

Protective Role of Octreotide in Acute and Chronic Lung Injuries

Abstract

Background: The treatment of acute respiratory distress syndrome (ARDS) has been the prominent concern in the clinic. Special attentions have been made to investigate the pathophysiological and pharmacological aspects of acute and chronic lung injuries. Appropriate drug treatment is the first priority in the treatment process of this disease. The aim of this study was to investigate the effects of octreotide (OCT), a somatostatin analog, on the models of acute and chronic lung injuries. **Methods:** Two models of acute and chronic lung injuries were performed by intratracheal injection of hydrochloric acid, and four groups were investigated for each model including sham control, octreotide alone, lung injury, and lung injury treated with OCT. In each group, systolic and diastolic blood pressures were measured directly, and blood cell counts, including red, white, and immune cells, were determined. The severity of lung injury was considered by lung tissue histology and arterial blood gas parameters. The function of kidneys as distance organs also was considered by the determination of biochemical parameters. **Results:** The results indicated that OCT potentially can improve blood pressure and blood cell parameters. The arterial blood gas indicators and histological lung scores were also improved by OCT in both models of acute and chronic lung injuries. **Conclusions:** OCT had multiple effects, such as the inhibition of immune cell infiltration storm, which can reduce acute and chronic lung injuries in rats. These data suggest that OCT should be considered as a therapeutic drug for lung injuries.

Keywords: Blood pressure, kidney function, lung injury, octreotide

Introduction

Lung injury is one of the most common clinical diseases, which is accompanied by a high mortality rate. The crisis of respiratory distress in COVID-19^[1,2] compelled researchers to make more efforts to find the pathophysiological mechanisms and newly forceful drugs to salvage patients.^[3] Acute lung injury (ALI) and chronic lung injury (CLI) are the two subtypes with different features of respiratory dysfunction. The mortality rate of ALI has been reported between 30% and 50%, and unfortunately, it increases up to 80% when combined with acute kidney failure.^[4] Lung fibrosis is prevalent after ALI and the incidence of fibrosis after the COVID-19 crisis was reported as 54%.^[5] Experimentally, fibrosis was observed on the 14th day after the induction of CLI in an animal model by intratracheal injection of hydrochloric acid (HCL).^[6]

Reportedly, some mechanisms have been explained about ALI, including

alveolo-vascular disturbance, inflammation, apoptosis, pulmonary edema, hypoxemia, and subsequently multiple organ failure, especially the kidneys.^[2] So, for CLI or lung fibrosis, the secretion of some fibrotic factors and excessive proliferation of pneumocyte II cells, fibroblasts, myofibroblasts, and the accumulation of collagens around the alveolar vasculature of lung tissues, which restrict the function of the respiratory system.^[7]

Octreotide (OCT), a somatostatin analog, has a high affinity for binding to the somatostatin subtype receptor 2 (SSTR₂) and induces different functions^[8,9] such as inhibiting macrophages (phagocytic cells derived from monocytes), reducing the production of some angiogenesis factors, reducing tissue growth hormones such as tissue growth factor (TGF- β), and reducing the activity of fibroblast cells.^[10,11] Although many effects of OCT have been defined, there are many questions about different aspects of it. OCT has different effects including the inhibition of immune cells in pulmonary fibrosis,^[10-12] anti-inflammatory effects,^[13] increasing endogenous antioxidants,^[14]

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and anti-hypersecretion.^[15] However, the effects of OCT on hemodynamic parameters, some blood parameters, and kidney functions in lung injury models are still ambiguous.

The incidence of poisoning with HCL is prevalent,^[16] and the intratracheal injection of it as a model of lung injury was selected for analyzing^[6,17] acute and chronic direct lung injuries^[6,18,19] and evaluating OCT effects. It is also necessary to mention that some controversial effects of OCT have been reported including increasing^[20] or decreasing blood pressure^[21-23] and decreasing glomerular filtration rate (GFR).^[24] Different results also indicated that OCT had no effect on the mortality rate of diabetic rats.^[25] Others have also reported that OCT is accompanied by decreasing^[15,26,27] or unchanged^[28,29] mortality rates. Accordingly, we designed this study to evaluate the effects of OCT on some indicators in the two models of lung injuries in rats.

Materials and Methods

Animals

In total, 71 male Wistar rats (240 ± 20 g) were used in this study. The animals were obtained from the animal house of the Pharmacy School, Isfahan University of Medical Sciences, that were entered to study after a 1-week adaptation in our laboratory animal room with appropriate temperature and humidity, and a 12/12 light–dark cycle. The animals had free access to food and water. The procedure of this research was confirmed by the Ethics Committee of Isfahan University of Medical Sciences (Code #: IR.MUI.AEC.1401.043).

Experimental groups

After the acclimatization of rats in the animal room, they were assigned into eight groups; four groups for each model of acute and chronic conditions. For the acute model, the groups included:

Sham control group (AC, $n = 7$): The animals received intratracheally injection of saline, and they intraperitoneally achieved saline for 2 days after intratracheal injection.

OCT group (AD, $n = 8$): The animals received intratracheal injection of saline, and they intraperitoneally achieved OCT for 2 days after intratracheal injection.

Acute lung injury group (ALI, $n = 13$): The animals received intratracheal injection of HCL, and they intraperitoneally achieved saline for 2 days after intratracheal injection.

Acute lung injury treated with OCT group (ALI+OCT, $n = 9$): The animals received intratracheal injection of HCL, they intraperitoneally achieved OCT for 2 days after intratracheal injection.

For the chronic model, the groups included:

Sham control group (CC, $n = 8$): The animals received an intratracheal injection of saline, and 14 days after injection they intraperitoneally achieved saline for 7 days.

OCT group (CD, $n = 7$): The animals received intratracheally injection of saline, and 14 days after injection they intraperitoneally achieved OCT for 7 days.

Chronic lung injury group (CLI, $n = 9$): The animals received an intratracheal injection of HCL, and 14 days after injection they intraperitoneally achieved saline for 7 days.

Chronic lung injury treated with OCT group (CLI+OCT, $n = 10$): The animals received an intratracheal injection of HCL, and 14 days after injection, they intraperitoneally achieved OCT for 7 days.

