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Thoracic epidural anesthesia with bupivacaine attenuates systemic inflammatory response and lung impairment associated with cerulein-induced pancreatitis in rats

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Thoracic epidural anesthesia with bupivacaine attenuates systemic inflammatory response and lung impairment associated with cerulein-induced pancreatitis in rats

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Aim: To evaluate the effects of thoracic epidural anesthesia (TEA) on acute pancreatitis (AP)-induced lung injury in a rat model.

Materials and methods: A total of 24 rats were divided into 3 groups: the control group (n = 8; pancreatitis), the bupivacaine group (n = 8; pancreatitis + 20 µL/h 0.5% bupivacaine), and the saline group (n = 8, pancreatitis + 20 µL/h saline). Pancreatitis was induced by 4 intraperitoneal injections of 50 µg/kg cerulein. At 24 h, blood was collected for determination of amylase, blood gas, tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β; lung samples were collected for the measurement of glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT), and myeloperoxidase (MPO) concentrations and for immunohistochemical examinations, apoptosis determination, and wet/dry ratio determinations. Pancreas samples were collected for the histological investigation to confirm AP.

Results: Serum amylase decreased significantly in the bupivacaine group when compared to the control and saline groups. Bupivacaine showed a significant decrease in the TNF-α and IL-1β concentrations and an increase in the GPx and SOD concentrations compared to both the saline and control groups. The wet/dry ratio showed a significant difference between the control and bupivacaine groups. Bupivacaine significantly decreased the injury score, apoptosis, and ICAM-1 secretion in the lung tissue.

Conclusion: The present study demonstrated that TEA with bupivacaine decreased the systemic inflammation and lung injury due to AP.

Key words: Thoracic epidural anesthesia, acute pancreatitis, lung damage

Ratlarda bupivakain ile sağlanan torakal epidural anestezi seruleinin tetiklediği akut pankreatit ile ilişkili sistemik inflamatuvar cevabı ve akciğer hasarını azaltmaktadır

Amaç: Bu çalışma, torakal epidural anestezinin (TEA), akut pankreatitin (AP) neden olduğu akciğer hasarına etkilerini rat modelinde değerlendirmek amacı ile yapılmıştır.

Yöntem ve gereç: Yirmi dört rat kontrol (n = 8; pankreatit), bupivakain (n = 8; pankreatit ve 20 µL/saat % 0,5 bupivakain) ve salin (n = 8; 20 µL/saat salin) gruplarına ayrıldı. Pankreatit 50 µg/kg serulein enjeksiyonunun 4 kez tekrarlanması ile induklendi. 24 saat sonra amilaz, kan gazı, tümör nekroz faktör (TNF)-α, interlökin (IL)-6 ve IL-1β belirlenmesi için kan; glutatyon peroksidaz (GPx), katalaz (CAT), myeloperoksidaz (MPO) konsantrasyonları, immünohistokimyasal

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incelemeler, apoptozis ve ıslak/kuru ağırlık oranlarının belirlenmesi için akciğer doku örnekleri alındı. Pankreatitin histolojik inceleme ile doğrulanması için pankreas örnekleri alındı.

Bulgular: Serum amilaz seviyeleri bupivakain grubunda kontrol ve salin gruplarına kıyasla anlamlı düşük bulundu. Bupivakain TNF- α ve IL-1 β seviyelerinde anlamlı azalma ve GPx ve SOD seviyelerinde anlamlı yükselme sağladı. Islak/kuru ağırlık oranlarının karşılaştırılmasında kontrol ve bupivakain grupları arasında anlamlı fark görüldü. Bupivakain tedavisi ile hasar skoru, apoptozis ve ICAM-1 salınımının azaldığı görüldü.

Sonuç: Bu çalışma bupivakain ile sağlanan TEA'nin AP'e bağlı gelişen sistemik inflamasyonu ve akciğer hasarını azalttığını göstermiştir.

Anahtar sözcükler: Torakal epidural anestezi, akut pankreatit, akciğer hasarı

Introduction

Acute pancreatitis (AP), a noninfectious inflammatory process of the pancreas, is complicated in its severe form by the development of multiple organ dysfunction syndrome with a mortality rate of 15%-20%. Regardless of etiology, once AP is initiated, the inflammatory events within the acinar cells will progress to a generalized systemic inflammatory response syndrome (SIRS). Among the systemic complications, pulmonary complications are the most frequent and potentially the most serious. Approximately one-third of patients with pancreatitis develop acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), which account for 60% of pancreatitis deaths in the first week (1). Recognition of these complications and their pathology may lead to more rapid diagnosis and better therapies.

