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Research Article
Exploring Beta Blockers' Efficacy in Sepsis-Induced Acute Lung Injury and HMGB1-sRAGE Interaction

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Abstract

Background and Objective: Beta-blockers improve cardiac function and prevent catecholamine-mediated hypermetabolism in critically ill patients. This study investigated the role of beta blockers in reducing inflammation in a sepsis model and their influence on acute lung injury (ALI). The study aimed to understand beta blockers' potential role in mitigating ALI risk in sepsis patients. **Materials and Methods:** Fifty Wistar albino rats were divided into five groups. The first group was the control and the remaining four had feces-induced peritonitis (FIP) to mimic sepsis. The second group was the FIP group, while the third, fourth and fifth groups received different intraperitoneal doses of beta-blockers: 10 mg/kg/day of propranolol, 2 mg/kg/day of metoprolol and 5 mg/kg/day of carvedilol. **Results:** Beta-blocker administration in FIP rats significantly decreased inflammatory biomarkers, including Tumor Necrosis Factor-alpha (TNF-α), lactic acid, Interleukin-6 (IL-6), malondialdehyde (MDA), high mobility group box 1 (HMGB1) and Interleukin-1 beta (IL-1β), compared to the FIP+Saline group. The FIP+beta blockers group exhibited elevated Soluble Receptors for Advanced Glycation End product (s-RAGE) levels compared to the FIP+saline group. Carvedilol, metoprolol and propranolol showed distinct mechanisms, resulting in biochemical improvements in sepsis and curative effects observed in computed tomography and histology. These findings suggested that beta-blockers may effectively prevent ALI side effects in sepsis treatments. **Conclusion:** Commencing beta-blocker treatment alongside standard sepsis therapy could potentially protect against adverse effects like ALI. It is recommended to consider adding beta-blockers to standard sepsis treatment regimens.

Key words: Sepsis, acute lung injury, beta-blockers, HMGB1, s-RAGE

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

When an infectious organism enters the body, it triggers a condition of sepsis, a systemic inflammatory reaction[1]. The major source of the cytokines that trigger this systemic inflammatory response include macrophages, lymphocytes, monocytes, T cells, B cells, NK cells, endothelium, epithelial and dendritic cells. The cytokines that are produced cause the development and activation of immune cells as well as the release of further cytokines[2]. Early (such TNF-α, IFN-γ and IL-1β) and late (like HMGB1) proinflammatory mediators are sequentially released as a result of this cascade[3]. All cell types' nuclei include the HMGB1 (High Mobility Group Box 1) protein. It is released either passively by injured tissue during an infection or actively by immune cells during an injury. A strong pro-inflammatory cytokine, HMGB1 has this function. In cases of severe sepsis, its secretion rises[3]. Receptor for Advanced Glycation End Products (RAGE) is an immunoglobulin derivative that functions as the receptor for advanced glycation end products. Endothelial cells are among the many cells that express it. It is present both free and affixed to the cell membrane. Leukocyte binding to RAGE triggers the inflammatory cascade, leading to the emergence of SIRS. It has been demonstrated that the amount of sRAGE in the circulation generally corresponds to the level of RAGE expressed in cells and the inflammatory process connected to the RAGE signaling pathway[4-6]. The severity of sepsis is assessed using HMGB1 and RAGE.

In sepsis, if treatment is not started in the early period, the process progresses rapidly and the resulting exaggerated immune response activates many cascades that lead to multi-organ dysfunction rather than destroying the source of infection[7]. Lung ranks first among injured organs and is the most frequently bankrupt organ[8]. Protein-rich edema accumulating in the lungs causes resistant hypoxemia, hardening of the lungs, decreased ventilation and respiratory failure[9]. Acute lung injury is the deadliest complication of sepsis. One of the crucial predictors of outcomes for individuals with sepsis is this factor[8].