Materials

The materials used in this study were including OCT acetate (Sandostatin® 50 µg/mL Caspian Tamin, Iran), ketamine (Alfasan Inc., Utrecht, Holland) and xylazine (Hoogstraten, België), HCL (37% w/v (Merck KGaA; 64271 Darmstadt, Germany), heparin sodium ampoule 5000 IU/mL (Darou Pakhsh, Iran), sampler tip (Alfalab, Iran), feeding tube (Supa, Iran), and polyethylene catheter (PE9658 Microtube Extrusions; Australia).

Induction of models

For the induction of acute and chronic lung injury models, HCL was used. Primarily, 1 mL of HCL was solubilized with 115.5 mL of distilled water to obtain 0.1 normal HCL (pH = 1). Then, 1.2 mL/kg diluted HCL was injected intratracheally after endotracheal intubation. Hygiene methods were done during the intubation or intratracheal injection, such as using disinfected devices with alcohol or using sterile saline. The intubation procedure was performed as follows. First, approximately 1 cm of the apex of the yellow sampler tip was cut, and the red feeding tube was cut to be 15 cm in length. Then, 1 cm from the end of the sampler tip was placed in hot water and curved to approximately 30 degrees. For intratracheal injection, rats were anesthetized with ketamine (70 mg/kg), and xylazine (5 mg/kg), and the animal was placed on a flat and vertical position by hooking the teeth on a wire. Under the pelvis of rats, a box was placed to prevent tracheal traction [Figure 1].

A pad with a diameter of 1 cm was placed under the rat's chest to extend its head and neck. In this position, the curved sampler tip was inserted into the pharynx, and the feeding tube was inserted into it. If the position of the sampler tip was suitable, the tube would enter the trachea. To confirm the endotracheal intubation, 2 mL of air volume with a syringe was pushed into and emptied from the tube rapidly and alternately. In this condition, the movement of the chest and the syringe must be simultaneous. Then, oxygenation was performed by putting the canola of oxygen near the nose for 5 min for spontaneous respiration of oxygen before and after endotracheal intubation. Immediately after the intratracheal injection of HCL or saline, 2 to 4 mL of air volume with a syringe must

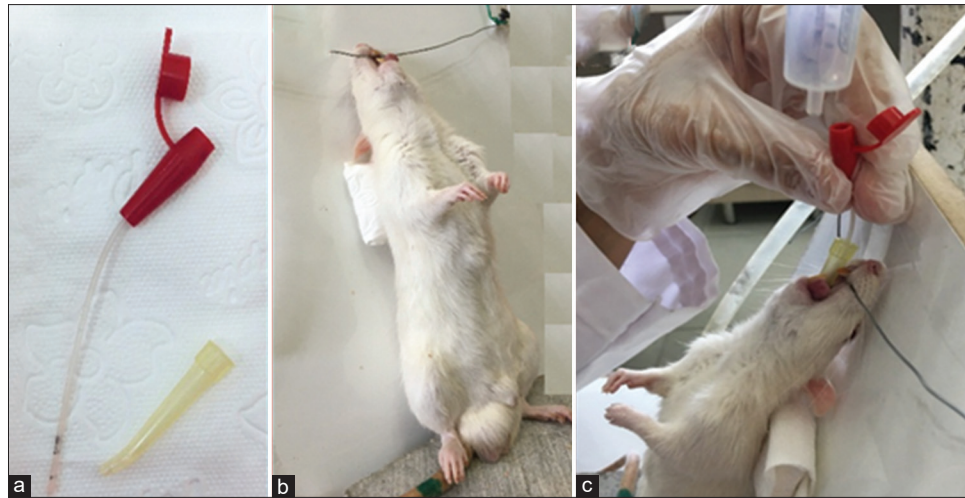


Figure 1: Tracheal intubation methods and materials. a: Red feeding tube and curved yellow sampler tip. b: Position of intubated rat. c: Endotracheal intubated rat

intermittently be injected into the tracheal tube for 1 min for the prevention of bronchospasm and death. After intratracheal injection, the animals were divided randomly into acute and chronic model groups.

Acute and chronic model groups

For the acute model, on the first day, 2 h after intratracheal injection, saline (0.5 mL) or OCT (100 µg/kg) was injected intraperitoneally and repeated on the second day. The animals were examined on the third day. For the chronic model, saline (0.5 mL) or OCT (100 µg/kg) was injected intraperitoneally from the 14th day after intratracheal injection to the 20th day, and the animals were examined on the 21st day.^[6,17]

Examinations

On the morning of the examination day, the rat was placed in the metabolic cage for 4 h to collect the urine volume without water restriction. Then, the animal was anesthetized with 70 mg/kg ketamine and 5 mg/kg xylazine, based on other studies about lung injury.^[30,31] Then, the following procedures were carried out.

1. Blood Pressure Measurements: After cannulation of trachea (for facilitate oxygenation), the carotid artery was catheterized for blood pressure measurement. An arterial catheter was inserted into the left carotid artery and connected to the bridge amplifier of the Power Lab System (Scientific Concepts, Melbourne, Australia).^[32] After the stabilization of blood pressure, 3 min was considered for recording the hemodynamic parameters including the mean arterial pressure ($MAP = \frac{SP + 2DP}{3}$), systolic pressure (SP), diastolic pressure (DP), and pulse pressure (PP = SP – DP).

2. Arterial Blood Gas Analysis: Two blood samples were taken from the arterial catheter with a heparinized

syringe, at the spontaneous breathing of atmospheric oxygen and 5 min after breathing of 100% oxygen, and they were immediately placed on ice. Measurement parameters including pH, partial pressure of carbon dioxide (PaCO₂), partial pressure of oxygen in the laboratory air-breathing (PaO₂:laboratory), partial pressure of oxygen after 5 min the breathing of 100% oxygen (PaO₂:FiO₂_{100%}), oxygen saturation in the laboratory air-breathing (SaO₂:laboratory) and oxygen saturation after 5 min the breathing of 100% oxygen (SaO₂:FiO₂_{100%}). To measure the above-mentioned parameters, the samples were kept on ice and transferred to the Alzahra Hospital rapidly and analyzed using an automated blood gas analyzer AVL 995-Hb.^[33]