Pulmonary complications of AP occur in almost 75% of cases, ranging from hypoxemia to ARDS (2,3). ARDS is the most serious systemic complication of AP. Pulmonary complications of AP are characterized by widespread inflammation and tissue damage due to the activation of pancreatic digestive enzymes, which are usually present in the inactive form in the pancreas tissue (4). Necrotic pancreatic tissue infections occur in 40%-70% of patients and are considered to be the most important risk factor for pulmonary fatalities from acute pancreatitis (5).

Thoracic epidural anesthesia (TEA) allows for superior pain therapy after abdominal and thoracic surgery and may reduce postoperative mortality (6,7). It has been established as a corner stone in multimodal perioperative care after surgery (7,8). In comparison with general anesthesia alone, the use of TEA reduces cardiopulmonary mortality (7). In

experimental settings, TEA has been reported to exert beneficial effects on gut mucosal blood flow and to augment intestinal perfusion in systemic hypotension (9,10). There is also evidence suggesting protective effects of epidural analgesia on gastrointestinal mucosal perfusion in acute pancreatitis (11). Clinical investigations have demonstrated a beneficial influence of TEA on intestinal motility and mucosal perfusion in critically ill patients with peritonitis (12). In pancreatitis, TEA is a therapeutic option for pain relief in selected cases, assuming the potential risks of its use in critically ill patients are thoroughly considered (13).

This study was conducted to evaluate the potential effects of TEA on pancreatitis-induced lung injury in a rat model of cerulein-induced AP. It was hypothesized that the systemic inflammatory response and lung injury induced by AP may be reduced by TEA maintained by bupivacaine.

Materials and methods

The experimental protocols were conducted with the approval of the Animal Research Committee at Gazi University, Ankara. All of the animals were maintained in accordance with the recommendations of the National Institute of Health Guidelines for the Care and Use of Laboratory Animals.

Animals and experimental design

Twenty-four male Sprague Dawley rats, weighing 250-300 g, received standard chow and were kept in a 12-h light-dark cycle. The rats were randomly divided into 3 groups according to a computer-generated list: the control group (n = 8; pancreatitis), the bupivacaine group (n = 8; pancreatitis induction followed by 20 μ L/h 0.5% bupivacaine), and the

saline group (n = 8, pancreatitis induction followed by 20 µL/h saline) (9,11,13).

The rats were placed on an electric heating pad under a warming light and anesthetized with 1.5% isoflurane in 50% oxygen through an agent-specific vaporizer via a face mask while the rats were spontaneously breathing. Epidural catheterization was performed using a microsurgical technique (13). Briefly, each rat was placed in the prone position. The lumbar vertebral column was flexed by placing a cylinder transversely under the lower abdomen. The fourth lumbar spinal process was exposed and cut. A small hole was drilled through the cranial margin of the intervertebral space L3-L4. Epidural catheters (a PE 10 tube with outer diameter of 0.61 mm) were inserted at L3-L4 and advanced to T6. A repeated negative liquor aspiration test excluded the subdural position of the catheter. All of the catheters exteriorized at the neck of the animal and were protected by a swivel device. After the completion of the experiment, the position of the catheter was verified by autopsy.

AP was induced by 4 intraperitoneal injections of 50 µg/kg cerulein (Sigma-Aldrich, Steinheim, Germany) diluted in saline at 1-h intervals (14). Epidural infusion was commenced immediately after the last cerulein injection and continued for 24 h.

Measurements

After 24 h, the rats were reanesthetized with 1.5% isoflurane in 50% oxygen, and blood samples were withdrawn via an aortic puncture and collected for amylase, blood gas, tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β analyses. Lung samples were collected for the measurement of glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT), and myeloperoxidase (MPO) concentrations, and for immunohistochemical examinations, apoptosis determination, and wet/dry ratio determinations. Pancreas samples were collected for the histological investigation to confirm AP.

Serum amylase measurements

Serum amylase was determined with a Beckman Coulter LX-20® system analyzer (Fullerton, CA, USA) using Beckman kits according to the supplier's specifications.

GPx, SOD, and CAT measurement

SOD activity was assayed by measuring the inhibition of adrenaline autoxidation, as previously described (15). CAT activity was determined by sonication of the tissues in a 50 mM phosphate buffer and the resulting suspension was centrifuged at 3000 × g for 10 min. The supernatant was used for the enzyme assay. CAT activity was measured by the rate of decrease in hydrogen peroxide absorbance at 240 nm (16).

