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Effect of celecoxib on intra-abdominal sepsis-induced lung injury in rats

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ABSTRACT

Objectives: This experimental study investigated the preventive effects of Celecoxib, a selective COX-2 inhibitor, on lung injury induced by intra-abdominal sepsis in rats. The study assessed Celecoxib's potential to mitigate the harmful impacts of sepsis on lung tissue.

Methods: Thirty male Wistar albino rats, divided into three groups: a normal control group, a sepsis-induced group treated with saline, and a sepsis-induced group treated with Celecoxib. Sepsis was induced using fecal intraperitoneal injection (FIP), followed by a one-hour administration of Celecoxib at 50 mg/kg/day to the treatment group. Biochemical analysis of lung tissue measured oxidative stress markers (malondialdehyde [MDA]) and pro-inflammatory cytokines (Tumor Necrosis Faftor-α [TNF-α]). Histopathological examination evaluated lung tissue damage, encompassing alveolar congestion, hemorrhage, inflammatory cell aggregation, and edema. Arterial blood gas analysis quantified partial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) pressures.

Results: Celecoxib-treated rats exhibited reduced oxidative stress markers with lower MDA levels, indicating decreased oxidative damage in lung tissue. Moreover, TNF-α and other pro-inflammatory cytokines were significantly reduced in lung tissues of Celecoxib-treated rats, indicating its anti-inflammatory effects. Histopathological examination revealed reduced lung tissue damage in Celecoxib-treated rats, including alveolar congestion, hemorrhage, and inflammatory cell aggregation. Arterial blood gas analysis showed improved oxygenation (PaO_2) in the Celecoxib-treated group compared to untreated sepsis rats.

Conclusions: Celecoxib demonstrated preventive effects against sepsis-induced lung injury in rats by mitigating oxidative stress and inflammation, thereby preserving lung tissue integrity-further research, including clinical trials, to validate its effectiveness and safety in human sepsis management.

Keywords: Celecoxib, lung injury, sepsis, anti-inflammation

Sepsis is a significant clinical condition with global implications, particularly within critical care units. The occurrence of multiple organ dysfunction during the hyperactive immune response to infections is closely linked to a significant mortality rate ranging from 25% to 52% [1]. The lungs, kidneys, and liver

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are among the organs that are primarily impacted in the early stages of sepsis. Dysfunction in two or three of these factors strongly correlates with increased mortality rates in patients with sepsis [2]. The hyperactive immune response aimed at combating and containing an infection leads to a phenomenon known as a "cytokine storm" [3]. Cytokines play a significant role as pleiotropic regulators in modulating the immune response and are crucial in the intricate pathophysiology of sepsis. By exhibiting dual pro- and anti-inflammatory characteristics, they can modulate the immune response in the context of infection.

Prior studies have investigated the effects of inhibiting inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α). At the same time, other research has explored the outcomes of suppressing Cyclooxygenase 2 (COX-2) activity in sepsis. For instance, Ozer *et al*. [4] conducted a study where they investigated the effects of administering infliximab (IFX), an antibody that targets TNF-α, as a preventive measure prior to cecal ligation and puncture (CLP) surgery. The findings of their research demonstrated improved survival rates in septic animals. Another study investigated a reduced mortality rate when Celecoxib (CLX), a specific COX-2 inhibitor, was applied after CLP [5]. The survival rates of 57% and 43% were reported in the studies, indicating the potential to improve these outcomes by adjusting the treatment dosage and timing [6]. As substantiated by prior research, these factors are widely recognized as pivotal in efficiently managing sepsis [7-9].

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are pathological conditions characterized by the sudden onset of respiratory failure, resulting in substantial morbidity and mortality [10]. Empirical evidence suggests that individuals who successfully recover from acute lung injury (ALI) experience a detrimental effect on their long-term quality of life [11]. Significant progress has been made in comprehending the epidemiological aspects, pathogenic mechanisms, and therapeutic approaches to this ailment. Nevertheless, additional advancements are required in order to diminish further the rates of mortality and morbidity associated with Acute Lung Injury (ALI) and acute respiratory distress syndrome (ARDS) [12].