3. Blood Cells, Prothrombin Time, Fibrinogen, and Renal Function Parameters: Under the maintenance of anesthesia, three blood samples were collected to measure prothrombin time (PT), fibrinogen, blood urea nitrogen (BUN), serum creatinine (Cr) and blood cell parameters. Blood cell parameters, such as red blood cell (RBC), hemoglobin (Hb), hematocrit (Hct), white blood cell (WBC), neutrophil (Neut), lymphocyte (Lymph), monocyte (Mono), eosinophil (Eos), basophil (Bas) and platelet (Plt) were measured in the laboratory with Mindray BC 6800 automated hematology analyzer focusing flow-DC method.^[34] PT and fibrinogen were measured by an automated blood coagulation analyzer (CN-3000, Sysmex Corporation, Kobe, Japan) with analytical kits (PT-Phen, HYPHEN BioMed, and FIBRIPHENTM HYPHEN BioMed, Neuville-sur-Oise, France).^[35,36] The Delayed time between sample taking and its transfer to tubes was lower than 45 s for preventing blood clot formation. BUN and Cr were analyzed with BS-2000 Mindray (Shenzhen Mindray Bio-Medical Electronics Co. Ltd., China) using enzymatic glutamate-dehydrogenase kits (Frasmad Persian Company).^[37,38]

4. Urine Volume Collection: All the animals were kept in metabolic cages for 4 h to obtain the urine volume (UV) for the determination of Cr clearance with the formulation of

$$\text{Cr clearance} = \frac{\text{Urine Cr} \times \text{UV}}{\text{Sertum Cr}}$$

5. Histological Lung Score and Tissue Water Content: After euthanasia under ketamine administration,^[39] the lungs were extracted. The upper lobe of the right lung was secluded, weighed, and stored in an oven at 60°C for 4 days, and the dry weight was measured. So, the wet/dry ratio was achieved. The lower lobe of the right lung of the acute model groups and the middle lobe of the right lung of the chronic model groups were placed in 10% formalin. They were cross-sectioned at 5 µm and all of them were stained with hematoxylin and eosin (H and E); moreover, for chronic model groups, Mason's trichrome staining also was used. Micrographs at ×100 and ×400 were evaluated from five fields of view per section in the light microscope (Olympus CX21, China).^[40,41]

Histological parameters were quantified by two pathologists who were blinded to the study. In the acute model groups, the H and E scoring was evaluated based on five parameters including Neut infiltration, acute vasculitis (accumulated Neut in vessel walls), interstitial edema, alveolar edema, or hemorrhage and alveolar macrophages, with grades of 0 to 4 for intensity as well as 0 to 4 for the diffusion of injury in visible fields. These grades were multiplied together to obtain the final score of each parameter from 0 to 16. In chronic model groups, the H and E scoring was evaluated based on two parameters including lymph infiltration and chronic vasculitis (accumulated lymph in the vessel walls), and the Mason trichrome scoring was depended on two parameters including interstitial macrophages and alveolar septal thickening, with a scale of 0 to 16 for each parameter.

Statistical analyses

All statistical analyses were performed with SPSS.22 software. The data were reported as mean ± standard error. The data of each model were compared with its own groups via one-way analysis of variance (ANOVA), followed by an least significant difference (LSD) post-hoc test. Both one-way ANOVA followed by LSD post-hoc test and repeated measure ANOVA analyses were applied for PaO₂ and SaO₂, pre and post-100% FiO₂ administration. Non-parametric data were compared to the Kruskal–Wallis test, followed by the Mann–Whitney post-hoc test. *P* values less than 0.05 (*P*<0.05) were considered as statistically significant.

Results

Hemodynamic Parameters: MAP, SP, and DP were significantly lower in ALI (*P* < 0.001) and in CLI (*P* < 0.001) groups. PP was significantly lower in ALI (*P* < 0.001) compared to the others. It was higher in

ALI+OCT compared to the ALI (*P* < 0.001) group and was lower compared to the AD (*P* = 0.005) group. There were no significant differences in PP in chronic model groups [Figure 2].

Kidney Function Parameters: In the acute model, no significant differences in BUN and Cr levels were observed among the groups. However, Cr clearance (*P* < 0.001) was significantly lower in ALI and ALI+OCT than the other groups, and UV (*P* < 0.001) was significantly lower in the ALI group [Figure 3]. Urea Cr was not different in the groups (*P* = 0.09).

In the chronic model, the level of BUN (*P* = 0.02) and Cr (*P* = 0.002) were increased in CC and CLI groups compared to CD and CLI+OCT groups, and Cr clearance was decreased (*P* = 0.002) in the CLI group compared to the others [Figure 3].

Arterial Blood Gas Indexes: The results of arterial blood gas indexes of acute and chronic models are demonstrated in Table 1. In the acute model groups, pH, PaO₂ and SaO₂ were significantly lower in the ALI group and PaCO₂ was significantly lower in the ALI+OCT group compared to the ALI group. In chronic model groups, PaO₂ and SaO₂ were significantly lower in the CLI group compared to the others. The results of CLI+OCT and ALI+OCT groups showed an improvement in lung injury.

The results indicated lower PaO₂:laboratory and PaO₂:FiO₂_{2100%} in ALI (*P* < 0.001) compared to the others, also lower PaO₂:FiO₂_{2100%} was shown in the CLI group (*P* = 0.001) compared to the other groups. In the acute model of lung injury, repeated measure ANOVA indicated lower PaO₂ and SaO₂ in the ALI group compared to other groups (*P*_{time} < 0.001, *P*_{time*group} = 0.827, *P*_{group} < 0.001). In the chronic model groups, the CLI group had the lowest rising of PaO₂ or the significantly weak response to FiO₂_{2100%} compared to the others (*P*_{time} < 0.001, *P*_{time*group} = 0.001, *P*_{group} = 0.002).

Blood Cell parameters, Prothrombin Time (PT), and Fibrinogen: The data for blood cells, PT, and fibrinogen levels, accompanied by statistical analyses, are presented in Table 2. In acute model groups, significantly higher RBC (*P* = 0.002), Hb (*P* = 0.001), Hct (*P* < 0.001), Plt (*P* = 0.002), and fibrinogen (*P* < 0.001) in ALI and ALI+OCT groups were observed, and the significant higher WBC (*P* = 0.06), Neut (*P* = 0.005), and fibrinogen (*P* < 0.001) were observed in the ALI group. The significantly lower Eos in the ALI+OCT and AD groups and higher in the ALI group were observed compared to the others (*P* = 0.009). Plt was significantly lower in the AD group compared to the others (*P* < 0.05). In chronic model groups, there was only a significantly higher Mono in the CLI group compared to the others (*P* = 0.02).