Cytokine measurement

The blood samples were obtained and placed in microcentrifuge tubes and the plasma was separated by centrifugation, immediately frozen, and stored at -80 °C until the time of assay. Plasma TNF-α, IL-6, and IL-1β levels were detected in a 96-well microtiter plate using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Jingmei Biotech, Beijing, China) according to the manufacturer's guidelines. All of the samples were tested in duplicate. The plate was read on ELx800 automated microplate readers (Bio-Tek Instruments, Winooski, VT, USA) at 450 nm. The concentrations of TNF-α, IL-6, and IL-1β were calculated from a standard curve and expressed in picograms per milliliter (pg/mL). The lower limit of detection for ELISA was 8-16 pg/mL.

Lung MPO activity assay

Tissues were homogenized (50 mg/mL) in 0.5% hexadecyltrimethylammonium bromide in 10 mM 3-(N-morpholino)propanesulfonic acid and were centrifuged at 15,000 × g for 40 min. The suspension was then sonicated 3 times for 30 s. An aliquot of supernatant was mixed with a solution of 1.6 mM tetramethylbenzidine and 1 mM hydrogen peroxide. Activity was measured spectrophotometrically as the change in absorbance at 650 nm at 37 °C, using a SpectraMax microplate reader (Molecular Devices, Sunnyvale, CA, USA). Results were expressed as milliunits of MPO activity per milligram of protein, determined with the Bradford assay.

Wet/dry ratio

For determination of lung edema, the left bronchus was carefully separated from the right bronchus and tied, and the left lung was severed. The lung was weighed immediately and dried at 60 °C in an oven for 72 h to determine the ratio of wet lung weight to dry lung weight.

Histology

The lung and the pancreas were removed immediately after the animals were killed and fixed in a mixture of 2% glutaraldehyde and 2% paraformaldehyde in 0.1 M cacodylate buffer, pH 7.4, for more than 24 h, then dehydrated with a graded alcohol series and embedded in paraffin at 52 °C. The sections were prepared and stained with hematoxylin and eosin for histological evaluation by a pathologist blinded to the study groups. The pancreatic sections were graded for the extent and severity of edema, infiltration, vacuolization, and necrosis according to the criteria outlined by Rongione et al. (17). The lung sections were assessed and scored using a scoring system developed by Simons et al. (18) to grade the degree of lung injury. Briefly, the lung injury was graded from 0 (normal) to 4 (severe) in 4 categories: intestinal inflammation, neutrophil infiltration, congestion, and edema.

Apoptosis detection

Paraffin blocks containing lung tissue specimens were cut into sections 6 mm thick, and the sections were stained for the detection of apoptosis using an apoptosis detection kit (ApopTag® Peroxidase Kits, Chemicon, USA & Canada) according to the manufacturer's instructions. Briefly, the sections were deparaffinized and rehydrated. When viewed under a standard light microscope, the apoptotic cells could be clearly distinguished by dark blue staining. The apoptotic cells were examined under light microscopy and counted throughout the whole lung section. Examination of the slides was carried out in a blinded fashion.

Immunohistochemistry

Formalin-fixed, paraffin-embedded lung tissue sections were cut into sections 4 µm thick. The slides were then deparaffinized in xylene, rehydrated in alcohol, and blocked for endogenous peroxidase using 3% hydrogen peroxide. Antigen retrieval was performed using 0.01 mol/L sodium citrate buffer (pH 6.0) through microwave processing and then the tissue sections were processed using the standard avidin-biotin-immunoperoxidase method. The slides were incubated in 10% normal goat serum for 30 min to prevent nonspecific staining. The sections were incubated for 2 h at room temperature with antirat

ICAM-1 (CD54) monoclonal antibody (clone 1A29, concentration: 1.03 mg/mL; Endogen, Woburn, MA, USA). Thereafter, the sections were incubated with biotinylated secondary antibodies, followed by avidin-biotin peroxidase complexes for 30 min. As the chromogen, 3-amino-9-ethylcarbazole substrate (Lab Vision, NeoMarkers, Fremont, CA, USA) was used, and Mayer hematoxylin was used as the counterstain. For the negative control, nonimmune serum was substituted for the primary antibody. The ICAM-1 expression was evaluated semiquantitatively and graded as follows: 0, negative; 1+, baseline or endogenous; and 2+, strong and uniform, in both alveolar capillaries and the large vessels of lung tissue. A pathologist reviewed the slides in a blinded fashion.

Statistical analysis

Statistical evaluation was performed using SPSS 11.5 software (SPSS, Chicago, IL, USA). Data of continuous variables were expressed as mean ± SD or the median (interquartile range). Statistical analysis was carried out by analysis of variance (one-way ANOVA) for data expressed as mean ± SD or by using the Kruskal-Wallis test for the data expressed as a median (interquartile range), followed by the appropriate post hoc tests including Tukey's or Conover's multiple comparison. $P < 0.05$ was considered significant.

