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Original Research Article

Protective effect of saroglitazar against sepsis-induced acute kidney injury in rats

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Abstract

Purpose: *To assess the effect of saroglitazar (a dual-acting peroxisome proliferator-activated receptor alpha (PPAR-α/γ) agonist in sepsis-induced acute kidney injury (S-AKI) using a rat model.*
Methods: *Female Wistar albino rats were divided into control (n = 12), and study group (n = 24; further divided into groups 1 and 2; n = 12 each) following cecal ligation and puncture (CLP) procedure. Control group received normal saline while study group 1 received normal saline and study group 2 received saroglitazar (2 mg/kg/day) intraperitoneally (IP) twice daily for 5 days. Biochemical markers (malondialdehyde (MDA), neutrophil extracellular traps (NETs), insulin-like growth factor (IGF) binding protein 7 (IGFBP-7), blood urea nitrogen (BUN), creatinine, and nod-like receptor protein 3 (NLRP3), neurolopin-1), histopathology of kidney, as well as enzyme-linked immunosorbent assay (ELISA) were employed to evaluate renal injury and therapeutic effects.*
Results: *Saroglitazar significantly reduced MDA, TNF-α, NETs, IGFBP-7, BUN, creatinine, NLRP3 and neuropilin-1 ($p < 0.05$) compared to control group. Histopathological analysis revealed significantly reduced tubular injury and inflammation in the study group compared to control group ($p < 0.01$)*
Conclusion: *Saroglitazar demonstrates protective and therapeutic effects against S-AKI in rats by reducing inflammation, oxidative stress, and cellular damage. Early saroglitazar use in septic patients may be beneficial, and further clinical studies are warranted to establish its efficacy and safety in managing S-AKI.*

Keywords: *Acute kidney injury, Saroglitazar, Sepsis, Neuropilin-1*

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INTRODUCTION

Acute kidney injury (AKI) commonly arises as an adverse consequence in patients hospitalized in the intensive care unit (ICU) due to sepsis. Sepsis-induced acute kidney renal injury (S-AKI) is a multifaceted and dynamic reaction triggered by the mitochondria. It encompasses inflammation, oxidative stress, impaired microvascular function, and tubular cells' adaptability to the septic condition. This not only increases the likelihood of chronic comorbidities but also significantly increases the mortality rate [1]. It is almost impossible to determine the exact onset of damage in sepsis. Preventing S-AKI is difficult because most patients have already

developed AKI by the time they seek medical attention. Therefore, it is important to provide supportive treatment and limit further damage [2].

Some biomarkers are used to determine AKI. Malondialdehyde (MDA) is a breakdown product of the chain reactions leading to the definitive oxidation of polyunsaturated fatty acids such as linolenic acid. Increased malondialdehyde (MDA) levels may reflect AKI as a measure of oxidative stress as well as cellular destruction [3]. Tumor necrosis factor-alpha (TNF-α) is a cytokine that plays a significant role in regulating inflammatory reactions. High levels of TNF-α indicate elevated levels of inflammation and the possibility of damage to kidney tissue [4]. Neutrophil extracellular traps (NETs) are extracellular structures made up of DNA, histones, and proteins formed from polymorphonuclear granules. Elevated NET levels are additionally linked to AKI as an indicator of inflammation [5]. Insulin-like growth factor (IGF) binding protein 7 (IGFBP-7) is a multifunctional protein that binds to several ligands, including IGFs. Elevated levels of IGFBP-7 suggest compromised kidney function [6]. When included in renal function testing, elevated levels of Blood Urea Nitrogen (BUN) and serum creatinine serve as adjunct indicators of kidney injury. Within the innate immune system is an inflammasome known as nod-like receptor protein 3 (NLRP3).