Lung water content: Analyses of the wet/dry ratio in Figure 4 showed a significant increase in the ALI

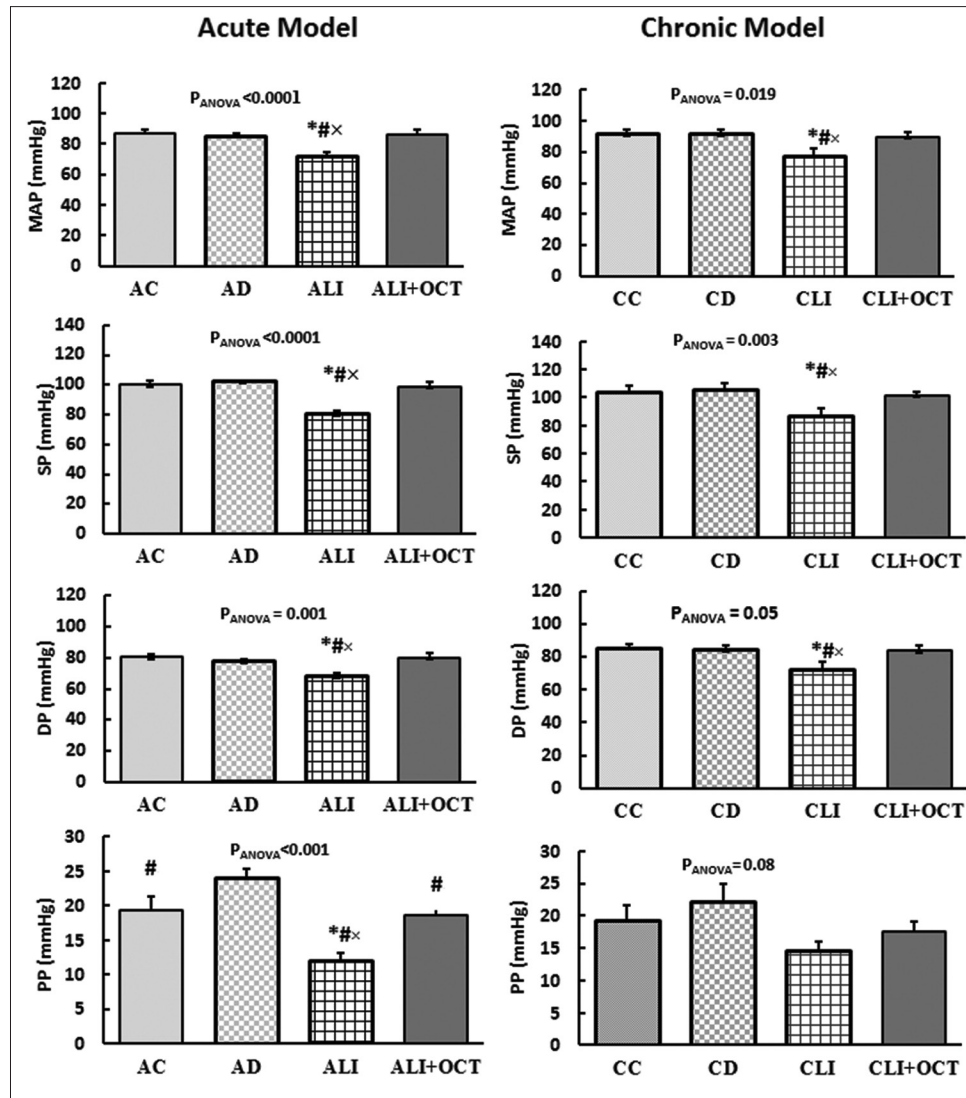


Figure 2: The mean arterial pressure (MAP), systolic pressure (SP), diastolic pressure (DP), and pulse pressure (PP) of acute and chronic model groups. Data are presented as mean $\pm$ standard error of mean. Comparisons between groups were made using ANOVA. AC: acute sham control, AD: acute octreotide, ALI: acute lung injury, and ALI+OCT: acute lung injury treated with octreotide. CC: chronic sham control, CD: chronic octreotide, CLI: chronic lung injury, and CLI+OCT: chronic lung injury treated with octreotide. *Significant difference compared to the AC or CC group, # significant difference compared to AD or CD group, x significant difference compared to the ALI+OCT group or the CLI+OCT group ($P < 0.001$)

Table 1: The blood gas indexes in acute and chronic model groups. Data are presented as mean $\pm$ standard error

Model	Groups	pH	PaCO ₂ (mmHg)	SaO ₂ :laboratory %	SaO ₂ :FiO ₂ 2100% %	PaO ₂ :laboratory (mmHg)	PaO ₂ :FiO ₂ 2100% (mmHg)
Acute	AC	7.32 $\pm$ 0.02	38.85 $\pm$ 3.07	91.6 $\pm$ 1.24	96.8 $\pm$ 0.44	78.24 $\pm$ 4.82	104.74 $\pm$ 4.10
	AD	7.34 $\pm$ 0.01	37.3 $\pm$ 2.54	92.2 $\pm$ 0.51	97.0 $\pm$ 0.31	76.33 $\pm$ 2.86	101.6 $\pm$ 0.86
	ALI	7.24 $\pm$ 0.03*#	44.08 $\pm$ 2.62x	68.78 $\pm$ 3.31*#x	87.8 $\pm$ 3.31*#x	45.15 $\pm$ 2.58*#x	74.76 $\pm$ 4.77*#x
	ALI + OCT	7.28 $\pm$ 0.04	33.02 $\pm$ 2.09	89.25 $\pm$ 4.0	95.8 $\pm$ 0.58	66.6 $\pm$ 1.40*	95.53 $\pm$ 2.81*
	P_{ANOVA}	0.05	0.026	<0.001	0.01	$P_{time} < 0.001$, $P_{time*group} = 0.827$, $P_{group} < 0.001$	
Chronic	CC	7.30 $\pm$ 0.01	41.43 $\pm$ 2.17	91.6 $\pm$ 0.81	97.1 $\pm$ 0.44	68.26 $\pm$ 1.48	114.4 $\pm$ 10.13
	CD	7.29 $\pm$ 0.03	39.35 $\pm$ 2.74	91.85 $\pm$ 0.44	96.0 $\pm$ 0.44	71.97 $\pm$ 2.35	98.34 $\pm$ 4.92
	CLI	7.29 $\pm$ 0.01	37.82 $\pm$ 3.00	88.37 $\pm$ 1.32*#x	93.72 $\pm$ 0.61*#x	66.84 $\pm$ 2.53	78.48 $\pm$ 2.52*#x
	CLI + OCT	7.32 $\pm$ 0.02	36.2 $\pm$ 1.52	91.4 $\pm$ 0.22	96.6 $\pm$ 0.35	71.46 $\pm$ 1.02	101.44 $\pm$ 3.55
	P_{ANOVA}	0.593	0.45	0.008	<0.001	$P_{time} < 0.001$, $P_{time*group} = 0.001$, $P_{group} = 0.002$	