Results

Supramaximal doses of cerulein injections resulted in severe AP in the rats. This was confirmed by the increase in serum amylase and histopathological findings of severe AP (Tables 1 and 2, Figure 1). Serum amylase decreased significantly in the bupivacaine group (9000 ± 2700 U/L) compared to the control ($25,000 \pm 3400$ U/L) and saline ($21,000 \pm 4600$ U/L) groups ($P < 0.05$; Table 1).

The blood gas analysis did not show any significant difference among the groups ($P > 0.05$; Table 1).

TNF- α , IL-1 β , and IL-6 concentrations are displayed in Figure 2. TNF- α and IL-1 β concentrations were significantly higher in the control and saline groups compared to the bupivacaine group ($P < 0.05$). The difference with regard to IL-6 was not significant among the groups.

Table 1. Blood gas, amylase, and wet/dry ratio levels of the groups.

	Control	Bupivacaine	Saline
PaO ₂	91 (66-108)	105 (93-113)	95 (88-102)
PaCO ₂	33.6 (31.7-40.4)	35.4 (33.8-37.5)	35.6 (30.5-40.3)
pH	7.38 (7.26-7.45)	7.42 (7.40-7.44)	7.44 (7.41-7.45)
Amylase (U/L)	25,000 ± 3400	9000 ± 2700*	21,000 ± 4600
Wet/dry ratio	5.1 ± 0.16	2.9 ± 0.25*	4.8 ± 0.47

*P < 0.05, bupivacaine group compared to the control and saline groups.

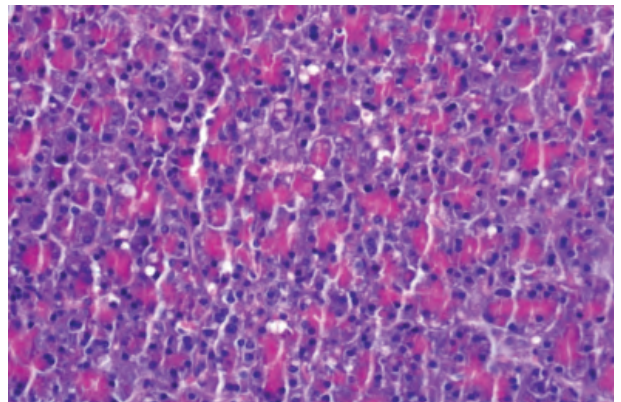
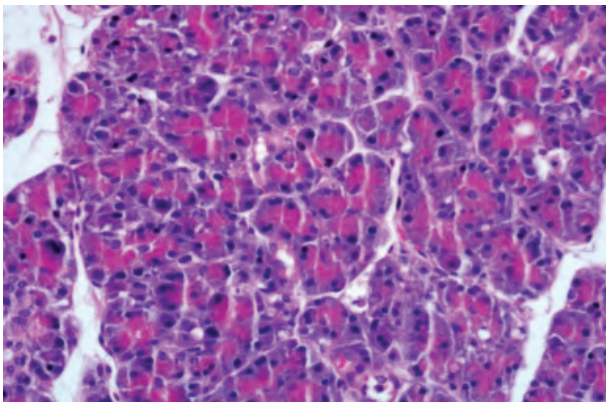
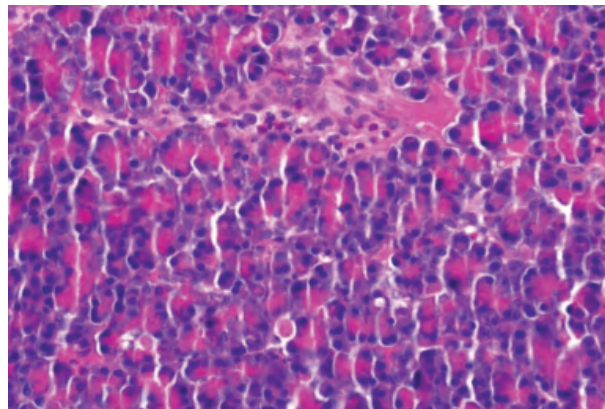


Figure 1. Pancreatic sections of rats in groups after 24 h of epidural bupivacaine infusion (hematoxylin and eosin, 400×).