Celecoxib is a pharmaceutical agent from non-steroidal anti-inflammatory drugs. This substance is frequently employed to alleviate pain, inflammation, and swelling resulting from various conditions, including arthritis, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and menstrual cramps [6]. The mechanism of action of Celecoxib involves the inhibition of COX-2, an enzyme. The enzyme COX-2 is accountable for synthesizing prostaglandins, bioactive lipid mediators that contribute to inflammation and pain perception [13]. Celecoxib works as a medicine by stopping the cyclooxygenase-2 (COX-2) pathway. This is a mechanism that stops prostaglandin production from the beginning. This mechanism of action ultimately results in the attenuation of inflammatory responses and the alleviation of pain [13].

Celecoxib differs from other non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and naproxen because it is a selective COX-2 inhibitor. This means that it mainly targets COX-2 and leaves COX-1 alone. The enzyme COX-1 plays a crucial role in synthesizing prostaglandins, which are essential for maintaining the protective mucosal lining in the gastrointestinal tract, which encompasses both the stomach and intestines [14].

This experimental study aims to evaluate the preventive effect of Celecoxib in a rat sepsis model in the primarily affected organ, the lung.

METHODS

Animals

The present study employed a sample of 30 male Wistar albino mature rats, whose average weight was 200 to 250 g. The experiments carried out in this study adhered to the guidelines specified in the Guide for the Care and Use of Laboratory Animals, as adopted by the National Institutes of Health in the United States. Following the acquisition of ethical approval from the Animal Ethics Committee (Ethical number: 2523075001) at Demiroğlu Bilim University, the laboratory rats utilized in the experiment were obtained from the Experimental Animal Laboratory at the same institution. The rats were granted unrestricted food availability and were housed in steel enclosures within a controlled environment, where the temperature was maintained at 22 ± 2 °C and a light/dark cycle of 12 hours was upheld.

Experimental Procedures

A research investigation was undertaken, encompassing a cohort of 30 rodents. A total of twenty rats were allocated randomly into three separate groups. The rats were subjected to the feces intraperitoneal-injection group (FIP) procedure to induce a sepsis model. A cohort of ten rats was partitioned into two distinct groups: one group received regular treatment, while the other group remained untreated and served as the control. The FIP rat model was established utilizing a methodology previously delineated by Karaali *et al*. [15]. The collection of fecal samples was followed by their suspension in a saline solution, creating a fecal saline solution. Subsequently, the subjects were administered intraperitoneal injections at 1 gram per kilogram of body weight. The formation of study groups was designed subsequently: Group 1 comprised a cohort of ten individuals designated as the study's control group. The subjects did not undergo any surgical interventions and were administered nutrition orally.

In contrast, Group 2 comprised ten individuals diagnosed with Feces Intraperitoneal Injection (FIP). The experimental cohort was administered an intraperitoneal placebo of 1 ml/kg/day of 0.9% NaCl saline. In Group 3, 10 subjects received an intraperitoneal administration of a combination of FIP and Celecoxib at 50 mg/kg/day. All interventions were administered after a one-hour Focused Intervention Protocol (FIP). The research inquiry was completed within a 24-hour duration. A total of six rats experienced mortality within the initial 24-hour period following the procedure, leading to their subsequent exclusion from the study. Four rats from the placebo group and two from the Celecoxib group were found to have expired.

Following the completion of the study, euthanasia was performed on all animals using cervical dislocation, utilizing an anesthesia protocol comprising Ketamine (100 mg/kg, Ketasol, Richterpharma AG Austria) and xylazine (50 mg/kg, Rompun, Bayer, Germany). Blood samples were collected through a cardiac puncture to conduct a biochemical analysis.

Determination of TNF-α in Plasma

The measurement of plasma TNF-α levels was conducted using enzyme-linked immunosorbent assay (ELISA) kits that were commercially available and obtained from Biosciences and Abcam. The measurements were performed following the manufacturer's provided guidelines. The plasma samples underwent dilution at a ratio of 1:2 by the manufacturer's guidelines. The quantification of TNF-α was conducted in duplicate.