AC: acute sham control, AD: acute octreotide, ALI: acute lung injury, and ALI + OCT: acute lung injury treated with octreotide. CC: chronic sham control, CD: chronic octreotide, CLI: chronic lung injury, and CLI + OCT: chronic lung injury treated with octreotide. *significant difference compared to AC or CC group, #significant difference compared to AD or CD group, x significant difference compared to ALI + OCT group or CLI + OCT group. For PaO₂ and SaO₂, both one-way ANOVA followed by LSD post hoc test and repeated measure ANOVA analyzes were applied

Table 2: Blood cells, PT, and fibrinogen parameter acute and chronic model groups. Data are presented as mean±standard error

Model	Groups	RBC (10 ⁶ /μL)	WBC (10 ³ /μL)	Hb (g/dL)	Hct (%)	Plt (10 ³ /μL)	Neut (10 ³ /μL)	Lymph (10 ³ /μL)	Mono (10 ³ /μL)	Eos (10 ³ /μL)	Fibrinogen (mg/dL)	PT (seconds)
Acute	AC	7.99±0.29	3.75±0.43	14.48±0.25	42.37±1.60	651.71±36.37	1.01±0.30	2.44±0.20	0.13±0.05	0.06±0.01	203.85±10.46	14.05±1.07
	AD	7.79±0.21	3.50±0.55	14.06±0.47	42.4±1.55	534.00±16.10*	1.02±0.17	2.16±0.54	0.10±0.03	0.03±0.01*	211.0±7.78	13.43±0.22
	ALI	8.76±0.20**	5.33±0.46**	15.86±0.38**	48.55±1.08**	711.15±41.43*	2.42±0.30**	2.72±0.30	0.18±0.04	0.06±0.01#x	298.0±21.31**	13.28±0.20
	ALI + OCT	8.87±0.17**	4.88±0.69	16.05±0.29**	48.47±0.95**	745.89±26.10*	1.80±0.36	2.70±0.49	0.15±0.03	0.03±0.00*	336.33±21.25**	14.66±0.96
Chronic	P _{ANOVA}	0.002	0.06	0.001	<0.001	0.002	0.005	0.475	0.560	0.009	<0.001	0.29
	CC	8.39±0.18	4.07±0.59	14.13±0.55	45.36±1.34	646.0±33.43	1.18±0.28	2.64±0.38	0.08±0.01	0.06±0.01	161.17±17.77	13.30±0.19
	CD	8.08±0.22	5.72±0.92	14.35±0.41	43.51 ±	630.71±46.66	1.42±0.22	3.58±0.87	0.13±0.04	0.06±0.02	185.32±7.20	13.31±0.31
	CLI	8.47±0.14	6.19±0.90	14.66±0.22	45.02±0.80	642.0±20.71	1.41±0.11	4.66±0.81	0.22±0.04*	0.04±0.01	136.55±9.36	13.33±0.23
Chronic	CLI + OCT	8.35±0.12	6.24±0.30	14.67±0.16	44.37±0.39	627.70±22.97	1.84±0.22	4.08±0.29	0.15±0.01	0.05±0.02	143.55±14.45	16.68±1.86
	P _{ANOVA}	0.42	0.11	0.63	0.43	0.96	0.17	0.14	0.02	0.88	0.08	0.08

AC: acute sham control, AD: acute octreotide, ALI: acute lung injury, and ALI+OCT: acute lung injury treated with octreotide. CC: chronic sham control, CD: chronic octreotide,

CLI: chronic lung injury, and CLI+OCT: chronic lung injury treated with octreotide. * significant difference compared to AC or CC group, # significant difference compared to AD or CD group, x significant difference compared to ALI+OCT group or CLI+OCT group (P<0.05)

group ($P < 0.001$) and in the ALI+OCT group ($P < 0.05$) compared to AC and AD groups, but wet/dry ratio was lower in the ALI+OCT group compared to the ALI group ($P < 0.05$). In the chronic model, this parameter was significantly increased in the CLI group compared to the others ($P < 0.05$).

Histological Parameters: In the acute model groups, significant differences in Neut infiltration ($P < 0.001$), acute vasculitis ($P < 0.001$), interstitial edema ($P < 0.001$), alveolar edema or hemorrhage ($P < 0.001$), and alveolar macrophages ($P < 0.001$) were observed in the ALI group compared to the other groups. In the ALI+OCT group, Neut infiltration ($P < 0.001$), acute vasculitis ($P < 0.001$), interstitial edema ($P = 0.006$), alveolar edema or hemorrhage ($P = 0.01$), and alveolar macrophages ($P < 0.001$) were significantly decreased compared to the ALI group [Figures 5 and 6].

In chronic model groups, significantly higher lymph infiltration ($P < 0.001$), chronic vasculitis ($P < 0.001$), interstitial macrophages ($P < 0.001$), and alveolar septal thickening ($P < 0.001$) were observed in the CLI group compared to the others. Although significantly higher lymph infiltration in the CLI+OCT group was observed ($P < 0.001$), it was significantly lower than in the CLI group ($P = 0.008$). Histological parameters showed that OCT could attenuate acute and chronic lung injuries [Figures 5 and 6].

