EXPERIMENTAL STUDY

Short-term protective effect of octreotide on the lungs of rats with experimentally induced sepsis

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ABSTRACT

BACKGROUND: Acute respiratory distress syndrome is a devastating complication of severe sepsis. Preclinical models suggest that direct lung injury begins with attack to the lung epithelium, but indirect lung injury results from systemic endothelial damage due to inflammatory mediators. The aim of the present study was to explore the effect of octreotide on lungs in a surgically induced sepsis model in rats.

METHODS: We used 32 male Sprague Dawley rats and divided into four groups. Group 1: Normal (non-operative and orally fed control, n=8); Group 2: Sham operated (n=8); Group 3: Cecal ligation and puncture (CLP) (untreated group, n=8); and Group 4: CLP and 100 µg/kg octreotide i.p. (n=8). For sepsis, CLP procedure was performed on 16 rats to induce a sepsis model. All groups were analyzed, their blood was taken for arterial blood gas analysis. For histological examination, lung tissues were removed and sections were prepared.

RESULTS: In histological examination, if we compare CLP + Octreotide with only CLP group in CLP + Octreotide group decreased inflammatory cell infiltration in alveolar and interstitial area as well as edema, bleeding, when CLP group was compared with octreotide group, all histopathological parameters improved significantly and the severity index decreased from 3 to 1. For arterial blood gas, when CLP and octreotide groups were compared with CLP group, it was observed that there was a significant change in favor of healing and that they almost came up to controls and sham group.

CONCLUSION: It could be hypothesized that it would be beneficial to administer octreotide for ameliorate lung injury state in sepsis patients.

Keywords: Acute respiratory distress syndrome; histopathology; octreotide; sepsis.

INTRODUCTION

Severe sepsis and septic shock are the common health problems affecting millions of patients each year. The overreaction of inflammatory mediators to infectious pathogens plays a key role in the pathogenesis, and the mortality rate due to septic shock is high. Acute respiratory distress syndrome (ARDS) is a devastating complication of severe sepsis.

Sepsis and acute lung injury (ARDS) have similar mechanisms, such as inflammation and endothelial dysfunction. In addition, severe sepsis is the most common etiology of ARDS, and patients with sepsis triggered ARDS have higher mortality rates than patients with other ARDS risk factors.[1]

The incidence of ARDS in adult patients with sepsis is approximately 6–7% in Western countries.[2,3] In patients with

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sepsis, progression to ARDS is rapid and is associated with an increased risk of in-hospital mortality.[2,3] On the other hand, early targeted treatment in patients with severe sepsis or septic shock reduced the proportion of patients receiving mechanical ventilation.[4] These findings suggest that the incidence of sepsis-related ARDS is relatively low, but treatment of the underlying sepsis and identification of patients at risk for developing ARDS are of great importance. To date, few studies have evaluated risk factors for developing ARDS in severe sepsis population. Lung damage prediction score, initial serum lactate level, and microbiologically proven infection are factors associated with an increased risk of ARDS in patients with severe sepsis.[3]

ARDS is a heterogeneous syndrome characterized by increased permeability of pulmonary capillary endothelial cells and alveolar epithelial cells. It can be difficult to distinguish from indirect injury (e.g., pneumonia sepsis), which may be the cause of injury either directly (e.g., pneumonia and gastric aspiration) or indirectly (e.g., non-pulmonary sepsis and trauma).

Preclinical models suggest that direct lung injury begins with attack to the lung epithelium, but indirect lung injury results from systemic endothelial damage due to inflammatory mediators.

Octreotide (OCT) (SMS 201–995) is a small octapeptide somatostatin (SST) analog with a much longer biological half-life than natural SST. OCT, a more potent and long-acting analog, has similar pharmacological effects to SST and is used in various indications such as acromegaly, gastrointestinal system (GIS) endocrine tumors, GIS bleeding, and pancreatitis.[2]

Recently, various antioxidant, anti-inflammatory, and antiapoptotic properties of octreotide have also been reported in several clinical trials and experimental models of ischemia-reperfusion (I/R) injury, abdominal compartment syndrome, radiation enteritis, pancreatitis, and sepsis. This drug has a wide safety margin and low side effect profile.[5]

The aim of this study is to investigate epidemiology, pathogenesis, and the role of octreotide in sepsis-induced ARDS and to investigate the early use options of this drug in the patients who took ARDS diagnosis.

MATERIALS AND METHODS

Animals

In this study, we used 37 male Sprague Dawley albino mature rats weighing 200–220 g. The experiments performed in this study have been carried out according to the rules in the Guide for the Care and Use of Laboratory Animals adopted by National Institutes of Health (U.S.A). Having received Animal Ethics Committee's consent, animals were fed ad libitum and housed in pairs in steel cages having a temperature-controlled environment (22±2°C) with 12 h light/dark cycles.

Experimental Procedures

Rats were randomly assigned into two groups and cecal ligation and puncture (CLP) procedure was performed on 16 rats to induce a sepsis model. Five rats died during the first 24 h following surgical procedure and were excluded from the study. There was no mortality in sham-operated group. Study groups were designed as follows: Group 1: Normal (non-operative and orally fed control, n=8); Group 2: Sham operated (n=8); Group 3: CLP (untreated group, n=8); and Group 4: CLP and 100 μg/kg octreotide (Sandostatin, Novartis) i.p. (n=8). For the surgical procedure, rats were anesthetized by intraperitoneal injection of a combination of ketamine hydrochloride at a dose of 80 mg/kg and 7 mg/kg xylazine hydrochloric (Alfazyne; Alfasan International BV, Woerden, Holland).

Under aseptic conditions, a 3 cm midline laparotomy was performed to allow exposure of the cecum with adjoining intestine. The cecum was ligated tightly with a 3.0 silk suture at its base under the ileocecal valve and punctured once with a 22-gauge needle. The cecum was then gently squeezed to extrude a small amount of feces from the perforation site. The cecum was returned to the peritoneal cavity, and the laparotomy incision was closed with 4-0 polyglactin 910 sutures. Following surgery, a recovery period was allowed to the animals and then they were placed in their cages.

In the sham group, only laparotomy was performed under aseptic conditions; but cecum of the rats was neither ligated nor punctured. In this model, rats were accepted as septic 5 h following CLP.[6]

All treatments were performed within the 1st h of surgical procedure. The study was completed after 24 h. At the end of the study, the animals were euthanized and blood samples were collected by cardiac puncture for biochemical and analysis; and bilateral pneumonectomy was performed for histopathological examination.

Arterial Blood Gas Analysis

Blood samples drawn from carotid artery in each group were collected (0.2 mL) at 24 h after the operation and PaO_2, $PaCO_2$, blood lactate, and PaO_2/FiO_2 (PaO_2/FiO_2: Oxygenation index) values were assayed using a blood gas analyzer.

Histopathological Examination of Lung

For histological study, all animals were anesthetized by ketamine (40 mg/kg, Alfamine®, Alfasan International B.V., Holland) and xylazine (4 mg/kg, Alfazyne®, Alfasan International B.V., Holland) i.p. and perfused with 200 ml of 4% formaldehyde in 0.1 M phosphate buffer saline. Formalin-fixed kidney

sections (5 μm) were stained with hematoxylin and eosin. All sections were photographed with Olympus C-5050 digital camera mounted on Olympus BX51 microscope.

The main histopathological lung damage score was calculated as previously described.[7] In brief, histopathological lung damage was assessed by scoring alveolar congestion, hemorrhage, infiltration or aggregation of leukocytes in air spaces/vessel walls, perivascular/interstitial edema, and thickness of the alveolar wall/hyaline membrane formation. The severity for each item was graded as 1 (0–25%), 2 (25–50%), 3 (50–75%), and 4 (75–100%).