Computed tomography is the gold standard imaging method for imaging parenchymal damage in ALI. Quantitatively, the hounsfield unit used to evaluate parenchymal density is between -1000 and +1000. The measurement is made for the area where ALI is suspected. By measuring the parenchyma density, it can be distinguished from normal lung tissue[10]. Another condition triggered by the severe inflammatory response in sepsis is sympathetic activation. Sympathetic activation is vital for maintaining systemic perfusion and oxygen delivery to vital organs. However, as the process progresses, vasoconstriction, tachycardia, tachycardia-related myocardial damage[11], further increase in inflammatory cytokine production[2], insulin resistance[12] and thrombogenicity[5] occur with excessive activation of catecholamines[13]. Beta adrenergic receptor antagonists (beta blockers) are used in the treatment of hypertension, cardiac arrhythmia, psychiatric, endocrine and neurological diseases. It has been suggested to be used in septic shock in order to prevent catecholamine-mediated hypermetabolism and reduce cardiac impact. The β-blocker drugs also have immunomodulatory effects[3,5].

Sepsis is a condition diagnosed in the emergency room. Its prognosis depends on prompt diagnosis and treatment in the emergency department. The objective of our research is to explore the potential protective and therapeutic benefits of β-blockers in acute lung injury arising from sepsis. This study aimed to assess the impact of β-blocker drugs on sepsis caused by feces-induced peritonitis in rats, by lung tomography findings, plasma TNF-α, lactic acid, IL-1β, IL-6, s-RAGE and HMGB1 levels.

MATERIALS AND METHODS

Study area: From March, 2021 to July, 2022, this investigation was conducted in Istanbul, Turkey at the Experimental Animals Application and Research Center of Demiroglu Science University.

Ethical approval: The experimental procedures of the study were authorized by the Animal Research Ethics Committee at Demiroglu Science University (Approval number: 06211004) and conducted following the global standards set by the US Institute of Health.

Animals: The research utilized a sample of 50 male Wistar albino rats weighing within the range of 200-250 g. The rats were provided with free access to food and confined to cages under a regulated temperature of 22±2°C, along with an automated light-dark cycle that lasted 12 hrs each.

Experimental procedures: To induce sepsis the method of feces induced peritonitis in rats was used[14]. Fecal material given into the peritoneum was obtained from the cecum, the amount was measured to be 1 g kg^{-1} of the rat and it was diluted in half with saline. The prepared fecal material was injected intraperitoneally into 40 rats. Ten rats that were not injected with feces were divided as a normal groups and no procedure was applied to them.

The study comprised five experimental groups: Group 1 served as the normal control and was neither subjected to FIP nor received any treatment (n = 10), Group 2 underwent FIP procedure only without any intervention (n = 10), Group 3, Group 4 and Group 5 received 10 mg/kg/day of propranolol (Dideral, 40 mg, Sanofi), 2 mg/kg/day of metoprolol (Beloc Ampul, 5 mg/5 mL, Astra Zeneca) and 5 mg/kg/day of carvedilol (Dilatrend, 25 mg, Deva), respectively, by intraperitoneal injection after one hour of FIP procedure (n = 10 for each group). The animals were provided with food and water without any restrictions and were housed in cages with a regulated temperature of 22±2°C and a light-dark cycle of 12 hrs. After a 24 hrs observation period, during which five rats died and were therefore excluded from the analysis (three from the placebo group, one from the propranolol group and one from the carvedilol group), the study was concluded. The deaths occurred within the first 24 hrs following the FIP procedure. The research adhered to the ethical guidelines established by the local experimental animal research ethics committee and the international standards prescribed by the US Institute of Health.

At the conclusion of the study, all animals were administered general anesthesia through injection with 100 mg kg^{-1} of Ketasol (manufactured by Richter Pharma AG Austria) and 50 mg kg^{-1} of Rompun (manufactured by Bayer, Germany). Once anesthetized, cervical dislocation was performed to euthanize the animals. After the animals were euthanized, blood samples were collected through a puncture made in the heart to carry out biochemical analyses.

Plasma analysis of TNF-α, Lactic Acid, IL-1β, IL-6, s-RAGE and HMGB1 levels: In order to measure the levels of various biomarkers in the plasma including TNF-α, Lactic Acid, IL-1β, IL-6, s-RAGE and HMGB1, the researchers employed Enzyme-Linked Immunosorbent Assay (ELISA) kits supplied by Biosciences, Abcam. Before conducting the analysis, the plasma samples were appropriately diluted in accordance with the kit manufacturer's guidelines. The TNF-a levels were measured in duplicate. The researchers also used a blood gas device (Radiometer America, Westlake, OH) to measure the level of lactic acid in the plasma samples.