Discussion

The results of this study demonstrated that acute and chronic models of lung injury had impaired lung function; however, OCT had practically ameliorative effects on both acute and chronic models.

MAP, SP, and DP decreased significantly in both ALI and CLI groups. The reason may be related to hypoxia, depression of contractility, and accumulation of metabolites and cytokines, which induce vasodilation.^[42-44] These beneficial cardiovascular effects of OCT in acute lung injury may be related to anti-inflammatory, hypoxia improvement, and mesenteric contraction^[45] which increase the venous return. Ketamine/xylazine, used in several studies with lung injury models,^[30,31] can reduce blood pressure in animals.^[46] The reduced blood pressure in ALI and CLI groups may be related to the synergistic effect of ketamine/xylazine accompanied by hypoxia that induces instability of cardiovascular function encountered to anesthetics.^[47-49] However, PP which is directly related to cardiac contractility can decrease after ketamine/xylazine anesthesia.^[50,51] The lowest PP was observed in the ALI group, which explained the suppressive effect of hypoxemia on contractility. PP in the ALI+OCT group was lower than that in the AC and AD groups but higher in the ALI group, demonstrating the beneficial effects of OCT on cardiovascular functions.

According to our results, the ALI group had lung dysfunction marked by oxygen exchange failure, decreased

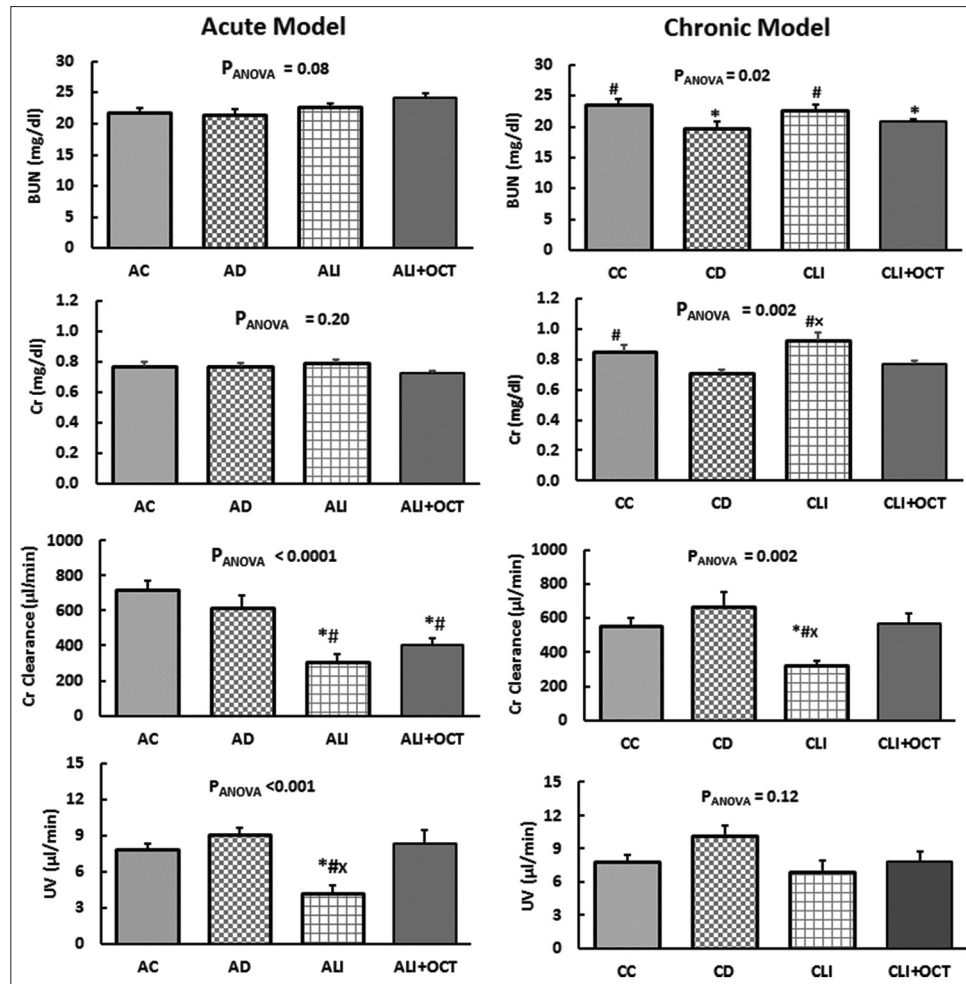


Figure 3: Kidney function parameters (serum levels of BUN and Cr, and Cr clearance) in acute and chronic model groups. Data are presented as mean $\pm$ standard error. Comparisons between groups were made using ANOVA. AC: acute sham control, AD: acute octreotide, ALI: acute lung injury, and ALI+OCT: acute lung injury treated with octreotide. CC: chronic sham control, CD: chronic octreotide, CLI: chronic lung injury, and CLI+OCT: chronic lung injury treated with octreotide. * significant difference compared to AC or CC group, # significant difference compared to AD or CD group, x significant difference compared to the ALI+OCT group or the CLI+OCT group ($P < 0.05$)

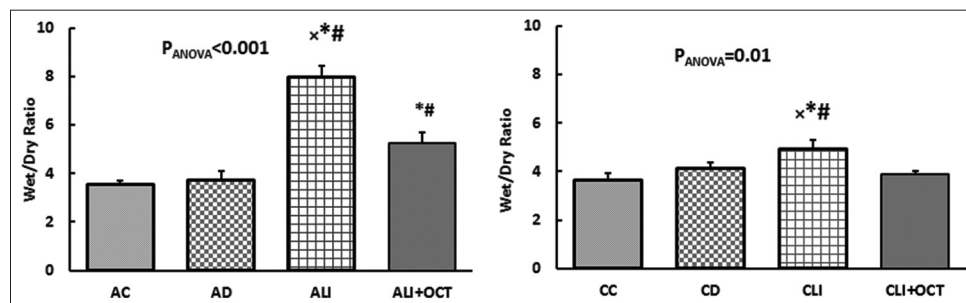


Figure 4: Wet/dry ratio (water content) in the acute and chronic models. Data are presented as mean $\pm$ standard error. Comparisons between groups were made using ANOVA. AC: acute sham control, AD: acute octreotide, ALI: acute lung injury, and ALI+OCT: acute lung injury treated with octreotide. CC: chronic sham control, CD: chronic octreotide, CLI: chronic lung injury, and CLI+OCT: chronic lung injury treated with octreotide. *Significant difference compared to AC or CC group, # significant difference compared to AD or CD group, x significant difference compared to the ALI+OCT group or the CLI+OCT group ($P < 0.05$)