Statistical Analysis

Results were presented as mean±SEM. Data were initially analyzed by one-way analyses of variance. Post hoc Tukey HSD test was applied for group comparisons. The differences between treatments and control values were determined by Student's t-test. $P<0.05$ was considered to be statistically significant.

RESULTS

Histopathological Findings

Histopathological examination revealed normal alveolar and intestinal structure in the control and operated sham groups. Compared to the control group, CLP group has inflammatory cell infiltration in alveolar and interstitial area as well as edema, bleeding. If we compare CLP + octreotide with only CLP group in CLP + octreotide group decreased inflammatory cell infiltration in alveolar and interstitial area as well as edema, bleeding (Fig. 1).

When the CLP group was compared with sham and control groups, all lung injury parameters were significantly increased in CLP group, and when CLP group was compared with octreotide group, all histopathological parameters improved significantly and the severity index decreased from 3 to 1 (Table 1).

Biochemical Analysis

Although there was no significant difference between sh-

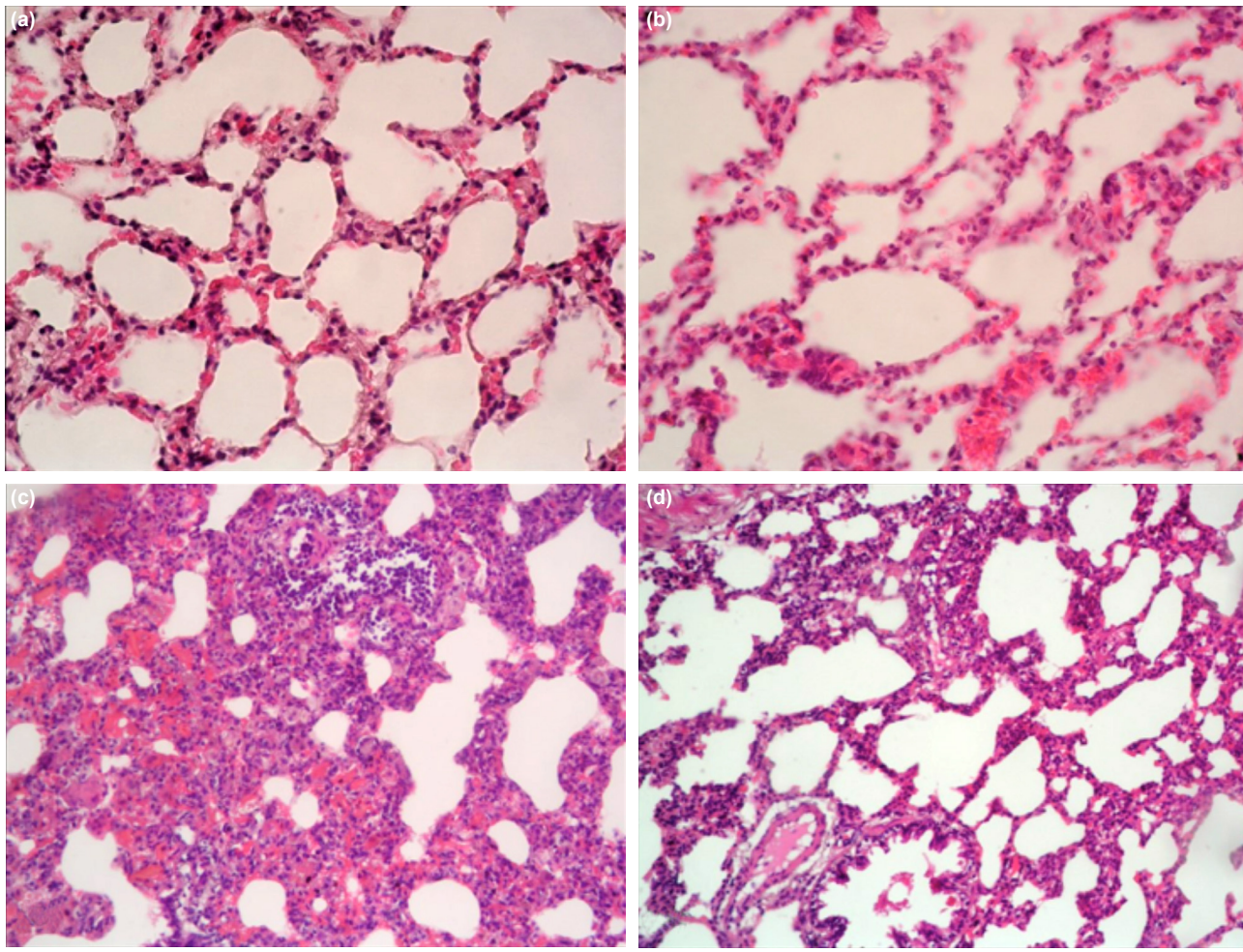

Figure 1. Lung tissue. Hematoxylin and eosin stain, ×20. **(a)** Control group, normal alveolar and interstitial structure, **(b)** sham-operated group, normal alveolar and interstitial structure, **(c)** CLP group, inflammatory cell infiltration in alveolar and interstitial area as well as edema, bleeding, **(d)** CLP and octreotide group, decreased inflammatory cell infiltration in alveolar and interstitial area as well as edema, bleeding. CLP: Cecal ligation and puncture.

Table 1. Histopathological lung damage was assessed by scoring AC, H, infiltration or AL, PE, and TA

	AC	H	AL	PE	TA
Control group	0.3±0.2	0.5±0.2	0.16±0.16	0.3±0.21	0.3±0.21
Sham-operated group	0.83±0.16	1.6±0.2	0.6±0.2	0.8±0.1	0.1±0.1
CLP group	3.3±0.5*	2.8±0.7*	3.3±0.8*	3.1±0.9*	2.3±0.8*
CLP and octreotide	1.6±0.1#	1.5±0.2#	0.6±0.1##	0.9±0.3##	1.8±0.4#

AC: Alveolar congestion; H: Hemorrhage; AL: Aggregation of leukocytes in air spaces/vessel walls; PE: Perivascular/interstitial edema; TA: Thickness of the alveolar wall/hyARDSne membrane formation; CLP: Cecal ligation and puncture. The severity for each item was graded as 1 (0–25%), 2 (25–50%), 3 (50–75%), and 4 (75–100%) *p<0.001, compared with control group or sham-operated group #p<0.05, compared with CLP group ##p<0.001, compared with CLP group.

Table 2. Blood gas analysis in all groups

	Control group	Sham-operated group	CLP group	CLP and octreotide
PaO_2 (mmHg)	97.2±5.06	93.1±6.27	47.61±7.57*	79.23±5.8#
$PaCO_2$ (mmHg)	35.16±0.9	37.5±1.98	48.5±4.14*	39.67±2.3#
PaO_2/FiO_2***	462.85±24.09	443.33±29.85	226.71±36.04*	377.28±27.6#
Lac (mmol/L)	0.7±0.2	0.9±0.1	2.2±0.6*	1.1±0.3#

***Breathing air (FiO_2) was accepted as 0.21. *P<0.05, compared with control group or sham-operated group **p<0.001, compared with control group or sham-operated group #p<0.05, compared with CLP group. CLP: Cecal ligation and puncture.

am-operated group and control group, the significant difference between controls and sham groups of the CLP group indicates that sepsis model was established and lung injury started among treated group. When CLP and octreotide groups were compared with CLP group, it was observed that there was a significant change in favor of healing and that they almost came up to controls and sham group (Table 2).