Release of proinflammatory cytokines, particularly IL-1β/IL-18, and activation of caspase-1 are responses to microbial infection and cellular damage [7]. All vertebrates have two neuropilins, one of which is neuropilin 1 (NRP1). Its functions are important in both healthy bodily functions and disease states. Changes in levels of NLRP3 and neuropilin-1 in the kidney may also be associated with inflammation and renal injury [8]. Peroxisome proliferator-activated receptors (PPARs) are a set of nuclear receptors that regulate several biological processes [9]. Many biological processes rely on target genes regulating the transport and oxidation of fatty acids (FAO), glucose metabolism, cholesterol transport, biosynthesis, apoptosis, and inflammatory response [9]. The PPAR, also known as peroxisome proliferator-activated receptor, consists of three different subtypes: PPAR α, PPAR β/δ, and PPAR γ. These subtypes are found in many mammals. In individuals, the PPAR γ genes are found on the third chromosome (3p25.2). The arrangement consists of 9 exons that cover a distance of over 100 kilobases. This gene generates four distinct forms of PPAR γ, namely γ 1, γ 2, γ 3, and γ 4. The PPAR γ is prevalent in the medullary collecting duct, paraurethral, and bladder epithelium cells [10].

Although not fully understood, studies suggest that PPAR γ plays a vital role in regulating the physiological functions of the kidney. The PPAR agonists are known to have the potential to delay and prevent the progression of many kidney diseases. Studies have demonstrated that PPARγ agonists decrease renal injury by inhibiting mesangial expansion, glomerulosclerosis, tubulointerstitial fibrosis, inflammation, lactation, and atrophy [10].

Saroglitazar is a dual-acting peroxisome proliferator-activated receptor agonist. Saroglitazar, an orally available agent with moderate PPAR activity is rapidly absorbed, and effective in treating diabetic dyslipidemia (DD) [11]. Various glitazar (tesaglitazar, muraglitazar, aleglitazar) were tried to treat DD, but their development was terminated due to side effects related to significant γ effects. Saroglitazar, a new dual PPARα/γ agonist with a dominant PPARα effect and moderate PPARγ effect, is devoid of these side effects [11]. The fact that it is taken orally and has fewer side effects makes it more preferred. In light of this information, more studies on the effect of saroglitazar to ameliorate renal injury are required. This study investigated the therapeutic effect of saroglitazar on acute renal injury generated by sepsis.

EXPERIMENTAL

Animals

A total of 36 albino Wistar female rats weighing between 200 – 250 g were used. The animals have unrestricted access to food and water and are housed in steel cages under standard conditions (22 ± 2 ^{o}C, and 12 h light/dark cycle). Ethical approval was obtained from the Animal Ethics Committee of Istanbul Demiroğlu Bilim University (approval no. 06.02.2023./0723120906) and the animals were cared for in compliance with the internationally accepted guide for the care and use of laboratory animals [12].

Treatment

Two sets of rats were randomly assigned into study (n = 24) and control groups (n = 12), and a sepsis model was created using a cecal ligation and puncture (CLP) technique [13]. Control group underwent no medical procedures and was fed orally. Study group was further divided into 2 groups of 12 rats each. Group 1 (n = 12) underwent CLP surgery and received saline

solution (intraperitoneally (IP) containing 0.9 %w/v sodium chloride. Group 2 (n = 12) underwent CLP surgery and received saroglitazar (Sigma Aldrich, St. Louis, Missouri, USA) at 2 mg/kg/day intraperitoneally for 5 days.

Equal volumes of volume replacement therapies were administered to Groups 1 and 2, which included 10 mL/kg/day of intraperitoneal 0.9 % w/v NaCl after the first hour following surgical operation (30 mL/kg of 0.9 % w/v NaCl). Treatment was administered twice daily every 12 h. The study was completed in 5 days. A total of 6 rats perished (2 rats in CLP and group 2, and 4 rats in group 1).

Cecal ligation and puncture (CLP) procedure

Using sterile methods, a 3 cm midline incision revealed the adjacent intestine and cecum. A 3.0 silk suture secured the cecum below the iliocecal valve. Thereafter, a 22-gauge needle punctured the cecum once. The cecum was gently compressed to remove some excrement from the puncture site. The laparotomy wound was closed with 4-0 polyglactin sutures after the cecum was reinserted.

The animals were allowed to recuperate before returning to their cages. Control group was not treated. Study groups comprising groups 1 and 2 developed sepsis 5 h after cecal ligation and puncture (CLP) [13].