Measurement of Lipid Peroxidation

Lipid peroxidation was measured in plasma samples by evaluating malondialdehyde (MDA) levels as a thiobarbituric acid reactive substance. The experimental procedure consisted of adding trichloroacetic acid and TBARS reagent to the plasma samples, followed by thorough mixing and subsequent incubation at 100 °C for 60 minutes. After the samples were cooled on ice, centrifugation was conducted at a speed of 3000 revolutions per minute for 20 minutes. Following this, absorbance was measured on the resultant supernatant at a specific wavelength of 535 nm.

Histopathological Examination of Lung

To perform histological analysis, anesthesia was administered to all animals using intraperitoneal injections of ketamine (40 mg/kg, Alfamine®, Alfasan International B.V., Holland) and xylazine (4 mg/kg, Alfazyne®, Alfasan International B.V., Holland). The subjects underwent perfusion with a 200 ml solution containing 4% formaldehyde in 0.1 M phosphate-buffered saline (PBS). The kidney sections, which were five µm thick and had been preserved in formalin, underwent staining using the hematoxylin and eosin (H&E) technique. The sections were obtained using an Olympus C-5050 digital camera securely attached to an Olympus BX51 microscope. The primary histopathological lung damage score was calculated using the methodology described in prior research investigations. To summarize, the assessment of histopathological lung injury encompassed the measurement of several parameters, namely alveolar congestion (A.C.), hemorrhage (H), leukocyte infiltration or aggregation in air spaces/vessel walls (A.L.), perivascular/interstitial edema (P.E.), and the thickness of the alveolar wall/hyaline membrane formation (T.A.). The severity of each item was evaluated utilizing a grading scale encompassing a range from 1 to 4. Each grade was associated with a distinct percentage range: Grade 1 denoted a severity level ranging from 0% to 25%, Grade 2 denoted a severity level ranging

from 25% to 50%, Grade 3 denoted a severity level ranging from 50% to 75%, and Grade 4 denoted a severity level ranging from 75% to 100% [15].

Arterial Blood Gas Analysis

Blood samples, measuring 0.2 mL, were obtained from the carotid artery of rats belonging to each experimental group precisely 24 hours after the surgical procedure. Subsequently, the gathered blood samples were subjected to analysis employing a blood gas analyzer in order to quantify the concentrations of PaO_2 and $PaCO_2$.

Statistical Analysis

The data are presented as mean values accompanied by the standard error of the mean (SEM). The data analyses were conducted using SPSS version 15.0 for Windows. The data underwent analysis using the non-parametric Mann-Whitney U test. Statistical significance was attributed to p-values that were equal to or less than 0.05

RESULTS

Malondialdehyde (MDA) (nM/mg protein)

Compared to the Normal Control group (11.2 ± 0.9 nM/mg protein), the FIP and Saline Group demonstrated a significant increase in MDA levels (43.2 ± 2.5 nM/mg protein, $p < 0.001$). However, the FIP and 50 mg/kg Celecoxib Group showed a partial attenuation of MDA levels (27.6 ± 1.9 nM/mg protein) compared to the FIP and Saline Group ($p < 0.01$) (Table 1).

Tumor Necrosis Factor-alpha (TNF-α) (pg/mL)

The FIP and Saline Group exhibited a significant elevation in TNF alpha levels (415.1 ± 13.9 pg/mL) compared to the Normal Control group (13.8 ± 2.3 pg/mL, $p < 0.001$). Conversely, the FIP and 50 mg/kg Celecoxib Group displayed a significant reduction in TNF alpha levels (151.3 ± 7.6 pg/mL) compared to the FIP and Saline Group ($p < 0.001$) (Table 1).

Alveolar Congestion (AC)

Compared to the Normal Control group (0.1 ± 0.1), the FIP and Saline Group demonstrated a significant increase in alveolar congestion (3.1 ± 0.1, p < 0.001). However, the FIP and 50 mg/kg Celecoxib Group showed a substantial reduction in alveolar congestion (0.6 ± 0.2) compared to the FIP and Saline Group ($p < 0.001$). (Table 2, Fig. 1).