DISCUSSION

Mortality and morbidity in sepsis are still one of the major health problems. Early diagnosis and treatment are important for minimizing mortality and morbidity. The initiation of supportive therapy, which is described as an early targeted treatment (in ICU or in emergency room), is the most important treatment approach that reduces mortality and morbidity, except antibiotherapy.[8–10]

Lung damage is the most common mortality cause and the most common organ which is affected in sepsis. ARDS is a clinical syndrome characterized by hypoxia and pulmonary injury. In this syndrome, the pulmonary barrier is disrupted; permeability, inflammation, cellular infiltration, and exudation are increased; necrosis has occurred; and as a result, ventilation perfusion is disrupted. In 2012, Berlin criteria to define ARDS were published. In this context, according to the degree of ARDS hypoxia; subgroups such as mild (PaO_2/FiO_2 = 200–300 mmHg), moderate (PaO_2/FiO_2 = 100–200 mmHg), and heavy (PaO_2/FiO_2 <100 mmHg) were established.[11]

In our study, PaO_2/FiO_2 values of rats were normal among controls and operated sham groups, whereas mild form was formed in CLP group (PaO_2/FiO_2 = 226.71±36.04 mmHg). In addition, the octreotide-treated rats were found to have a PaO_2/FiO_2 value close to controls and operated sham group, but significantly improved compared to the CLP group.

For now, we observe that lungs are the first organ affected by immunomodulators after sepsis. This process often results with ARDS. In patients with sepsis, many free oxygen radicals are secreted from activated immune system cells; this causes oxidative damage to the body. Therefore, it is stated that it has an important place in the treatment of sepsis in protecting from oxidative damage.[12,13] Many treatments have been conducted to prevent ARDS in sepsis; and they are still underway. However, for some of these therapies, a clear result has been reached; while for others, it has not.

In the study of McAuley et al.,[14] the effect of the use of statins for ARDS after sepsis on the clinic was examined and it was not clear whether the patient's prognosis had changed. Alhazzani et al.[15] reported that statins were not suitable for the use of ARDS after sepsis and did not have an impact on prognosis, and additional studies were required for clearer results. In the study of Kruger and Terblanche,[16] statins were tried as treatment but no clear benefit was found on prognosis. As statins have antioxidant and anti-inflammatory effect,[15] future studies may show that peptides and statins are superior to each other on this issue.

Many studies have been conducted in the literature regarding the role of platelets on sepsis and ARDS and are still underway. Toner et al.'s[17] study also investigated the effect of aspirin on prognosis in patients with sepsis and ARDS, and stated that they've made observational analysis that it might be useful. In the study of Das,[18] it was found that the administration of essential fatty acids with aspirin increased gas exchange in patients with septic ARDS; thus, it decreases the time to connect to the mechanic ventilator and stay in the intensive care unit. In the study of Gordon et al.,[19] the effect of ibuprofen on sepsis and ARDS was investigated; and they stated that ibuprofen prevents fever, tachypnea, tachycardia, lactic acidosis, and hypoxemia, thus prevents the deterioration of prognosis in patients with sepsis; but all of this study's do not affect mortality and organ failure. Information about octreotide mortality and healing process in ARDS is almost non-existent. Future studies will clarify these issues.

Lactate is an important indicator for the deterioration of oxygenation and predicting mortality according to many studies in the literature. In addition, it has been shown in the literature that the release of lactate from damaged organs directly shows damage.[20,21] Pulmonary lactate release in patients with ARDS is associated with the severity of lung injury. When interpreting lactate levels related to systemic hypoxia in arterial blood gas; the effect of pulmonary lactate release should also be considered. Dettmer et al.[22] reported that lactate increased secondary to lung damage in patients with ARDS. Moussa et al.'s[23] study also showed that the most serious damage is direct release of lactate from the organ.

There are also studies showing that ARDS is associated with mortality in increasing lactate levels. In a study conducted by Kamo et al.[6] on the significance of lactate levels in ARDS patients, it was shown that increased lactate levels in blood gas were associated with mortality. In our study; we found that lactate levels increased compared to the other groups and this situation created the ARDS model in sepsis; that it was higher for CLP group compared to controls and operative sham group; that lactate levels in octreotide group were almost similar to controls and operated sham groups and this improvement was statistically significant.

Many studies have shown that SST is secreted during inflammation and suppresses inflammation. The fact that SST is short acting and requires IV infusion creates difficulty for treatment.[24,25] In an experimental study in which SST and N-acetyl cysteine were used together, Ferrer et al.[3] showed that they had protective effect against multiple organ failure caused by oxidative stress in intestinal ischemia.

OCT is also one of the peptides that are being studied to reduce the immunomodulators and resulting oxygen radicals and inhibits their effects in sepsis and sepsis-induced ARDS.[5,26] In a study by Sener et al.,[27] it was shown that octreotide relieves sepsis-induced oxidative stress in pelvic and ovarian sepsis conditions. Moosmann and Behl[28] reported that peptide hormones may act as antioxidants. Paran et al.[29] reported that they administered octreotide to patients with acute pancreatitis; and that the rate of ARDS and sepsis and the duration of hospital stay of octreotide-administered patients have decreased. The study by Fiedler et al.[30] showed that octreotide treatment in patients with necrotizing pancreatitis reduces the ARDS rate and mortality. In the study of Czakó et al.,[31] octreotide administration in patients with acute pancreatitis was shown to reduce oxygen radicals and antioxidant effect.[32] Moreover, Huang et al.[33] compared hemofiltration treatment with hemofiltration + octreotide in patients with acute pancreatitis with ARDS complication, they observe that hemofiltration plus octreotide group improves clinically about lung injury similar to our study.

In our study, lung contusion, bleeding, leukocyte aggregation into the alveoli, perivascular edema, and thinness of the alveolar wall of octreotide treatment group were significantly less compared to the group without treatment. It was observed that lung damage was decreased histologically, PaO_2 value was increased, and $PaCO_2$ value was reduced in octreotide-treated rats with sepsis compared to non-treated peers. In the study of Liu et al.[34] use of somatostatin improves histopathologically lung injury similarly to our study.

Conclusion

OCT is an peptide which has various properties like an antioxidant which reduces inflammation and induces apoptosis and secretion of anti-inflammatory agents. Replication of these findings in preclinical and clinical human populations might provide huge innovations and directions to classical treatment options that target the prevention of lung injury. There is considerable value in the current study since it has shown these benefits at the histological, biochemical levels in octreotide-administered group. We think that the use of octreotide in the pre-treatment of sepsis in emergency room in patients will decrease the ARDS rate, the mortality and morbidity.

Ethics Committee Approval: This study was approved by the Ege University Faculty of Medicine Animal Experimental Ethics Committee (Date: 16.04.2018, Decision No: 25180416).

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: S.E.B., O.E.; Design: S.E.B., O.E.; Supervision: S.E.B., O.E.; Materials: A.E.; Data: A.E.; Analysis: M.A.E., G.Y.; Literature search: A.Ç.; Writing: A.Ç.; Critical revision: S.E.B., A.E., M.A.E., G.Y., A.Ç., O.E.

Conflict of Interest: None declared.