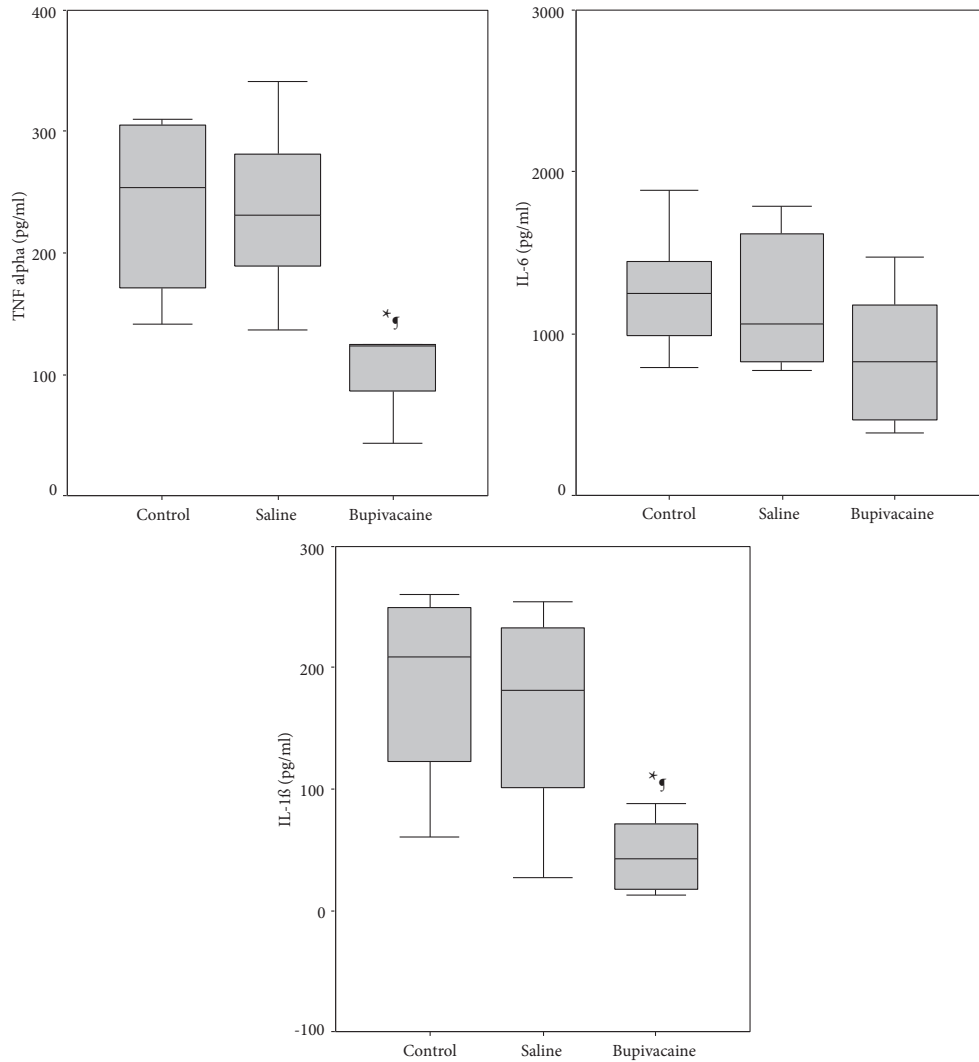


Figure 2. Plasma TNF- α , IL-6, and IL-1 β concentrations in the control, bupivacaine, and saline groups. Values are expressed as median (horizontal line) and interquartile range (bar). *P < 0.05 compared to control group; †P < 0.05 compared to saline group.

Table 2. Histopathological examination, apoptosis evaluation, and ICAM-1 expression of the groups.

	Control	Bupivacaine	Saline
Injury score (pancreas)	3.7 \pm 0.6	3.1 \pm 0.4	3.9 \pm 0.9
Injury score (lungs)	2.7 \pm 0.3	1.2 \pm 0.6*	2.5 \pm 0.4
Apoptosis (lungs)	85%	69%†	77%
ICAM-1 (lungs)	23.6 \pm 8.7	11.5 \pm 6.3*	19.4 \pm 1.2

*P < 0.05, bupivacaine group compared to the control and saline groups.

†P = 0.001, bupivacaine group compared to the control group.