Hemorrhage (H)

The FIP and Saline Group exhibited a significant increase in hemorrhage (2.5 ± 0.3) compared to the Normal Control group (0.2 ± 0.2, $p < 0.001$). Conversely, the FIP and 50 mg/kg Celecoxib Group displayed a partial reduction in hemorrhage (0.8 ± 0.2) compared to the FIP and Saline Group ($p < 0.001$). (Table 2, Fig. 1).

Aggregation in Air Spaces/Vessel Walls (A.L.)

In comparison to the Normal Control group (0.1 ± 0.1), the FIP and Saline Group showed a significant increase in aggregation in air spaces/vessel walls (2.2 ± 0.1, $pp < 0.001$). On the other hand, the FIP and 50 mg/kg Celecoxib Group demonstrated a partial reduction in aggregation (0.9 ± 0.1) compared to the FIP and Saline Group ($p < 0.001$). (Table 2, Fig. 1).

Perivascular/Interstitial Edema (P.E.)

The FIP and Saline Group exhibited a significant increase in perivascular/interstitial edema (2.6 ± 0.3) compared to the Normal Control group (0.2 ± 0.1, $p <$

Table 1. The results of the biochemical analysis in the three study groups: Normal control, FIP and saline group, and FIP and 50 mg/kg celecoxib group

	Normal control	FIP and saline	FIP and 50 mg/kg celecoxib
MDA (nM/mg protein)	11.2 ± 0.9	43.2 ± 2.5**	27.6 ± 1.9$^{\#}$
TNF-α (pg/ml)	13.8 ± 2.3	415.1 ± 13.9**	151.3 ± 7.6$^{\#\#}$

Results were presented as mean ± SEM. MDA = Malondialdehyde, TNF = Tumor Necrosis Factor, FIP = Fecal Intraperitoneal Statistical analyses were performed by one- way ANOVA. *$p < 0.05$, **$p < 0.001$ different from normal groups; #$p < 0.01$, ##$p < 0.001$ different from FIP and saline group.

Table 2. The results of the histopathological examination of the lung in the three study groups: Normal control, FIP and saline group, and FIP and 50 mg/kg celecoxib group

	Normal control	FIP and saline	FIP and 50 mg/kg celecoxib
AC (alveolar congestion)	0.1 ± 0.1	3.1 ± 0.1*	0.6 ± 0.2##
H (hemorrhage)	0.2 ± 0.2	2.5 ± 0.3**	0.8 ± 0.2##
AL (aggregation in air spaces/vessel walls)	0.1 ± 0.1	2.2 ± 0.1**	0.9 ± 0.1##
PE (perivascular/interstitial edema)	0.2 ± 0.1	2.6 ± 0.3**	1.4 ± 0.2#
TA (thickness of the alveolar wall)	0.1 ± 0.1	2.6 ± 0.4**	1.1 ± 0.1##

Results were presented as mean ± SEM. FIP = Fecal Intraperitoneal

Statistical analyses were performed by one- way ANOVA. *$p < 0.01$, ** $p < 0.001$ different from normal groups; # $p < 0.05$, ## $p < 0.001$ different from FIP and saline group

0.001). Conversely, the FIP and 50 mg/kg Celecoxib Group displayed a partial reduction in edema (1.4 ± 0.2) compared to the FIP and Saline Group ($p < 0.05$). (Table 2, Fig. 1).

Thickness of the Alveolar Wall (T.A.)

In contrast to the Normal Control group (0.1 ± 0.1), the FIP and Saline Group demonstrated a significant increase in the thickness of the alveolar wall (2.6 ± 0.4, $p < 0.001$). However, the FIP and 50 mg/kg Celecoxib Group showed a substantial reduction in alveolar wall thickness (1.1 ± 0.1) compared to the FIP and Saline Group ($p < 0.001$). (Table 2, Fig. 1).

Partial Pressure of Oxygen (PaO_2) in mmHg

Compared to the Normal Control group (104.2 ± 5.3 mmHg), the FIP and Saline Group demonstrated a significant reduction in PaO_2 (65.2 ± 8.1 mmHg, $p < 0.01$). However, the FIP and 50 mg/kg Celecoxib Group showed a partial improvement in PaO_2 (78.5 ± 6.3 mmHg) compared to the FIP and Saline Group ($p < 0.05$) (Table 3).