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REFERENCES

1. Nguyen HB, Rivers EP, Abrahamian FM, Moran GJ, Abraham E, Trzeciak S, et al. Severe sepsis and septic shock: Review of the literature and emergency department management guidelines. Ann Emerg Med 2006;48:28–54. [CrossRef]
2. Tang C, Lan C, Wang C, Liu R. Amelioration of the development of multiple organ dysfunction syndromeby somatostatin via suppression of intestinal mucosalmast cells. Shock 2005;3:470–5. [CrossRef]
3. Ferrer JV, AricetaJ, Guerrero D, Balen E, Herrera J, Lera JM. Prevention by somatostatine and N-acetlycisteine of multiorgan failure mediated by oxidativestressafterintestinal ischemia. Transplant Proc 1999;31:2570–1. [CrossRef]
4. Marik PE. Vitamin C for the Treatment of Sepsis: The scientific rationale. Pharmacol Ther 2018;189:63–70. [CrossRef]
5. Kaçmaz A, Polat A, User Y, Tilki M, Ozkan S, S¸ener G. Octreotide improves reperfusion-induced oxidative injury in acute abdominal hypertension in rats. J Gastrointest Surg 2004;8:113–9. [CrossRef]
6. Kamo T, Tasaka S, Suzuki T, Asakura T, Suzuki S, Yagi K, et al. Prognostic values of the Berlin definition criteria, blood lactate level, and fibroproliferative changes on high-resolution computed tomography in ARDS patients. BMC Pulm Med 2019;19:37. [CrossRef]
7. Erbas O, Taskiran D. Sepsis-induced changes in behavioral stereotypy in rats; involvement of tumor necrosis factor-alpha, oxidative stress, and dopamine turnover. J Surg Res 2014;186:262–8. [CrossRef]
8. Kwon WY, Suh GJ, Kim KS, Kwak YH. Niacin attenuates lung inflammation and improves survival during sepsis by downregulating the nuclear factor-κB pathway. Crit Care Med 2011;39:328–34. [CrossRef]
9. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 2003;31:1250–6. [CrossRef]
10. Martin GS, Mannino DM, Eaton S, Moss M.M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546–54. [CrossRef]
11. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: The Berlin definition. JAMA 2012;307:2526–33. [CrossRef]
12. Goode HF, Webster NR. Free radicals and anitioxidants in sepsis. Crit Care Med 1993;21:1770–6. [CrossRef]
13. Crimi E, Sica V, Slutsky AS, Zhang H, Williams-Ignarro S, Ignarro LJ, et al. Role of oxidative stress in experimental sepsis and multisystem organ dysfunction. Free Radic Res 2006;40:665–72. [CrossRef]
14. McAuley D, Charles PE, Papazian L. Statins in patients with sepsis and ARDS: Is it over? We are not sure. Intensive Care Med 2017;43:677–9.
15. Alhazzani W, Truwit J. Statins in patients with sepsis and ARDS: İs it over? Yes. Intensive Care Med 2017;43:672–4. [CrossRef]
16. Kruger PS, Terblanche M. Statins in patients with sepsis and ARDS: İs it over? No. Intensive Care Med 2017;43:675–6. [CrossRef]
17. Toner P, McAuley DF, Shyamsundar M. Aspirin as a potential treatment in sepsis or acute respiratory distress syndrome. Crit Care 2015;19:374.
18. Das UN. Combination of aspirin with essential fatty acids is superior to aspirin alone to prevent or ameliorate sepsis or ARDS. Lipids Health Dis 2016;15:206. [CrossRef]
19. Gordon RB, Arthur PW, James AR, Roland S, Warren RS, Kenneth PS, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. N Engl J Med 1997;336:912–8. [CrossRef]
20. Wu WH, Niu YY, Zhang CR, Xiao LB, Ye HS, Pan DM, et al. Combined APACH II score and arterial blood lactate clearance rate to predict the prognosis of ARDS patients. Asian Pac J Trop Med 2012;5:656–60.
21. Iscra F, Gullo A, Biolo G. Bench-to-bedside review: Lactate and the lung. Crit Care 2002;6:327–9. [CrossRef]
22. Dettmer MR, Mohr NM, Fuller BM. Sepsis-associated pulmonary complications in emergency department patients monitored with serial lactate: An observational cohort study. J Crit Care 2015;30:1163–8. [CrossRef]
23. Moussa MD, Santonocito C, Fagnoul D, Donadello K, Pradier O, Gaussem P, et al. evaluation of endothelial damage in sepsis-related ARDS using circulating endothelial cells. Intensive Care Med 2015;41:231–8.
24. Chan MM, Chan MM, Mengshol JA, Fish DN, Chan ED. Octreotide: a drug often used in the critical care setting but not well understood. Chest 2013;144:1937–45. [CrossRef]
25. Seboek D, Linscheid P, Zulewski H, Langer I, Christ-Crain M, Keller U, et al. Somatostatin is expressed and secreted by human adipose tissue upon infection and inflammation. J Clin Endocrinol Metab 2004;89:4833–9. [CrossRef]
26. Kaçmaz A, Polat A, User Y, Tilki M, Ozkan S, Sener G. Octreotide: A new approach to the management of acute abdominal hypertension. Peptides 2003;24:1381–6. [CrossRef]
27. Sener G, Cetinel S, Erkanli G, Gedik N, Yeğen BC. Octreotide ameliorates sepsis-induced pelvic inflammation in female rats by a neutrophil-dependent mechanism. Peptides 2005;26:493–9. [CrossRef]
28. Moosmann B, Behl C. Secretory peptide hormones are biochemical antioxidants: Structure-activity relationship. Mol Pharmacol 2002;61:260–8. [CrossRef]
29. Paran H, Mayo A, Paran D, Neufeld D, shwarts I, Zissin R, et al. Octreotide treatment in patients with severe acute pancreatitis. Dig Dis Sci 2000;45:2247–51. [CrossRef]
30. Fiedler F, JaureingG, Keim V, Richter A, Bender HJ. Octreotide treatment in patients with necrotizing pancreatitis and pulmonary failure. İntensive Care Med 1996;22:909–15. [CrossRef]
31. Czakó L, Hegyi P, Takács T, Góg C, Farkas A, Mándy Y, et al. Effects of octreotide on acute necrotizing pancreatitis in rabbits. World J Gastroenterol 2004;10 2082–6. [CrossRef]
32. Zhang X, Feng G, Weng W, Liang J, Lin N, Cai Y, et al. Protective effects of baicalin and octreotide on intestinal mucosa of rats with severe acute pancreatitis. Turk J Gastroenterol 2009;20:108–15.
33. Huang L, Zhu H, Gu J. Octreotide and continuous hemofiltration versus continuous hemofiltration alone in severe acute pancreatitis complicated with acute respiratory distress syndrome. J Coll Physicians Surg Pak 2019;29:758–87. [CrossRef]
34. Liu R, Wang CH, Huang MH, Li X, Qiang O, Tang CW. Therapeutic effect of somatostatin on acute respiratory distress syndrome in experimental rats. [Article in Chinese]. Sichuan Da Xue Xue Bao Yi Xue Ban 2006;37:412–5.

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ABSTRACT

BACKGROUND: Acute respiratory distress syndrome is a devastating complication of severe sepsis. Preclinical models suggest that direct lung injury begins with attack to the lung epithelium, but indirect lung injury results from systemic endothelial damage due to inflammatory mediators. The aim of the present study was to explore the effect of octreotide on lungs in a surgically induced sepsis model in rats.

METHODS: We used 32 male Sprague Dawley rats and divided into four groups. Group 1: Normal (non-operative and orally fed control, n=8); Group 2: Sham operated (n=8); Group 3: Cecal ligation and puncture (CLP) (untreated group, n=8); and Group 4: CLP and 100 µg/kg octreotide i.p. (n=8). For sepsis, CLP procedure was performed on 16 rats to induce a sepsis model. All groups were analyzed, their blood was taken for arterial blood gas analysis. For histological examination, lung tissues were removed and sections were prepared.

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CONCLUSION: It could be hypothesized that it would be beneficial to administer octreotide for ameliorate lung injury state in sepsis patients.