Measurement of lipid peroxidation: A technique that utilizes thiobarbituric acid reagents was employed to measure the amount of malondialdehyde (MDA) present in the plasma to quantify lipid peroxidation. To do this, plasma was mixed with trichloroacetic acid and Thiobarbituric Acid Reactive Substances (TBARS) and incubated at a temperature of 100°C for 60 min. The mixture was then cooled on ice and centrifuged at a speed of 3000 rpm. The resulting precipitate was measured at a wavelength of 535 nm[14].

Histopathological examination of lung: To conduct a histological study, a biopsy was taken from the lungs of the rats. Before the biopsy, the rats were given ketamine and xylazine through intraperitoneal injection. During the procedure, a solution of 4% formaldehyde in 200 mL of 0.1 M phosphate-buffered saline (PBS) was administered into the rats' veins. This solution was used to fix the lung tissue and prevent any degradation.

After fixing the lung tissue sections with formalin, a staining process was carried out using Hematoxylin and Eosin (H&E) to generate a clear image of the tissue at a thickness of 5 µm. These sections were examined under an Olympus BX51 microscope (Olympus, Tokyo, Japan) and the histological images were taken with an Olympus C-5050 digital camera (Olympus, Tokyo, Japan). The extent of lung damage was evaluated by calculating a lung damage score. In order to obtain a comprehensive evaluation of the sample, the histological score was calculated by taking into account several factors, including alveolar congestion (AC), leukocyte infiltration or aggregation in air spaces or vessel walls (AL), hemorrhage (H), the thickness of the alveolar wall or hyaline membrane formation (TA) and perivascular or interstitial edema (PE). Each of these factors was carefully assessed to determine its contribution to the overall score. By combining these individual evaluations, a more nuanced and complete picture of the sample's histological status could be obtained, enabling a more accurate assessment of the experimental outcomes. The severity of each parameter was graded on a scale of 1 (0-25%), 2 (25-50%), 3 (50-75%) or 4 (75-100%)[15].

CT examination of the lung: During the tomography, the region from the level of the C3 vertebra to the diaphragm was scanned. The imaging process covered the area from the top to the bottom of the lungs. The images were reconstructed in a non-overlapping manner, with a 1 mm distance between each section. The size of the image matrix was set at 512 by 512. A specific kernel, called "KernelBr64," was used during the reconstruction process[16].

The evaluation of the tomographies was done by two radiologists who did not know the laboratory findings of the animals and which group they belonged to. Six regions in the lungs were determined for the detection of acute lung injury. The study analyzed six regions of interest (ROIs) in both lungs, comprising two ROIs in the upper zone, two in the middle zone and two in the lower zone, each with an area of 2.153 mm^2. After these regions were determined, they were examined in axial sections in the parenchyma window. While determining these regions, attention was paid to avoiding the great vessels, airways and bones.

Analysis of arterial blood gas: As 0.2 mL of blood was drawn from the carotid artery of all rats 24 hrs after the operation. A blood gas device was used to determine the PaO_2 and $PaCO_2$ levels from this blood taken.

Statistical analysis: The SPSS version 24.0 for Windows was used to analyze the study's data. Mean and standard deviation was used to show the numerical data. The data's normal distribution was examined using the Shapiro-Wilk test. The one-way ANOVA test was used to compare the data across three groups, whereas the independent T-test was utilized to evaluate the parametric data between two groups. There was a significant difference between the groups, according to the one-way ANOVA test findings. It was observed that the variances were equally distributed in the homogeneity analysis between the variances made to see which categorical variable caused this difference. In the *post hoc* analysis, Dunnett's Test was used to compare the control group (FIP and saline) with other categorical variables (FIP and propranolol, FIP and metoprolol and FIP and carvedilol). The data were presented at a 95% confidence interval. The $p<0.05$ was considered statistically significant.