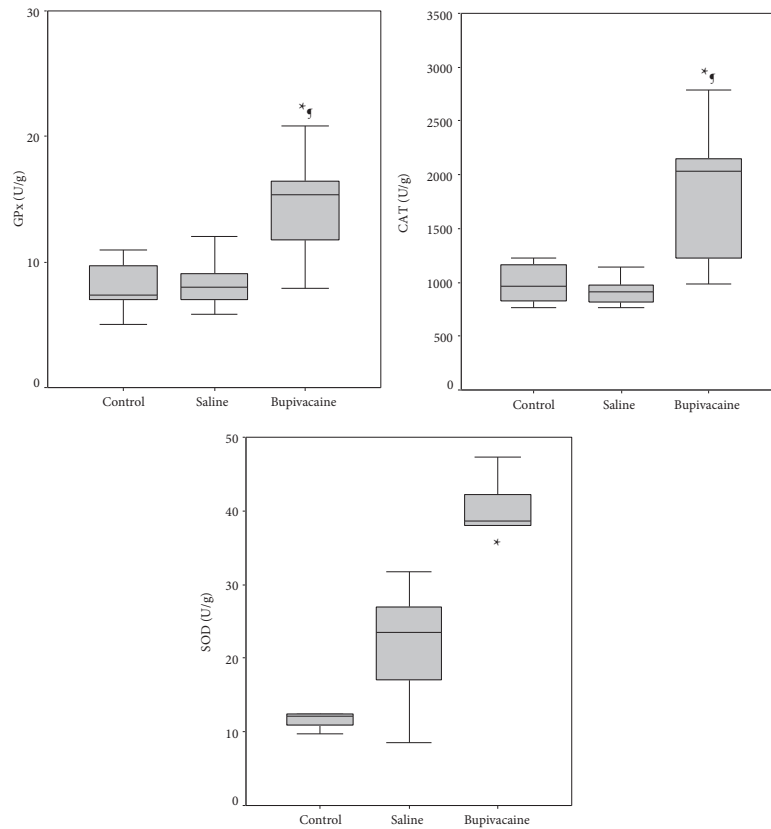


Figure 3. Lung tissue, GPx, CAT, and SOD concentrations in the control, bupivacaine, and saline groups. Values are expressed as median (horizontal line) and interquartile range (bar). *P < 0.05 compared to control group; †P < 0.05 compared to saline group.

GPx and SOD levels increased significantly in the bupivacaine group [15.3 (6.57) and 38.6 (6.02), respectively] compared to both the control [7.4 (2.85) and 12.2 (2.05), respectively] and saline groups [8.0 (2.13) and 23.5 (14.55), respectively], while the CAT levels of the rats in the bupivacaine group [2038.0 (944.75)] significantly increased compared to the control group [966.0 (399.75)] (P < 0.05; Figure 3). Epidural infusion of bupivacaine resulted in a significant decrease in MPO expression in the saline and control groups (P < 0.05; Figure 4).

The wet/dry ratio comparison showed a significant decrease in the bupivacaine group (2.9 ± 0.25) when compared to the control (5.1 ± 0.16) and saline (4.8 ± 0.47) groups (P < 0.05; Table 1).

Examination of the hematoxylin and eosin-stained lung sections showed that the pulmonary injury score was significantly decreased by epidural bupivacaine infusion (1.2 ± 0.6) compared to rats in the control (2.7 ± 0.3) and saline (2.5 ± 0.4) groups (P

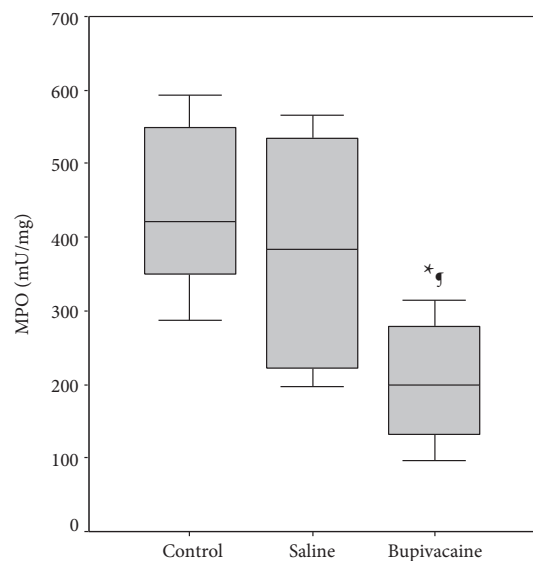


Figure 4. Lung tissue and MPO concentrations in the control, bupivacaine, and saline groups. Values are expressed as median (horizontal line) and interquartile range (bar). *P < 0.05 compared to control group; †P < 0.05 compared to saline group.

< 0.05; Table 2 and Figure 5). Treatment with epidural infusion of bupivacaine (63%) caused a significant decrease in the percentage of apoptotic cells when compared to the control (85%) group ($P < 0.05$; Table 2 and Figure 6).

Lung tissue immunohistochemical staining showed a decrease in the expression of ICAM-1 levels in the bupivacaine group (11.5 ± 6.3) group compared to the control (23.6 ± 8.7) and saline (19.4 ± 1.2) groups ($P < 0.01$; Table 2).