PaO_2 and SaO_2 , increased pulmonary edema, and disturbed histological lung tissue in the ALI+OCT group, which explained the improvement of lung injury. In the CLI group, the weak response to $FiO_{2,100\%}$ can be related to pulmonary shunt, which can be induced by peri-alveolar fibrosis or

alveolar septal thickening or alveolar edema^[52,53] that we observed in histological results. In the fibrotic phase, alveoli are susceptible to the induction of pulmonary shunt,^[54] and the anti-fibrotic effect of OCT may benefit in reducing alveolar-arterial PaO_2 diverse ($PA-aO_2$), ventilation/

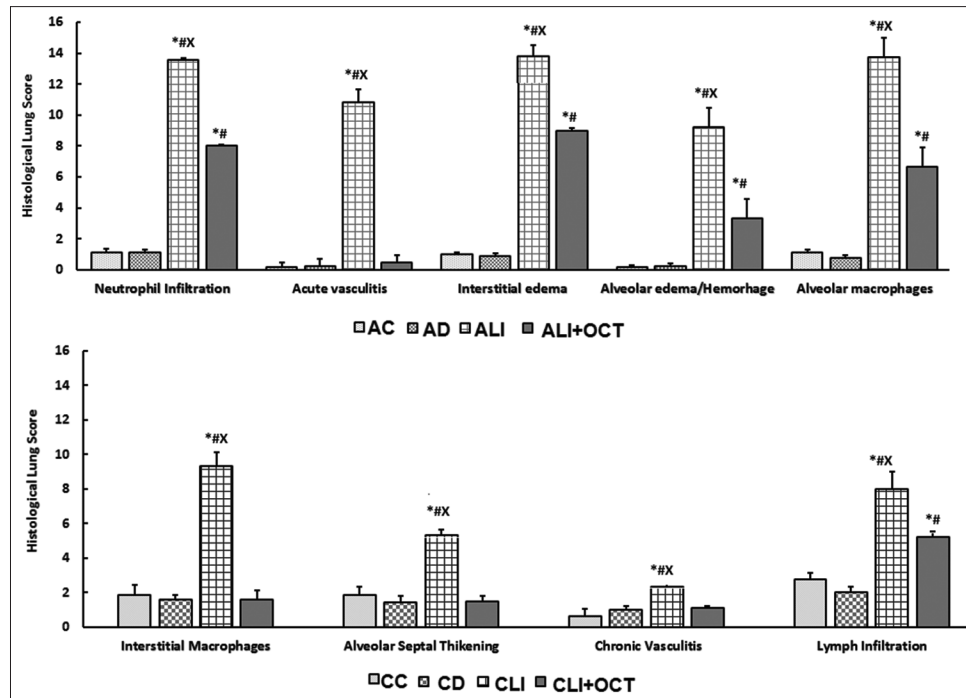


Figure 5: Histological parameters in acute model groups (top panel) and chronic model groups (bottom panel). Data are presented as mean $\pm$ standard error. Comparisons between groups were made using the Kruskal–Wallis test. AC: acute sham control, AD: acute octreotide, ALI: acute lung injury, and ALI+OCT: acute lung injury treated with octreotide. CC: chronic sham control, CD: chronic octreotide, CLI: chronic lung injury, and CLI+OCT: chronic lung injury treated with octreotide. *Significant difference compared to AC or CC group, # significant difference compared to the ALI+OCT group or the CLI+OCT group ($P < 0.05$)