RESULTS

Analysis of biochemical results: In this study, the researchers measured various biochemical markers in the plasma of different groups of rats. The levels of HMGB1, Lactic acid, IL-6, MDA, TNF-α and IL-1β were notably elevated in the FIP+saline group when compared to the control group. However, as comparison to the FIP+saline group, these markers were lower in the FIP+propranolol group ($p = 0.038$) (Table 1). Similarly, in the FIP+metoprolol group and FIP+carvedilol group, the levels of these markers were present at lower levels than in the FIP+saline group ($p<0.001$) (Table 1). In the study, s-RAGE levels were assessed and were found to be markedly decreased in the FIP+saline group compared to the control group, indicating impaired lung function. On the other hand, s-RAGE levels were significantly higher in the FIP+propranolol, FIP+metoprolol and FIP+carvedilol groups compared to the FIP+saline control group, suggesting a potential protective effect of these treatments against lung injury. These findings suggest that s-RAGE could serve as a valuable biomarker for assessing the efficacy of therapeutic interventions for lung injury (Table 1).

Table 1: Comparison results of all parameters between groups

	MDA		IL-6		IL 1-Beta		TNF-alfa		Lactic acid		s-RAGE		HMGB1	
	(nM mg^{-1} protein)	p-value	(pg mL^{-1})	p-value	(pg mL^{-1})	p-value	(pg mL^{-1})	p-value	(mmol L^{-1})	p-value	(pg mL^{-1})	p-value	(pg mL^{-1})	p-value
FIP and saline group	21.7±1.5	<0.001	21452.7±1454.5	<0.001	2416.2±47.9	<0.001	485.6±27.1	<0.001	3.5±0.6	<0.001	2110.7±98.3	<0.001	2.58±0.3	0.014
Normal control	3.3±1.8		5.1±0.3		2.2±0.1		10.2±1.7		1.2±0.1		2451.0±102.8		1.2±0.1	
FIP and saline group	21.7±1.5	<0.001	21452.7±1454.5	0.008	2416.2±47.9	<0.001	485.6±27.1	0.018	3.5±0.6	0.038	2110.7±98.3	0.040	2.58±0.3	0.044
FIP and propranolol	4.9±1.04		3841.1±115.3		1510.8±68.2		218.7±13.3		2.3±0.5		2742.2±171.5		2.1±0.2	
FIP and saline group	21.7±1.5	<0.001	21452.7±1454.5	<0.001	2416.2±47.9	<0.001	485.6±27.1	<0.001	3.5±0.6	0.004	2110.7±98.3	<0.001	2.58±0.3	0.024
FIP and metoprolol	6.3±0.9		2274.8±89.5		1065.1±74.3		191.5±18.4		1.9±0.4		2951.8±119.3		1.5±0.4	
FIP and saline group	21.7±1.5	<0.001	21452.7±1454.5	0.017	2416.2±47.9	0.021	485.6±27.1	0.016	3.5±0.6	0.014	2110.7±98.3	0.042	2.58±0.3	0.020
FIP and carvedilol	5.02±1.1		3312.7±77.4		3312.7±77.4		268.5±27.4		2.5±0.8		2410.5±69.2		1.7±0.1	

One-way ANOVA Test used, *post hoc*/Dunnett Test used for comparison between groups