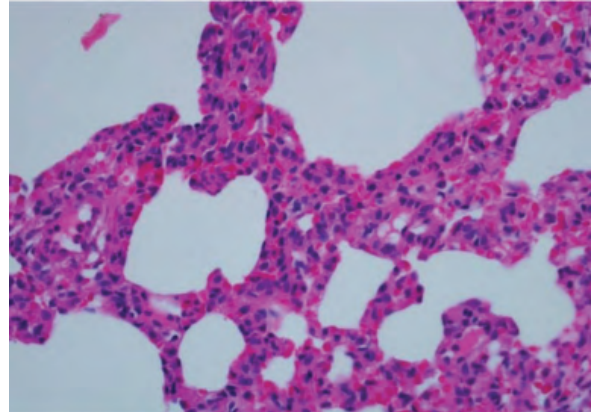
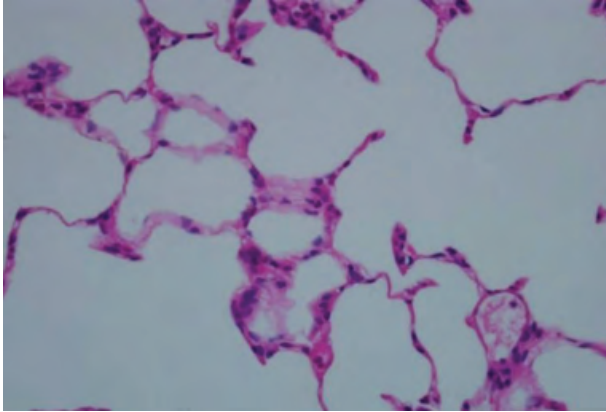


Figure 5. Lung sections of rats in groups after 24 h of epidural bupivacaine infusion (hematoxylin and eosin, 400 \times).

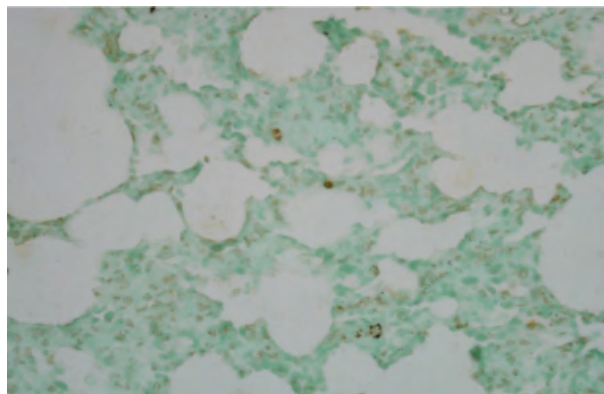
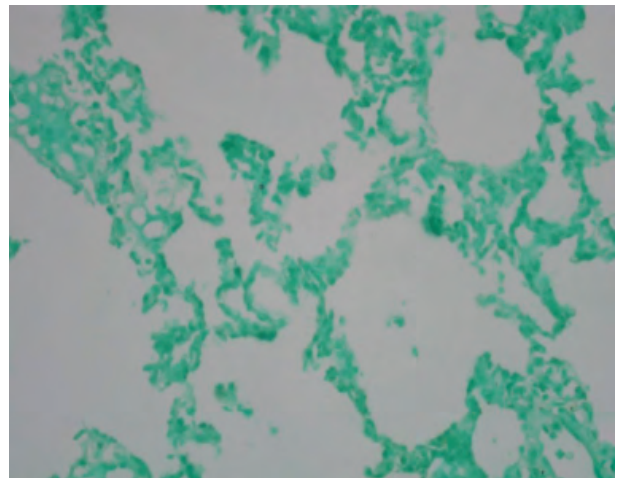
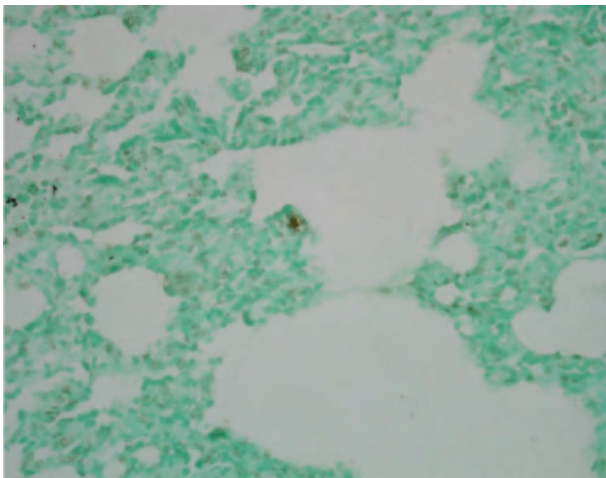


Figure 6. Apoptotic cell detection in the lung tissue of the groups after 24 h of epidural bupivacaine infusion.