Keywords: Acute respiratory distress syndrome; histopathology; octreotide; sepsis.

INTRODUCTION

Severe sepsis and septic shock are the common health problems affecting millions of patients each year. The overreaction of inflammatory mediators to infectious pathogens plays a key role in the pathogenesis, and the mortality rate due to septic shock is high. Acute respiratory distress syndrome (ARDS) is a devastating complication of severe sepsis.

Sepsis and acute lung injury (ARDS) have similar mechanisms, such as inflammation and endothelial dysfunction. In addition, severe sepsis is the most common etiology of ARDS, and patients with sepsis triggered ARDS have higher mortality rates than patients with other ARDS risk factors.[1]

The incidence of ARDS in adult patients with sepsis is approximately 6–7% in Western countries.[2,3] In patients with

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sepsis, progression to ARDS is rapid and is associated with an increased risk of in-hospital mortality.[2,3] On the other hand, early targeted treatment in patients with severe sepsis or septic shock reduced the proportion of patients receiving mechanical ventilation.[4] These findings suggest that the incidence of sepsis-related ARDS is relatively low, but treatment of the underlying sepsis and identification of patients at risk for developing ARDS are of great importance. To date, few studies have evaluated risk factors for developing ARDS in severe sepsis population. Lung damage prediction score, initial serum lactate level, and microbiologically proven infection are factors associated with an increased risk of ARDS in patients with severe sepsis.[3]

ARDS is a heterogeneous syndrome characterized by increased permeability of pulmonary capillary endothelial cells and alveolar epithelial cells. It can be difficult to distinguish from indirect injury (e.g., pneumonia sepsis), which may be the cause of injury either directly (e.g., pneumonia and gastric aspiration) or indirectly (e.g., non-pulmonary sepsis and trauma).

Preclinical models suggest that direct lung injury begins with attack to the lung epithelium, but indirect lung injury results from systemic endothelial damage due to inflammatory mediators.

Octreotide (OCT) (SMS 201–995) is a small octapeptide somatostatin (SST) analog with a much longer biological half-life than natural SST. OCT, a more potent and long-acting analog, has similar pharmacological effects to SST and is used in various indications such as acromegaly, gastrointestinal system (GIS) endocrine tumors, GIS bleeding, and pancreatitis.[2]

Recently, various antioxidant, anti-inflammatory, and antiapoptotic properties of octreotide have also been reported in several clinical trials and experimental models of ischemia-reperfusion (I/R) injury, abdominal compartment syndrome, radiation enteritis, pancreatitis, and sepsis. This drug has a wide safety margin and low side effect profile.[5]

The aim of this study is to investigate epidemiology, pathogenesis, and the role of octreotide in sepsis-induced ARDS and to investigate the early use options of this drug in the patients who took ARDS diagnosis.

MATERIALS AND METHODS

Animals

In this study, we used 37 male Sprague Dawley albino mature rats weighing 200–220 g. The experiments performed in this study have been carried out according to the rules in the Guide for the Care and Use of Laboratory Animals adopted by National Institutes of Health (U.S.A). Having received Animal Ethics Committee's consent, animals were fed ad libitum and housed in pairs in steel cages having a temperature-controlled environment (22±2°C) with 12 h light/dark cycles.

Experimental Procedures

Rats were randomly assigned into two groups and cecal ligation and puncture (CLP) procedure was performed on 16 rats to induce a sepsis model. Five rats died during the first 24 h following surgical procedure and were excluded from the study. There was no mortality in sham-operated group. Study groups were designed as follows: Group 1: Normal (non-operative and orally fed control, n=8); Group 2: Sham operated (n=8); Group 3: CLP (untreated group, n=8); and Group 4: CLP and 100 μg/kg octreotide (Sandostatin, Novartis) i.p. (n=8). For the surgical procedure, rats were anesthetized by intraperitoneal injection of a combination of ketamine hydrochloride at a dose of 80 mg/kg and 7 mg/kg xylazine hydrochloric (Alfazyne; Alfasan International BV, Woerden, Holland).

Under aseptic conditions, a 3 cm midline laparotomy was performed to allow exposure of the cecum with adjoining intestine. The cecum was ligated tightly with a 3.0 silk suture at its base under the ileocecal valve and punctured once with a 22-gauge needle. The cecum was then gently squeezed to extrude a small amount of feces from the perforation site. The cecum was returned to the peritoneal cavity, and the laparotomy incision was closed with 4-0 polyglactin 910 sutures. Following surgery, a recovery period was allowed to the animals and then they were placed in their cages.

In the sham group, only laparotomy was performed under aseptic conditions; but cecum of the rats was neither ligated nor punctured. In this model, rats were accepted as septic 5 h following CLP.[6]

All treatments were performed within the 1st h of surgical procedure. The study was completed after 24 h. At the end of the study, the animals were euthanized and blood samples were collected by cardiac puncture for biochemical and analysis; and bilateral pneumonectomy was performed for histopathological examination.

Arterial Blood Gas Analysis

Blood samples drawn from carotid artery in each group were collected (0.2 mL) at 24 h after the operation and PaO_2, $PaCO_2$, blood lactate, and PaO_2/FiO_2 (PaO_2/FiO_2: Oxygenation index) values were assayed using a blood gas analyzer.

Histopathological Examination of Lung

For histological study, all animals were anesthetized by ketamine (40 mg/kg, Alfamine®, Alfasan International B.V., Holland) and xylazine (4 mg/kg, Alfazyne®, Alfasan International B.V., Holland) i.p. and perfused with 200 ml of 4% formaldehyde in 0.1 M phosphate buffer saline. Formalin-fixed kidney

sections (5 μm) were stained with hematoxylin and eosin. All sections were photographed with Olympus C-5050 digital camera mounted on Olympus BX51 microscope.

The main histopathological lung damage score was calculated as previously described.[7] In brief, histopathological lung damage was assessed by scoring alveolar congestion, hemorrhage, infiltration or aggregation of leukocytes in air spaces/vessel walls, perivascular/interstitial edema, and thickness of the alveolar wall/hyaline membrane formation. The severity for each item was graded as 1 (0–25%), 2 (25–50%), 3 (50–75%), and 4 (75–100%).

Statistical Analysis

Results were presented as mean±SEM. Data were initially analyzed by one-way analyses of variance. Post hoc Tukey HSD test was applied for group comparisons. The differences between treatments and control values were determined by Student's t-test. $P<0.05$ was considered to be statistically significant.

RESULTS

Histopathological Findings

Histopathological examination revealed normal alveolar and intestinal structure in the control and operated sham groups. Compared to the control group, CLP group has inflammatory cell infiltration in alveolar and interstitial area as well as edema, bleeding. If we compare CLP + octreotide with only CLP group in CLP + octreotide group decreased inflammatory cell infiltration in alveolar and interstitial area as well as edema, bleeding (Fig. 1).

When the CLP group was compared with sham and control groups, all lung injury parameters were significantly increased in CLP group, and when CLP group was compared with octreotide group, all histopathological parameters improved significantly and the severity index decreased from 3 to 1 (Table 1).