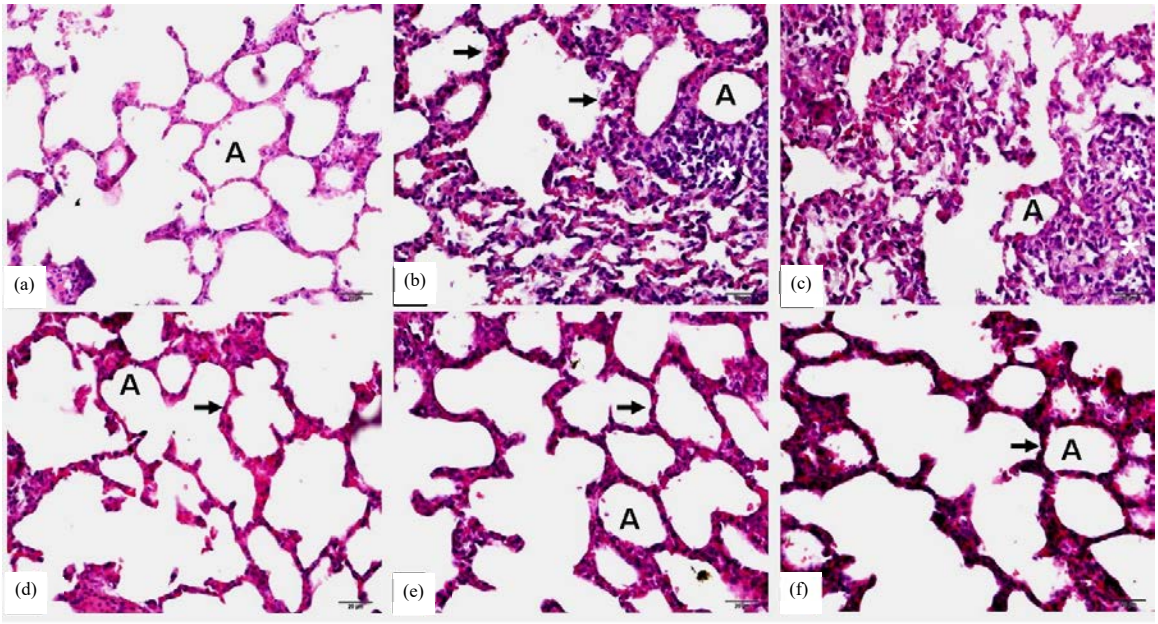

Fig. 1(a-f): Lung histopathology x40 magnification H&E staining. A: Normal control group lung, (a) Alveoli, (b-c) FIP group showed severe histopathologic alteration related to increased alveolar inflammation (*) and septal thickness (arrow), (d) FIP and propranolol group showed decreased inflammation and septal thickening (arrow), (e) FIP and metoprolol group showed decreased inflammation and septal thickening (arrow) and (f) FIP and carvedilol group showed decreased inflammation and septal thickening (arrow)

Table 2: Comparison results of blood gas analysis between groups

Groups	PaO_2 (mmHg)	p-value	$PaCO_2$ (mmHg)	p-value
FIP and saline group	85.9±6.5	0.008	32.7±2.7	<0.001
Normal control	101.7±9.9		38.5±3.4	
FIP and saline group	85.9±6.5	0.026	32.7±2.7	<0.001
FIP and propranolol	94.5±5.6		40.8±3.1	
FIP and saline group	85.9±6.5	0.014	32.7±2.7	<0.001
FIP and metoprolol	97.4±7.4		43.2±4.2	
FIP and saline group	85.9±6.5	0.032	32.7±2.7	<0.001
FIP and carvedilol	92.1±4.3		35.9±3.5	

One-way ANOVA Test used, *post hoc*/Dunnett Test used for comparison between groups

In blood gas analysis PaO_2 in the FIP+propranolol, FIP+metoprolol, FIP+carvedilol treatment groups were significantly higher compared to the FIP+saline group and $PaCO_2$ in the FIP+propranolol, FIP+metoprolol groups are significantly higher compared to FIP+saline group. FIP+carvedilol treatment group doesn't have a significant change compared to other groups (Table 2).

Assessment of lung damage severity through histological scoring and CT imaging: The lung injury levels for the FIP+saline group were considerably greater than those for the control group in terms of TA, PE, H, AL and AC. Lung injury ratings for the FIP+propranolol group compared to the FIP+saline group were considerably lower (Fig. 1 and Table 3). The FIP+metoprolol group had significantly lower levels of lung injury compared to the FIP+saline group, as indicated by Fig. 1 (Table 3). Lung injury levels for FIP+carvedilol therapy compared to the FIP+saline group were considerably reduced for the thickness of the alveolar wall or hyaline membrane formation (TA), perivascular or interstitial edema (PE), hemorrhage (H), leukocyte infiltration or aggregation in air spaces or vessel walls (AL) and alveolar congestion (AC) (Fig. 1 and Table 3).

A significant increase in the computed tomography (CT) hounsfield unit (HU) value of the lung was observed in the FIP+saline group compared to the control group. On the other hand, the lung tissue HU level in the FIP+propranolol, FIP+metoprolol and FIP+carvedilol treatment groups demonstrated a significant reduction relative to the FIP+saline control group, as demonstrated by Fig. 1 and 2.