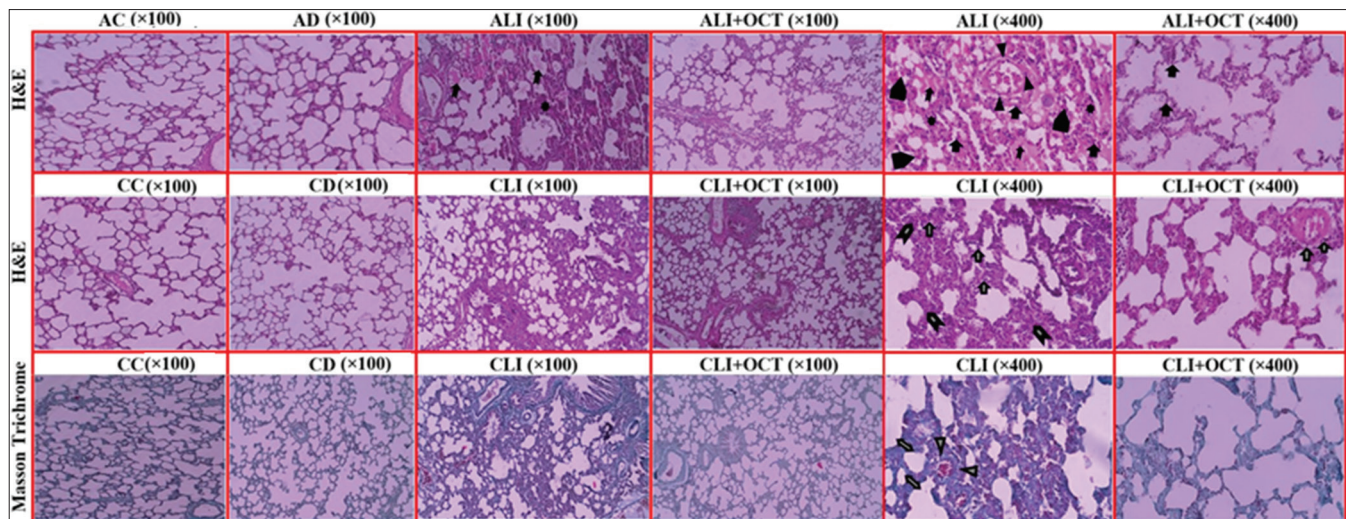


Figure 6: Histological microphotographs obtained from the lung tissue of all groups, in $\times 100$ and $\times 400$ magnifications. The microphotographs of H&E and Masson trichrome staining showed obviously different lung scores in acute and chronic model groups. AC: acute sham control, AD: acute octreotide, ALI: acute lung injury, and ALI+OCT: acute lung injury treated with octreotide. CC: chronic sham control, CD: chronic octreotide, CLI: chronic lung injury, and CLI+OCT: chronic lung injury treated with octreotide. In the acute model groups, H&E staining revealed Neut infiltration (▲), acute vasculitis (▲), interstitial edema (▲), alveolar edema or hemorrhage (▲), and alveolar macrophages (▲). In chronic model groups, H&E and Masson trichrome staining revealed Lymph infiltration (▲), chronic vasculitis (▲), revealed interstitial macrophages (▲), and alveolar septal thickening (▲)

blood flow ratio (V/Q) mismatch, right-to-left shunting, or impairment of oxygen diffusion, collagen density, and secretion of fibrotic factors such as TGF- β .^[55] Alveolar septal thickening is usually followed by the accumulation of collagen, macrophages, and fibrotic secretions of them around alveolar spaces in the chronic phase.^[54]

Regarding kidney parameters, creatinine clearance was reduced in the ALI and CLI groups; moreover, in the CLI group, BUN and Cr increased, and in the ALI group, the urinary volume reduced. Reportedly increasing BUN and Cr^[56] and reducing UV^[57,58] have already been defined as kidney injury. Probably, indifference in Cr in the ALI group

can be related to the penetration or accumulation of Cr into the lungs.^[59,60] According to this reason, one retrospective cohort study explained that patients with ARDS and lower serum Cr had a higher mortality rate.^[61]

Reduced Cr clearance in ALI and ALI+OCT groups may be related to the insufficient dosage of OCT for renal protection or the lower organ injury.^[62-65] Improved kidney parameters in the CLI+OCT group defined the beneficial effect of OCT.

Corroborated to our results of UV, there are studies that showed several hormones (i.e., growth hormone,^[66] renin–angiotensin–aldosterone, catecholamines^[67,68] have increased in distress time. These hormones can induce water and salt retention or promotion of inflammatory reactions; however, OCT (somatostatin analog) can reduce these hormones.^[9] Also, there are studies that showed it could decrease serum Cr,^[67] and improve kidney functions of patients with diabetes,^[69] and it has anti-inflammatory and tissue repair functions.^[70]

The increase in RBC, Hb, and HCT in the acute phase of lung injury, which was already explained,^[71] may be due to the spleen contraction^[72] because of a minor role in the adaption to hypoxia. Moreover, due to erythropoiesis, erythroblasts can be produced from the bone marrow and enter the peripheral blood. According to the biological reports, rats may be resistant to hypoxic conditions, because they have lower deformability and aggregation of RBCs than humans^[73] but a higher production of them.^[74]

In the ALI group, Neut and Eos increased significantly because of inflammatory reactions,^[75] and Neut accumulation was observed in the alveolar, interstitial, and perivascular lung tissues. Neut, as a hallmark of ARDS, can induce several cytotoxic events, including the release of granular enzymes, neutrophil extracellular traps (NETs), various pro-inflammatory cytokines,^[76] exaggeration of lung vessels function (acute vasculitis), phagocytosis, and pyroptosis (cell death that is associated with inflammation) of epithelial cells by alveolar macrophages.^[77,78] Our results demonstrate that OCT can inhibit the penetration of Neut, macrophages, and permeability of fluid into the lung.

In the CLI group, the number of blood mono and accumulated interstitial macrophages in the lungs significantly increased, but such observation was not observed in the CLI+OCT group. Reportedly, fibrotic processes related to monocytes and macrophages have been created by the penetration of monocytes into the lungs and the transformation to macrophages that release fibrotic cytokines and factors, for example, interleukin 4 (IL-4), IL-13, IL-33, and TGF- β , osteopontin, and collagen.^[79,80]

Also, increased blood monocyte numbers may represent negative prognostic biomarkers in patients with idiopathic pulmonary fibrosis.^[81] OCT reduced blood monocyte number probably with the inhibition of the monocyte

infiltration into the lungs, induction of autophagia, or augmented SSTR₂ in the macrophages as reported in the inflammation models. Interestingly, in recent studies, macrophage autophagy has been investigated for ARDS treatment.^[82]

Reportedly, there are concerns about the inhibitory effect of OCT on pancreatic enzyme excretion, which may induce disturbance absorption of vitamins A, D, E, and K1. Although long-time administration of OCT could induce vitamin K deficiency, which is characterized by elongated PT,^[83] our results did not indicate a significant difference in PT between all the groups.^[84] Also, thrombocytopenia is a rarely adverse effect with OCT,^[85] so our result showed a significantly lower Plt in the AD group of the acute model; however, in other groups of the acute and chronic models, it was not observed.

Fibrinogen is a non-specific inflammatory marker that is involved in the coagulation/anticoagulation pathway that was increased in ALI and ALI+OCT groups. The increase in plasma fibrinogen cannot be an apt marker for predicting the progression of ARDS,^[59] because it can penetrate and accumulate in the lungs such as other plasma proteins.^[59,60] Fibrinogen increased in ALI and ALI+OCT groups [Table 2] because of the inflammation phase; however, in the ALI group, the water content and histological scores potentially increased, which may define higher inflammation and higher lung permeability.

Conclusions

In summary, several parameters of acute and chronic lung injuries such as hemodynamic parameters, blood gases, immune cells in the blood and lungs, histological lung scores, and some kidney functions improved by OCT.^[86] In addition to these beneficial effects, adverse effects were not observed. Therefore, OCT can be considered for clinical studies on immunopathophysiological parameters of ARDS and lung fibrosis.

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Author contribution

GZ: Running the experiments, involved in article preparation, research design, and data analysis

ZP and SC: Involved in experiments, data analysis, and article preparation

BM and AT: Involved in pathology investigation

MN: Designed the research protocols, implemented the statistical analyses, and involved in the final verification of the article.

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Conflicts of interest

There are no conflicts of interest.

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