Biochemical Analysis

Although there was no significant difference between sh-

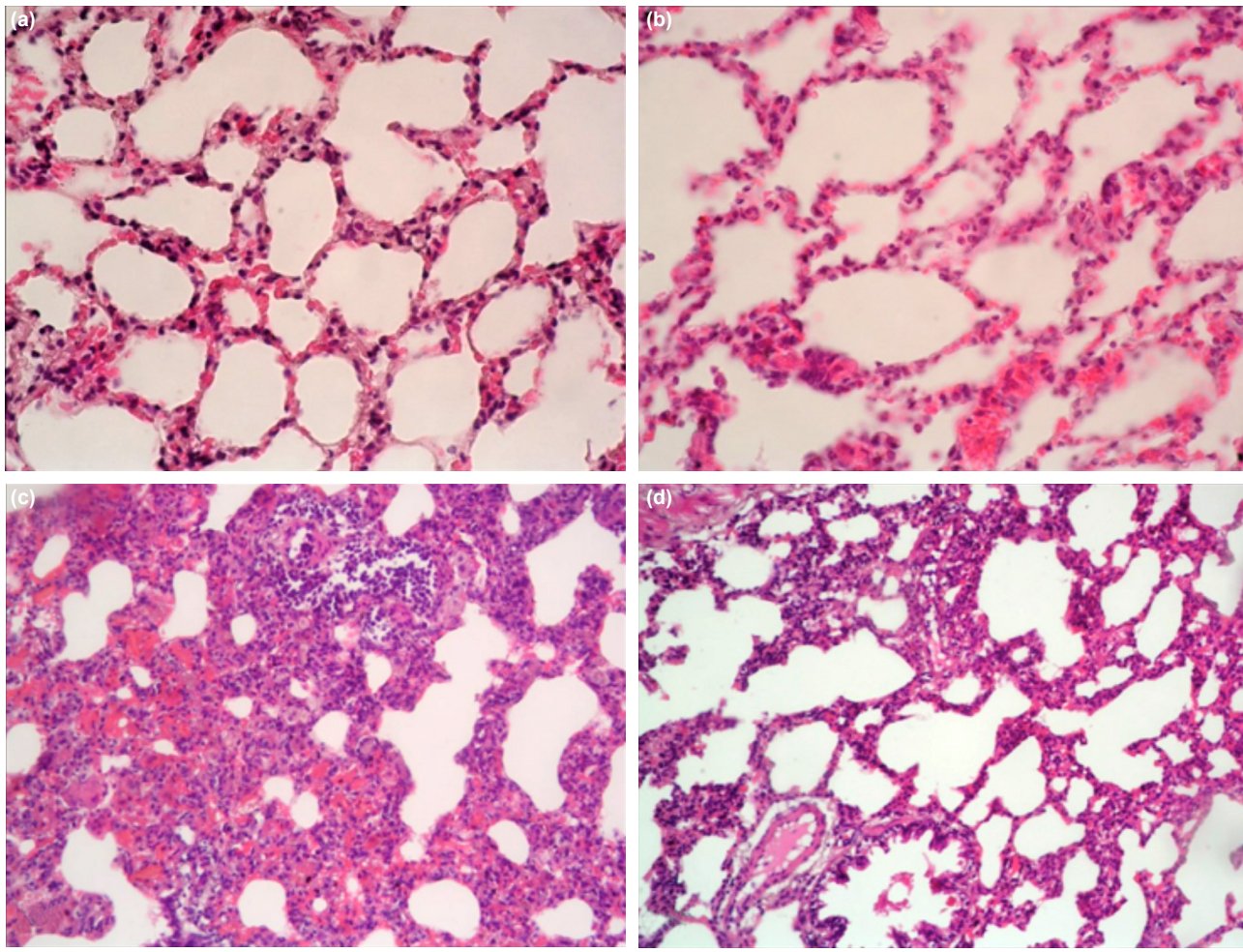

Figure 1. Lung tissue. Hematoxylin and eosin stain, ×20. **(a)** Control group, normal alveolar and interstitial structure, **(b)** sham-operated group, normal alveolar and interstitial structure, **(c)** CLP group, inflammatory cell infiltration in alveolar and interstitial area as well as edema, bleeding, **(d)** CLP and octreotide group, decreased inflammatory cell infiltration in alveolar and interstitial area as well as edema, bleeding. CLP: Cecal ligation and puncture.

Table 1. Histopathological lung damage was assessed by scoring AC, H, infiltration or AL, PE, and TA

	AC	H	AL	PE	TA
Control group	0.3±0.2	0.5±0.2	0.16±0.16	0.3±0.21	0.3±0.21
Sham-operated group	0.83±0.16	1.6±0.2	0.6±0.2	0.8±0.1	0.1±0.1
CLP group	3.3±0.5*	2.8±0.7*	3.3±0.8*	3.1±0.9*	2.3±0.8*
CLP and octreotide	1.6±0.1#	1.5±0.2#	0.6±0.1##	0.9±0.3##	1.8±0.4#

AC: Alveolar congestion; H: Hemorrhage; AL: Aggregation of leukocytes in air spaces/vessel walls; PE: Perivascular/interstitial edema; TA: Thickness of the alveolar wall/hyARDSne membrane formation; CLP: Cecal ligation and puncture. The severity for each item was graded as 1 (0–25%), 2 (25–50%), 3 (50–75%), and 4 (75–100%) *p<0.001, compared with control group or sham-operated group #p<0.05, compared with CLP group ##p<0.001, compared with CLP group.

Table 2. Blood gas analysis in all groups

	Control group	Sham-operated group	CLP group	CLP and octreotide
PaO_2 (mmHg)	97.2±5.06	93.1±6.27	47.61±7.57*	79.23±5.8#
$PaCO_2$ (mmHg)	35.16±0.9	37.5±1.98	48.5±4.14*	39.67±2.3#
PaO_2/FiO_2***	462.85±24.09	443.33±29.85	226.71±36.04*	377.28±27.6#
Lac (mmol/L)	0.7±0.2	0.9±0.1	2.2±0.6*	1.1±0.3#

***Breathing air (FiO_2) was accepted as 0.21. *P<0.05, compared with control group or sham-operated group **p<0.001, compared with control group or sham-operated group #p<0.05, compared with CLP group. CLP: Cecal ligation and puncture.

am-operated group and control group, the significant difference between controls and sham groups of the CLP group indicates that sepsis model was established and lung injury started among treated group. When CLP and octreotide groups were compared with CLP group, it was observed that there was a significant change in favor of healing and that they almost came up to controls and sham group (Table 2).

DISCUSSION

Mortality and morbidity in sepsis are still one of the major health problems. Early diagnosis and treatment are important for minimizing mortality and morbidity. The initiation of supportive therapy, which is described as an early targeted treatment (in ICU or in emergency room), is the most important treatment approach that reduces mortality and morbidity, except antibiotherapy.[8–10]

Lung damage is the most common mortality cause and the most common organ which is affected in sepsis. ARDS is a clinical syndrome characterized by hypoxia and pulmonary injury. In this syndrome, the pulmonary barrier is disrupted; permeability, inflammation, cellular infiltration, and exudation are increased; necrosis has occurred; and as a result, ventilation perfusion is disrupted. In 2012, Berlin criteria to define ARDS were published. In this context, according to the degree of ARDS hypoxia; subgroups such as mild (PaO_2/FiO_2 = 200–300 mmHg), moderate (PaO_2/FiO_2 = 100–200 mmHg), and heavy (PaO_2/FiO_2 <100 mmHg) were established.[11]

In our study, PaO_2/FiO_2 values of rats were normal among controls and operated sham groups, whereas mild form was formed in CLP group (PaO_2/FiO_2 = 226.71±36.04 mmHg). In addition, the octreotide-treated rats were found to have a PaO_2/FiO_2 value close to controls and operated sham group, but significantly improved compared to the CLP group.

For now, we observe that lungs are the first organ affected by immunomodulators after sepsis. This process often results with ARDS. In patients with sepsis, many free oxygen radicals are secreted from activated immune system cells; this causes oxidative damage to the body. Therefore, it is stated that it has an important place in the treatment of sepsis in protecting from oxidative damage.[12,13] Many treatments have been conducted to prevent ARDS in sepsis; and they are still underway. However, for some of these therapies, a clear result has been reached; while for others, it has not.