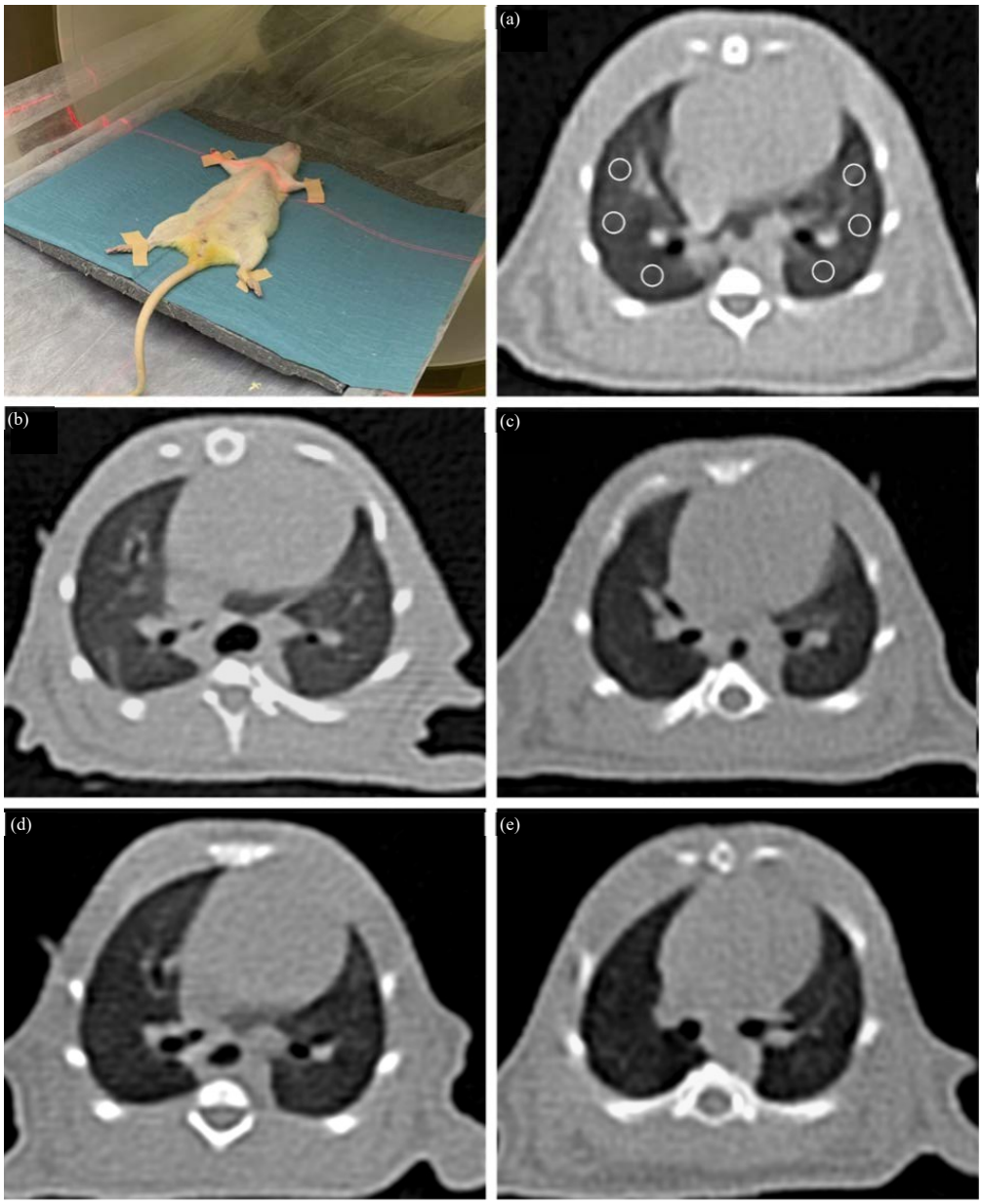

Fig. 2(a-e): Axial CT images of lung at the level of the heart, six ROI placed with the same size at the same location (a) Normal control group lung, (b) FIP group showed increased density of lung, (c) FIP and propranolol group decreased density of lung, (d) FIP and metoprolol group decreased density of lung and (e) FIP and carvedilol group decreased density of lung

