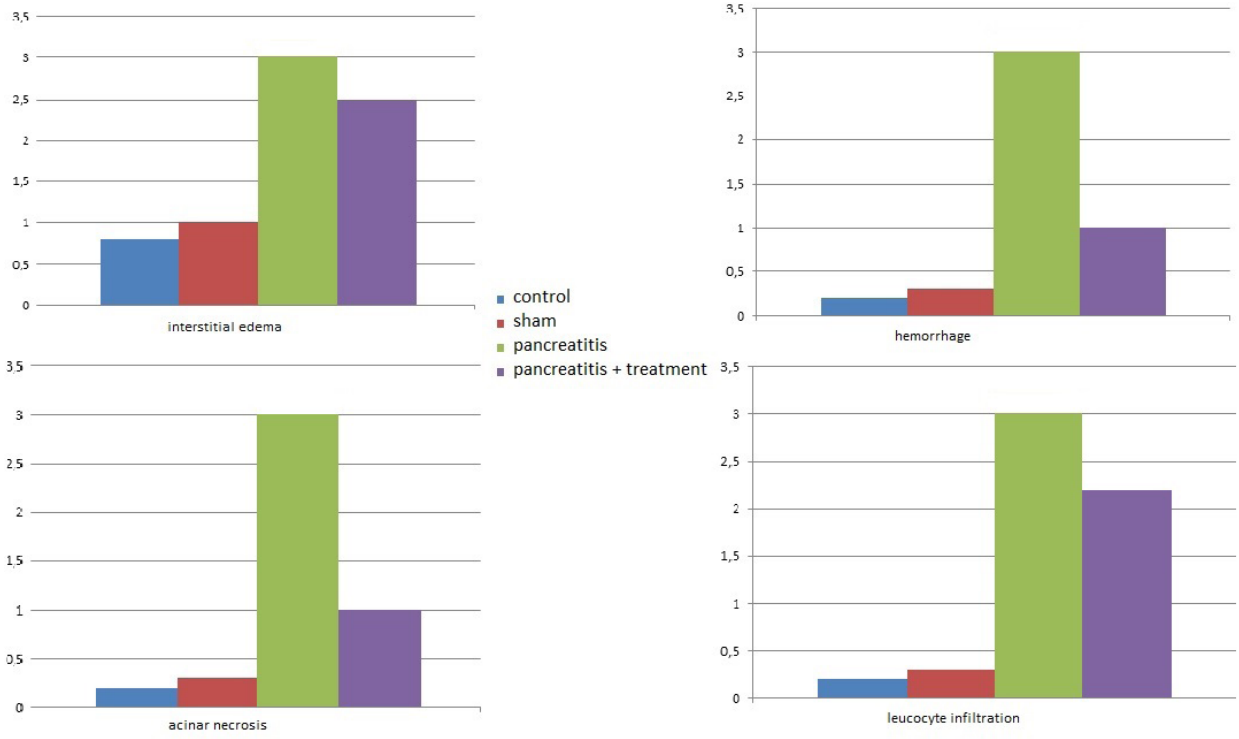

Figure 3. Comparison of the groups in terms of interstitial edema, hemorrhage, acinar necrosis, leukocyte infiltration.

to irreversible cellular damage (23). Activated neutrophils and monocytes that infiltrate the pancreatic interstitium are probably the sources of tissue-damaging oxygen radicals (24). The ROS are the mediators that play a key role in tissue damage; however, the formation of extracellular ROS alone is not responsible for the typical enzymatic and morphological changes in acute pancreatitis. In our study, the CAT, SOD, GSH-Px, NO (protein), NO (fresh tissue), MDA, GSH (fresh tissue), and PC levels increased in the tissue as indicators of the formation of ROS in the pancreatic tissue.

Trimetazidine has no direct hemodynamic effect. It has been used for about 4 decades as an agent that optimizes the energy metabolism in myocardial cells during ischemic injury. It prevents metabolic changes induced by ischemia in the cell, preserving the cellular oxygen consumption and protecting the energy potential of the ischemic cell (25). It prevents the reduction of ATP content in the cell, reduces intracellular acidity, and protects cells against the harmful effects of ROS (9, 10-26). There are data suggesting that trimetazidine regulates the mPTP located on the mitochondrial inner membrane, as well as its metabolic effects such as anti-ischemic effects, decrease in fatty acid oxidation, and glucose oxidation stimulation (14). One of the mitochondrial protective mechanisms of the drug is that it prevents mitochondrial swelling caused by high intra-mitochondrial Ca^{2+}owingto pro-oxidants. In addition, the pancreatic microcirculation is disturbed in acute pancreatitis that to the development of ischemia and inflammation, and the release of ROS increases. In our experimental study, trimetazidine reduced the serum AST, ALT, amylase, and lipase levels and LDH levels decreased in the treatment group, although not the reductions were not statistically significant, in acute pancreatitis-induced rats. A statistically significant decrease in tissue levels of CAT, SOD, GSH-Px, NO (protein), NO (fresh tissue), MDA, GSH (fresh tissue), and PC was seen owing to reduced inflammation at the cellular level by means of the aforementioned properties of the agent.

In contrast, there was a significant increase in edema, acinar cell necrosis, hemorrhage, and perivascular inflammation histopathologically with the deterioration of microcirculation in the pancreatitis group. In the rats in the treatment group receiving trimetazidine, an anti-ischemic and anti-oxidant drug, there was a significant improvement in the histopathological changes, especially in

edema, hemorrhage, and leukocyte infiltration during the course of acute pancreatitis.

Nonetheless, there are some limitations to this study. In the histopathological examination, we were unable to evaluate leukocyte infiltration through the myeloperoxidase activity. In addition, we might have observed more robust results using additional parameters such as chemiluminescence measurements in the tissue for the evaluation of the role of ROS. Furthermore, we were unable to analyze systemic and/or local levels of cytokines such as IL-1β, IL-6, or TNF-α in our study. Therefore, further comprehensive and large-scale studies are required to establish a definite conclusion.

In conclusion, our study results suggest that trimetazidine can significantly reduce the biochemical and histopathological alterations occurring in the early phase of acute pancreatitis and preserve the pancreas with reduced mortality. We recommend further studies to gain a better understanding of the underlying mechanisms of these processes.

Ethics Committee Approval: Ethics committee approval was received for this study from the İnönü University School of Medicine Ethics Committee for Animal Experiments (02.05.2012/225).

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