In the study of McAuley et al.,[14] the effect of the use of statins for ARDS after sepsis on the clinic was examined and it was not clear whether the patient's prognosis had changed. Alhazzani et al.[15] reported that statins were not suitable for the use of ARDS after sepsis and did not have an impact on prognosis, and additional studies were required for clearer results. In the study of Kruger and Terblanche,[16] statins were tried as treatment but no clear benefit was found on prognosis. As statins have antioxidant and anti-inflammatory effect,[15] future studies may show that peptides and statins are superior to each other on this issue.

Many studies have been conducted in the literature regarding the role of platelets on sepsis and ARDS and are still underway. Toner et al.'s[17] study also investigated the effect of aspirin on prognosis in patients with sepsis and ARDS, and stated that they've made observational analysis that it might be useful. In the study of Das,[18] it was found that the administration of essential fatty acids with aspirin increased gas exchange in patients with septic ARDS; thus, it decreases the time to connect to the mechanic ventilator and stay in the intensive care unit. In the study of Gordon et al.,[19] the effect of ibuprofen on sepsis and ARDS was investigated; and they stated that ibuprofen prevents fever, tachypnea, tachycardia, lactic acidosis, and hypoxemia, thus prevents the deterioration of prognosis in patients with sepsis; but all of this study's do not affect mortality and organ failure. Information about octreotide mortality and healing process in ARDS is almost non-existent. Future studies will clarify these issues.

Lactate is an important indicator for the deterioration of oxygenation and predicting mortality according to many studies in the literature. In addition, it has been shown in the literature that the release of lactate from damaged organs directly shows damage.[20,21] Pulmonary lactate release in patients with ARDS is associated with the severity of lung injury. When interpreting lactate levels related to systemic hypoxia in arterial blood gas; the effect of pulmonary lactate release should also be considered. Dettmer et al.[22] reported that lactate increased secondary to lung damage in patients with ARDS. Moussa et al.'s[23] study also showed that the most serious damage is direct release of lactate from the organ.

There are also studies showing that ARDS is associated with mortality in increasing lactate levels. In a study conducted by Kamo et al.[6] on the significance of lactate levels in ARDS patients, it was shown that increased lactate levels in blood gas were associated with mortality. In our study; we found that lactate levels increased compared to the other groups and this situation created the ARDS model in sepsis; that it was higher for CLP group compared to controls and operative sham group; that lactate levels in octreotide group were almost similar to controls and operated sham groups and this improvement was statistically significant.

Many studies have shown that SST is secreted during inflammation and suppresses inflammation. The fact that SST is short acting and requires IV infusion creates difficulty for treatment.[24,25] In an experimental study in which SST and N-acetyl cysteine were used together, Ferrer et al.[3] showed that they had protective effect against multiple organ failure caused by oxidative stress in intestinal ischemia.

OCT is also one of the peptides that are being studied to reduce the immunomodulators and resulting oxygen radicals and inhibits their effects in sepsis and sepsis-induced ARDS.[5,26] In a study by Sener et al.,[27] it was shown that octreotide relieves sepsis-induced oxidative stress in pelvic and ovarian sepsis conditions. Moosmann and Behl[28] reported that peptide hormones may act as antioxidants. Paran et al.[29] reported that they administered octreotide to patients with acute pancreatitis; and that the rate of ARDS and sepsis and the duration of hospital stay of octreotide-administered patients have decreased. The study by Fiedler et al.[30] showed that octreotide treatment in patients with necrotizing pancreatitis reduces the ARDS rate and mortality. In the study of Czakó et al.,[31] octreotide administration in patients with acute pancreatitis was shown to reduce oxygen radicals and antioxidant effect.[32] Moreover, Huang et al.[33] compared hemofiltration treatment with hemofiltration + octreotide in patients with acute pancreatitis with ARDS complication, they observe that hemofiltration plus octreotide group improves clinically about lung injury similar to our study.

In our study, lung contusion, bleeding, leukocyte aggregation into the alveoli, perivascular edema, and thinness of the alveolar wall of octreotide treatment group were significantly less compared to the group without treatment. It was observed that lung damage was decreased histologically, PaO_2 value was increased, and $PaCO_2$ value was reduced in octreotide-treated rats with sepsis compared to non-treated peers. In the study of Liu et al.[34] use of somatostatin improves histopathologically lung injury similarly to our study.

Conclusion

OCT is an peptide which has various properties like an antioxidant which reduces inflammation and induces apoptosis and secretion of anti-inflammatory agents. Replication of these findings in preclinical and clinical human populations might provide huge innovations and directions to classical treatment options that target the prevention of lung injury. There is considerable value in the current study since it has shown these benefits at the histological, biochemical levels in octreotide-administered group. We think that the use of octreotide in the pre-treatment of sepsis in emergency room in patients will decrease the ARDS rate, the mortality and morbidity.

Ethics Committee Approval: This study was approved by the Ege University Faculty of Medicine Animal Experimental Ethics Committee (Date: 16.04.2018, Decision No: 25180416).

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Authorship Contributions: Concept: S.E.B., O.E.; Design: S.E.B., O.E.; Supervision: S.E.B., O.E.; Materials: A.E.; Data: A.E.; Analysis: M.A.E., G.Y.; Literature search: A.Ç.; Writing: A.Ç.; Critical revision: S.E.B., A.E., M.A.E., G.Y., A.Ç., O.E.

Conflict of Interest: None declared.