Table 3: Comparison results of histological score and CT findings between groups

	AC	p-value	H	p-value	AL	p-value	PE	p-value	TA	p-value	CT Hounsfield unit (HU)	p-value
FIP and saline group	3.2±0.1	0.001	1.3±0.1	0.004	2.7±0.2	0.002	3.2±0.2	0.001	2.6±0.1	0.002	-443.5±11.5	0.028
Normal control	0.2±0.2		0.3±0.1		0.2±0.1		0.1±0.1		0.1±0.1		-649.1±17.3	
FIP and saline group	3.2±0.1	<0.001	1.3±0.1	<0.001	2.7±0.2	<0.001	3.2±0.2	0.016	2.6±0.1	<0.001	-443.5±11.5	<0.001
FIP and propranolol	0.8±0.2		0.5±0.1		0.9±0.3		1.1±0.1		0.9±0.2		589.5±8.2	
FIP and saline group	3.2±0.1	<0.001	1.3±0.1	<0.001	2.7±0.2	<0.001	3.2±0.2	<0.001	2.6±0.1	0.021	-443.5±11.5	<0.001
FIP and metoprolol	0.9±0.2		0.4±0.2		0.8±0.1		0.9±0.2		1.4±0.2		-578.4±4.5	
FIP and saline group	3.2±0.1	<0.001	1.3±0.1	<0.001	2.7±0.2	<0.001	3.2±0.2	0.026	2.6±0.1	<0.001	-443.5±11.5	<0.001
FIP and carvedilol	1.2±0.1		0.5±0.2		0.6±0.3		1.3±0.4		1.2±0.1		-561.2±6.6	

One-way ANOVA Test used, *post hoc*/Dunnett Test used for comparison between groups

DISCUSSION

In this study, the potential therapeutic benefits of beta blockers, specifically propranolol, metoprolol and carvedilol, in mitigating acute lung injury (ALI) and inflammation in a sepsis-induced rat model were examined. We observed significant changes in inflammatory biomarkers such as HMGB1, lactic acid, IL-6, MDA, TNF-α and IL-1β across various treatment groups. The levels of these markers were notably lower in the FIP+Propranolol, FIP+Metoprolol and FIP+carvedilol groups compared to the FIP+saline group.

Additionally, this study assessed s-RAGE levels as a potential biomarker for lung injury. We found that s-RAGE levels were markedly decreased in the FIP+saline group compared to the control group, indicating impaired lung function. However, s-RAGE levels were significantly higher in the FIP+propranolol, FIP+metoprolol and FIP+carvedilol groups, suggesting a potential protective effect of these treatments against lung injury.

Furthermore, blood gas analysis revealed higher PaO_2 levels in the FIP+propranolol, FIP+metoprolol and FIP+carvedilol treatment groups compared to the FIP+saline group. Histological scoring and CT imaging demonstrated reduced lung injury severity in the FIP+propranolol, FIP+metoprolol and FIP+carvedilol groups relative to the FIP+saline group.

Sepsis is a case with high mortality rates in emergency and intensive care units. Quick and effective interventions, starting from the emergency services, will help to reduce the death rate[17]. New biomarkers and drugs are being tested to enable these early interventions to begin[18]. The clinical benefit and harm rates of b-blockers as a promising treatment are not yet known.

The HMGB1, a potent proinflammatory cytokine, is responsible for the late inflammatory response in sepsis and the lethal effects of endotoxins. It is evaluated as one of the markers of local and systemic inflammation in animal studies[19]. There are studies indicating that sRAGE is also a biomarker showing the severity of sepsis. It is known that sRAGE reduces its proinflammatory effects in the blood by binding HMGB1 in the blood[11]. There is no study yet in which sRAGE and HMGB1 levels are evaluated by computed tomography and histopathology in acute lung injury. As seen in our study, beta blockers significantly increase the amount of sRAGE. Similarly, the decrease in the value of HMGB1 in rats receiving beta-blockers indicates the protective effect of beta-blockers on the prevention of cytokine storms in sepsis and thus acute lung injury.

In new treatment approaches for sepsis, cytokine-based strategies are at the forefront of the new generation of treatment methods. Numerous investigations have explored the potential benefits of targeting HMGB1 with antibodies or selective antagonists in a variety of preclinical models of inflammatory diseases, such as sepsis and lethal endotoxemia, indicating promising protective effects[20-23]. In this study, increasing the amount of sRAGE with beta-blockers provides an indirect antagonism by causing a decrease in the amount of HMGB1.