Partial Pressure of Carbon Dioxide ($PaCO_2$) in mmHg

In comparison to the Normal Control group (42.3 ± 3.5 mmHg), the FIP and Saline Group displayed a significant decrease in $PaCO_2$ (32.3 ± 2.5 mmHg, $p < 0.05$). There was no significant difference in PaCO2 between the FIP and 50 mg/kg Celecoxib Group (33.1 ± 4.9 mmHg) and the FIP and Saline Group (Table 3)

DISCUSSION

This study examines the potential protective effects of Celecoxib in mitigating lung damage induced by sep-

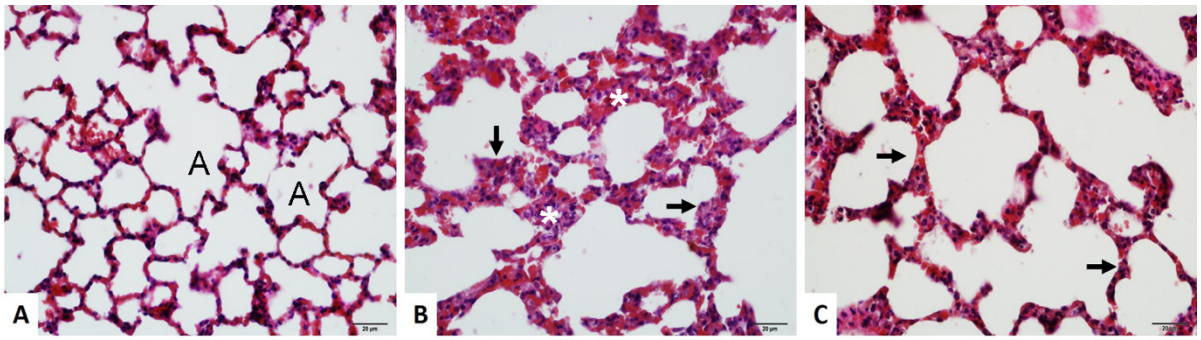

Fig. 1. Lung histopathology x40 magnification H&E staining. (A) Normal control group lung, (A = Alvelol), (B) FIP groups showed severe histopathologic alteration related to increased alveolar inflammation (*) and septal thickness (arrow), (C) FIP and 1 ml/kg % 0.9 NaCl saline (placebo) groups showed severe histopathologic alteration related to increased alveolar inflammation (*) and septal thickness (arrow), and (D) FIP and 50 mg/kg Celecoxib groups showed decreased inflammation and septal thickening (arrow)

Table 3. The results of the blood gas analysis in the three study groups: Normal control, FIP and saline group, and FIP and 50 mg/kg celecoxib group

	Normal control	FIP and saline	FIP and 50 mg/kg celecoxib
PaO_2 (mmHg)	104.2 ± 5.3	65.2 ± 8.1*	78.5 ± 6.3#
$PaCO_2$ (mmHg)	42.3 ± 3.5	32.3 ± 2.5*	33.1 ± 4.9

Blood gase analysis: results were presented as mean ± SEM. FIP = Fecal Intraperitoneal

Statistical analyses were performed by one- way ANOVA and post- hoc Bonferroni test. * $p < 0.05$, different from normal groups; #$p < 0.05$ different from FIP and saline group

sis. Sepsis is a critical medical condition distinguished by an aberrant immune response to infection, resulting in extensive inflammation and impaired organ function, such as ALI and ARDS. The lungs are particularly vulnerable to the detrimental effects of sepsis due to the massive release of pro-inflammatory cytokines and chemokines, leading to endothelial and epithelial cell injury, increased vascular permeability, and infiltration of inflammatory cells.

The results of this study demonstrate that Celecoxib administration exerts a protective role against sepsis-induced lung damage. Histopathological examination revealed that septic animals treated with Celecoxib exhibited reduced alveolar congestion, hemorrhage, aggregation in air spaces/vessel walls, and perivascular/interstitial edema compared to untreated septic animals [16]. These findings suggest that Celecoxib attenuates lung inflammation and edema, preserving the lung architecture. In a study by Liu [17], they describe similar results histologically in a model of lung injury induced by hyperoxia in rats.