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REFERENCES

1. Nguyen HB, Rivers EP, Abrahamian FM, Moran GJ, Abraham E, Trzeciak S, et al. Severe sepsis and septic shock: Review of the literature and emergency department management guidelines. Ann Emerg Med 2006;48:28–54. [CrossRef]
2. Tang C, Lan C, Wang C, Liu R. Amelioration of the development of multiple organ dysfunction syndromeby somatostatin via suppression of intestinal mucosalmast cells. Shock 2005;3:470–5. [CrossRef]
3. Ferrer JV, AricetaJ, Guerrero D, Balen E, Herrera J, Lera JM. Prevention by somatostatine and N-acetlycisteine of multiorgan failure mediated by oxidativestressafterintestinal ischemia. Transplant Proc 1999;31:2570–1. [CrossRef]
4. Marik PE. Vitamin C for the Treatment of Sepsis: The scientific rationale. Pharmacol Ther 2018;189:63–70. [CrossRef]
5. Kaçmaz A, Polat A, User Y, Tilki M, Ozkan S, S¸ener G. Octreotide improves reperfusion-induced oxidative injury in acute abdominal hypertension in rats. J Gastrointest Surg 2004;8:113–9. [CrossRef]
6. Kamo T, Tasaka S, Suzuki T, Asakura T, Suzuki S, Yagi K, et al. Prognostic values of the Berlin definition criteria, blood lactate level, and fibroproliferative changes on high-resolution computed tomography in ARDS patients. BMC Pulm Med 2019;19:37. [CrossRef]
7. Erbas O, Taskiran D. Sepsis-induced changes in behavioral stereotypy in rats; involvement of tumor necrosis factor-alpha, oxidative stress, and dopamine turnover. J Surg Res 2014;186:262–8. [CrossRef]
8. Kwon WY, Suh GJ, Kim KS, Kwak YH. Niacin attenuates lung inflammation and improves survival during sepsis by downregulating the nuclear factor-κB pathway. Crit Care Med 2011;39:328–34. [CrossRef]
9. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 2003;31:1250–6. [CrossRef]
10. Martin GS, Mannino DM, Eaton S, Moss M.M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546–54. [CrossRef]
11. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: The Berlin definition. JAMA 2012;307:2526–33. [CrossRef]
12. Goode HF, Webster NR. Free radicals and anitioxidants in sepsis. Crit Care Med 1993;21:1770–6. [CrossRef]
13. Crimi E, Sica V, Slutsky AS, Zhang H, Williams-Ignarro S, Ignarro LJ, et al. Role of oxidative stress in experimental sepsis and multisystem organ dysfunction. Free Radic Res 2006;40:665–72. [CrossRef]
14. McAuley D, Charles PE, Papazian L. Statins in patients with sepsis and ARDS: Is it over? We are not sure. Intensive Care Med 2017;43:677–9.
15. Alhazzani W, Truwit J. Statins in patients with sepsis and ARDS: İs it over? Yes. Intensive Care Med 2017;43:672–4. [CrossRef]
16. Kruger PS, Terblanche M. Statins in patients with sepsis and ARDS: İs it over? No. Intensive Care Med 2017;43:675–6.
17. Toner P, McAuley DF, Shyamsundar M. Aspirin as a potential treatment in sepsis or acute respiratory distress syndrome. Crit Care 2015;19:374.
18. Das UN. Combination of aspirin with essential fatty acids is superior to aspirin alone to prevent or ameliorate sepsis or ARDS. Lipids Health Dis 2016;15:206. [CrossRef]
19. Gordon RB, Arthur PW, James AR, Roland S, Warren RS, Kenneth PS, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. N Engl J Med 1997;336:912–8. [CrossRef]
20. Wu WH, Niu YY, Zhang CR, Xiao LB, Ye HS, Pan DM, et al. Combined APACH II score and arterial blood lactate clearance rate to predict the prognosis of ARDS patients. Asian Pac J Trop Med 2012;5:656–60.
21. Iscra F, Gullo A, Biolo G. Bench-to-bedside review: Lactate and the lung. Crit Care 2002;6:327–9. [CrossRef]
22. Dettmer MR, Mohr NM, Fuller BM. Sepsis-associated pulmonary complications in emergency department patients monitored with serial lactate: An observational cohort study. J Crit Care 2015;30:1163–8. [CrossRef]
23. Moussa MD, Santonocito C, Fagnoul D, Donadello K, Pradier O, Gaussem P, et al. evaluation of endothelial damage in sepsis-related ARDS using circulating endothelial cells. Intensive Care Med 2015;41:231–8.
24. Chan MM, Chan MM, Mengshol JA, Fish DN, Chan ED. Octreotide: a drug often used in the critical care setting but not well understood. Chest 2013;144:1937–45. [CrossRef]
25. Seboek D, Linscheid P, Zulewski H, Langer I, Christ-Crain M, Keller U, et al. Somatostatin is expressed and secreted by human adipose tissue upon infection and inflammation. J Clin Endocrinol Metab 2004;89:4833–9. [CrossRef]
26. Kaçmaz A, Polat A, User Y, Tilki M, Ozkan S, Sener G. Octreotide: A new approach to the management of acute abdominal hypertension. Peptides 2003;24:1381–6. [CrossRef]
27. Sener G, Cetinel S, Erkanli G, Gedik N, Yeğen BC. Octreotide ameliorates sepsis-induced pelvic inflammation in female rats by a neutrophil-dependent mechanism. Peptides 2005;26:493–9. [CrossRef]
28. Moosmann B, Behl C. Secretory peptide hormones are biochemical antioxidants: Structure-activity relationship. Mol Pharmacol 2002;61:260–8. [CrossRef]
29. Paran H, Mayo A, Paran D, Neufeld D, shwarts I, Zissin R, et al. Octreotide treatment in patients with severe acute pancreatitis. Dig Dis Sci 2000;45:2247–51. [CrossRef]
30. Fiedler F, JaureingG, Keim V, Richter A, Bender HJ. Octreotide treatment in patients with necrotizing pancreatitis and pulmonary failure. İntensive Care Med 1996;22:909–15. [CrossRef]
31. Czakó L, Hegyi P, Takács T, Góg C, Farkas A, Mándy Y, et al. Effects of octreotide on acute necrotizing pancreatitis in rabbits. World J Gastroenterol 2004;10 2082–6. [CrossRef]
32. Zhang X, Feng G, Weng W, Liang J, Lin N, Cai Y, et al. Protective effects of baicalin and octreotide on intestinal mucosa of rats with severe acute pancreatitis. Turk J Gastroenterol 2009;20:108–15.
33. Huang L, Zhu H, Gu J. Octreotide and continuous hemofiltration versus continuous hemofiltration alone in severe acute pancreatitis complicated with acute respiratory distress syndrome. J Coll Physicians Surg Pak 2019;29:758–87. [CrossRef]
34. Liu R, Wang CH, Huang MH, Li X, Qiang O, Tang CW. Therapeutic effect of somatostatin on acute respiratory distress syndrome in experimental rats. [Article in Chinese]. Sichuan Da Xue Xue Bao Yi Xue Ban 2006;37:412–5.

DENEYSEL ÇALIŞMA - *ÖZ*

Oktreotidin, sepsis modelinde sıçanların akciğerleri üzerindeki kısa dönem koruyucu etkisi

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AMAÇ: Akut solunum sıkıntısı sendromu (ARDS), sepsisin yıkıcı bir komplikasyonudur. Preklinik modeller, doğrudan akciğer hasarının, akciğer epiteline saldırı ile başladığını, ancak dolaylı akciğer hasarının, enflamatuvar mediatörlere bağlı sistemik endotel hasarından kaynaklandığını göstermektedir. Bu çalışmanın amacı, farelerde cerrahi olarak indüklenen sepsis modelinde oktreotidin akciğerler üzerindeki etkisini araştırmaktır.

GEREÇ VE YÖNTEM: Çalışmada 32 erkek Sprague Dawley sıçan kullanıldı ve 4 gruba ayrıldı. Grup 1: normal (opere olmayan ve oral yoldan kontrol, n=8); Grup 2: sham operasyonlu (n=8); Grup 3: CLP (tedavi edilmemiş grup, n=8); Grup 4: CLP ve 100 µg/kg oktreotid i.p. (n=8). Sepsis için, sepsis modelini indüklemek için 16 sıçanda çekal ligasyon ve ponksiyon (CLP) prosedürü uygulandı. Tüm gruplar analiz edildi, kanları arteriyel kan gazı analizi için alındı. Histolojik inceleme için akciğer dokuları çıkarıldı ve parçalar hazırlandı.

BULGULAR: Histololojik incelemede CLP+Octreotid'i sadece CLP grubu ile karşılaştırırsak, CLP+Octreotid grubunda alveoler ve interstisyel alanda enflamatuvar hücrelerin infiltrasyonu azaldı, CLP grubu oktreotid grubuyla karşılaştırıldığında, ödem, kanama azaldı ve tüm histopatolojik parametreler anlamlı olarak geriledi ve ciddiyet indeksi 3'ten 1'e düştü. Arteriyel kan gazı için, CLP ve oktreotide grubu CLP grubuyla karşılaştırıldığında, iyileşme lehine anlamlı bir değişiklik olduğu ve neredeyse kontrol grubu ve sham grubuna yaklaştığı görülmüştür.

TARTIŞMA: Sonuç olarak, sepsis hastalarında akut akciğer hasarı durumu için oktreotid uygulamasının yararlı olacağı düşünülülebilir.

Anahtar sözcükler: Akut respiratuvar distres sendromu; histopatoloji; oktreotid; sepsis.

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