Propranolol is categorized as a non-selective beta-blocker, which has been the focus of numerous studies. These studies have suggested that propranolol could offer potential benefits in cases of sepsis and sepsis-like inflammatory processes such as those seen in COVID-19 patients. One of the purported mechanisms of action for propranolol is its ability to decrease the release of cytokines, specifically TNF-alpha, within the blood and plasma. Additionally, it has been reported that Propranolol can enhance metabolic function in lung tissue[24].

Acute lung injury is a condition that involves intense inflammation in the alveolar space due to an influx of active neutrophils, leading to a cytokine storm. Among the various beta-blockers investigated, metoprolol, which is a selective beta1 blocker, was found to effectively alleviate inflammation and reduce neutrophil infiltration and interaction with other cell types. Consequently, the patients showed better oxygenation levels and required fewer days of hospitalization in the intensive care unit. These findings suggested that metoprolol treatment is a low-cost and safe therapeutic approach for managing patients suffering from acute lung injury[25].

Carvedilol is a non-selective β-blocker with α-blocking, vasodilator and antioxidant effects. The potential mechanisms underlying the favorable effects of carvedilol remain unclear and it is not fully understood whether its beneficial impact involves the inhibition of proinflammatory cytokines beyond the inhibition of the elevated sympathetic activity. In the study, it was observed that carvedilol suppressed TNF-α and IL-6 plasma levels in both ischemic and non-ischemic DCM patients[26].

Results of this study were consistent with earlier research indicating that the FIP+metoprolol, FIP+propranolol and FIP+carvedilol groups demonstrated improvements in thorax CT and histological evaluation. The decrease in proinflammatory markers such as TNF-a, IL-6, IL 1 Beta, lactic acid, an increase in s-RAGE and a decrease in HMGB1 also indicate that the inflammatory process has decreased and that there has been an improvement.

There is an established understanding that the use of beta-adrenergic blockers is associated with a decrease in mortality and morbidity by preventing the increased catecholamine levels in the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) epidemic through the adrenergic system and also by suppressing the increased catecholaminergic state in Acute Respiratory Distress Syndrome (ARDS) and sepsis due to COVID-19[27]. Beta adrenergic blockers reduce the attachment sites of COVID-19 by blocking Angiotensin-Converting Enzyme 2 (ACE2) receptors in the lungs. It is also known that they reduce mucus secretion by decreasing IL-6. They also block the renin-angiotensin system from the beginning by reducing sympathetic activation. All these processes prevent the cytokine storm from starting or increasing to a level with bad consequences[27]. Similarly, in this study, the beta-blockers showed a protective effect from ALI by increasing the sRAGE level and decreasing the HMGB1 level, unlike oxidative stress, proinflammatory cytokines and other studies, without being superior to each other.

This study has some limitations. Primarily, it is imperative to conduct further studies to elucidate the underlying mechanism through which beta blockers exert their effect in sepsis and acute lung injury (ALI). Secondly, the beta blockers levels can also be measured and can be compared with the severity of ALI. Finally, the pathology can be measured at the molecular level.

CONCLUSION

Current article findings strengthen the hypothesis about the protective effect of metoprolol, carvedilol and propranolol histologically, biochemically and radiologically in the FIP-induced ALI model. No superiority was observed between them. It is recommended to consider adding beta blockers to the standard treatment regimen to combat sepsis. More animal and human studies were needed on this subject.

SIGNIFICANCE STATEMENT

Sepsis is a life-threatening condition that can lead to acute lung injury (ALI) and other complications. The findings of this study suggested that the beta-blockers, including propranolol, metoprolol and carvedilol, may have a protective effect against the development of ALI in sepsis patients. This was evidenced by the significant decrease in pro-inflammatory cytokines and oxidative stress markers, as well as the increase in s-RAGE levels, observed in the beta blocker-treated groups compared to the saline-treated group. Furthermore, the beta blockers showed biochemical improvement and healing effects in both computed tomography and histology. These results supported the potential use of beta blockers as an adjunct treatment for sepsis to mitigate the risk of developing ALI.

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