Discussion

The present study demonstrated that TEA, a clinically relevant sympathetic block, attenuated the severity of AP and AP-induced lung injury. This effect was shown by reduced apoptosis, ICAM-1 expression, increased antioxidant enzyme activities, decreased lung MPO levels, wet/dry ratios, and proinflammatory cytokine expression.

AP is a multifactorial disease caused by the activation of several inflammatory mediators, and damage progresses along similar pathways regardless of the etiology (19). There are 3 phases of AP: local inflammation of the pancreas, a generalized inflammatory response, and, finally, sepsis with multiple organ damage (20). Recruitment and activation of various inflammatory cells leads to acinar cell injury and causes an elaboration of various proinflammatory mediators such as TNF and interleukins (20,21). An imbalance in the pathway results in sustained or exaggerated SIRS, followed by widespread tissue damage and death from multiple organ damage (20,21).

Gastrointestinal injury is the key factor of developing systemic inflammatory and infectious complications in AP. The mucosal barrier function is impaired in AP with increased permeability to both micromolecules and macromolecules. Mucosal hypoperfusion is the crucial factor in the pathophysiology of the gut barrier (22). In clinical studies, impaired tissue oxygenation, as measured by decreased intramucosal pH, has been demonstrated in AP (23,24). In the rat model of edematous and necrotizing AP, microvascular injury was described in the colon mucosa, liver, and lungs (25-27).

Severe AP attacks are often associated with acute lung injury. Arterial hypoxemia, pulmonary infiltrates, and pleural effusions may develop as complications of acute pancreatitis. In addition to alternations in the pulmonary vascular barrier and progressive pulmonary edema, ALI in AP is characterized by distal airway contractions, intraalveolar edema, endothelial cell damage, leukocyte sequestration, increased pulmonary MPO activity, apoptosis, and ICAM-1 secretions. The inflammatory mediators during acute pancreatitis could lead to the release of a large number of inflammatory mediators and various active substances into the blood, which subsequently

enter the lungs through the circulatory system and result in lung injury and ICAM-1 expression (28).

The method used in the present study ameliorated the systemic inflammation, wet/dry ratios, ICAM secretion, and apoptosis in the lung tissue; however, these results are not sufficient to declare a therapeutic effect on acute lung injury without showing an improvement in oxygenation and mortality.

The use of TEA in intensive care patients has become a subject of increasing interest (29-31). It has been shown that the use of TEA reduces cardiopulmonary mortality when compared with general anesthesia (7). Bernhardt et al. (30) studied a group of 121 patients with severe acute pancreatitis who were admitted to an intensive care unit, and they demonstrated the effectiveness and safety of epidural anesthesia.

The aim of using TEA in critically ill patients is to benefit from its favorable effects on microcirculation of the tissues of the heart, gut, and lungs (16). The mechanisms by which TEA influences pulmonary function may derive from segmental blocks, with redistribution of the blood flow from the segments with maintained or increased sympathetic activity toward the intestinal track (13). TEA also improves mucosal oxygenation and reduces endotoxin concentrations in conditions of deprived mucosal oxygenation (32).

Sielenkämper et al. (9) demonstrated that gut mucosal perfusion increases during TEA as a result of sympathetic nerve blockade, and this provides a beneficial interorgan redistribution of blood flow. A study by Freise et al. (11) showed that TEA reduced intestinal injury, modified systemic inflammatory response, and reduced mortality in a rat model. Lauer et al. (33) proved that TEA improved pancreatitis-associated impairment of pulmonary vasoreactivity and gas exchange. In the present study, TEA maintained by bupivacaine reduced the lung injury in critically ill rats. This was proven by the decreased apoptotic cell death, decreased ICAM-1 secretion, and increased antioxidant activity in the lung tissues.

In conclusion, the present study demonstrated that TEA with bupivacaine decreased the systemic inflammation and lung injury due to AP. This finding may be clinically interesting in altering the SIRS, multiple organ dysfunction, and mortality of AP

when used for both anesthesia and pain control. However, these effects could not be explained only with sympathetic blocks, because the systemic effect of epidurally given bupivacaine cannot be excluded unless compared with a control group of intravenous

bupivacaine. More studies evaluating oxygenation and mortality have to be done to show the clinical validity and therapeutic effects of TEA with bupivacaine in terms of agent and doses for humans in critical care units.

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