Furthermore, the biochemical analysis showed a significant decrease in oxidative stress markers, such as MDA, in the lungs of septic animals treated with Celecoxib. Oxidative stress is a crucial contributor to the pathogenesis of sepsis-induced lung injury, and Celecoxib's antioxidant properties likely play a crucial role in mitigating oxidative damage in lung tissue. By reducing oxidative stress, Celecoxib may protect lung cells from oxidative injury and maintain their function. Mazhari *et al*. [18]'s study, observed a decreased MDA in a group that takes Celecoxib and prevents oxidative stress in varicocele.

Moreover, Celecoxib treatment decreased pro-inflammatory cytokines, such as TNF-alpha, in the lung tissue of septic animals. These cytokines are critical mediators of the inflammatory response in sepsis, and their excessive production contributes to tissue damage. Celecoxib's anti-inflammatory effects, mainly through inhibition of COX-2, may attenuate the inflammatory cascade, leading to reduced lung injury. COX-2 has a crucial role in inflammation) process, the significant effect of Celecoxib in the septic process is by inhibiting COX-2 [17]. The results of the biochemical analysis revealed that FIP induction led to a significant increase in oxidative stress marker MDA and pro-inflammatory cytokine TNF alpha levels. These findings align with previous studies that have shown the involvement of oxidative stress and inflammation in the pathogenesis of FIP [17-19]. Celecoxib administration at 50 mg/kg significantly reduced MDA and TNF alpha levels, indicating its potential to alleviate oxidative stress and inflammation in FIP. Celecoxib's anti-inflammatory and antioxidant properties likely contribute to these effects, as it inhibits the cyclooxygenase-2 enzyme and reduces the production of pro-inflammatory mediators [20, 21]. Similarly, Gurusamy *et al*. [19] study show the anti-inflammatory effect of Celecoxib in acute lung injury in mice with COX-2 inhibition.

Additionally, Celecoxib enhances the lung's barrier function by preserving the expression of tight junction proteins, such as occludin and claudin-5 [22]. The integrity of the lung's endothelial and epithelial barriers is critical for preventing fluid leakage and maintaining lung homeostasis. As shown in preventing gut barrier tight junction failure [23], Celecoxib's protective effects on tight junction proteins may attenuate lung edema and vascular leakage.

The overall findings of this study suggest that Celecoxib, through its anti-inflammatory, antioxidant, and barrier-protective properties, plays a beneficial role in mitigating sepsis-induced lung damage. By modulating the inflammatory response and oxidative

stress, Celecoxib may prevent excessive lung tissue injury and improve lung function in septic animals. These promising results warrant further investigations to explore the potential therapeutic use of Celecoxib as an adjunct treatment in clinical settings for sepsis-associated lung injury and ARDS.

Limitations

It is essential to acknowledge the limitations of this study, such as the animal model used, the dosing regimen of Celecoxib, and the specific mechanisms underlying its protective effects in sepsis-induced lung damage. Further studies, including clinical trials, are needed to validate these findings and determine the safety and efficacy of Celecoxib in human sepsis patients.

CONCLUSION

The present study provides evidence supporting the protective effects of Celecoxib against sepsis-induced lung damage. By targeting inflammation, oxidative stress, and barrier function, Celecoxib holds potential as a therapeutic agent to mitigate the devastating consequences of sepsis on the lungs. These findings contribute to the growing research on potential treatments for sepsis-induced organ dysfunction, particularly in acute lung injury. They may pave the way for developing novel therapeutic strategies to improve the clinical outcomes of septic patients.

Authors' Contribution

Study Conception: ESB, OE, CD; Study Design: EE, ESB; Supervision: OE, CD; Funding: N/A; Materials: OE; Data Collection and/or Processing: YU, OE; Statistical Analysis and/or Data Interpretation: OE, ESB; Literature Review: ESB; Manuscript Preparation: ESB, CD and Critical Review: OE, GY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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