Evaluation of parameters/indices

Biochemical parameters

The animals were put to sleep after treatment, and blood samples were taken for biochemical examination via heart puncture. The kidneys were also removed for histological analysis. The animals were sacrificed using cervical dislocation, and 2 mL of blood was collected following heart puncture for biochemical examination. Ketamine (100 mg/kg, Ketasol, Richterpharma AG Austria) and xylazine (50 mg/kg, Rompun, Bayer, Germany) were used to induce anesthesia. After that, the kidney was removed for histological examination.

Urea and creatinine

Concentrations of creatinine and urea were measured using an automated analysis system along with spectrophotometric techniques. The results were expressed in milligrams per deciliter (mg/dL).

Kidney biochemical analysis

Kidneys were extracted after decapsulation and kept at -20 ^{o}C until additional biochemical testing was performed. A glass homogenizer was used to homogenize the kidney tissues in phosphate-buffered saline (PBS) at a volume 5 times the volume of the recovered tissue, which had a pH ratio of 7.4. After that, the homogenate was centrifuged at 5,000 g for 15 min. The Bradford technique was used to determine protein content of the tissue and bovine serum albumin was utilized as the reference standard. Levels of NLRP3 and neuropilin-1 were quantified using ELISA kits.

Lipid peroxidation

After the plasma was treated with trichloroacetic acid and thiobarbituric acid reactive substances (TBARS) reagent, it was well mixed and incubated at 100 ^{o}C for 60 min. After that, the samples were placed on ice to chill, and centrifuged for 20 min at 3 rpm. Absorbance was measured at 535 nm. Levels of MDA were expressed in nanomolar (nM) units, and tetraethoxypropane was utilized as the reference for calibration.

Plasma TNF-α, NETs, and IGFBP-7 levels

The TNF-α, IGFBP-7, and NET levels in plasma samples were measured using enzyme-linked immunosorbent assay (ELISA) kits (Biosciences and Abcam). The assays were conducted in strict adherence to the manufacturer's protocols.

Histopathological examination of the kidney

Following surgical removal, the kidney was immersed in 10 % formaldehyde solution prepared with 0.1 mM phosphate-buffered saline (PBS) for 72 h. Histological analysis of 5 µm thick kidney sections, preserved in formalin, was carried out using hematoxylin and eosin (H & E) staining. Images of stained sections were captured using an Olympus BX51 microscope paired with an Olympus C-5050 digital camera. An Image-Pro Express 1.4.5 system (Media Cybernetics, Inc., USA) was employed for morphological analysis. Each sample was examined in 10 microscopic fields at a magnification of ×20. The observer conducting the assessment was blinded to the group identities to ensure objectivity. A semi-quantitative method was utilized to assess various kidney tissue abnormalities, including tubular epithelial necrosis, accumulation of necrotic debris in the lumen, tubular dilatation, hemorrhage, and interstitial inflammation across

all study groups. Kidney scoring abnormality was classified as 0 – 5 % (score 0), 6 – 20 % (score 1), 21 – 40 % (score 2), 41 – 60 % (score 3), 61 – 80 % (score 4), and 81 – 100 % (score 5) [14].

Statistical analysis

Data was analyzed using Statistical Packages for Social Sciences (SPSS version 22.0; Inc., Chicago, USA). Results were presented in mean ± standard error of the mean (SEM) and compared using Mann-Whitney U test for non-parametric data, and the Student's t-test for group comparisons. $P < 0.05$ was considered statistically significant.

RESULTS

Mortality and survival

The study began with 24 animals divided equally between study groups and 12 in control group As the study progressed, number of animals in control group, while group 3 (received aroglitazar treatment) remained consistent in size (Figure 1).

Biochemical markers

Study group treated with saroglitazar exhibited significantly lower MDA, TNF-α, NETs, IGFBP-7, BUN, creatinine, NLRP3 and significantly higher neuropilin-1 levels ($p < 0.05$; Table 1).

Kidney histopathology

Kidneys of control group (Figure I A and B) exhibited well-defined renal tubules (t) and glomeruli (G), consistent with normal renal structure (Figure 2). However, kidneys of Group 1 displayed significant histological changes associated with tubular injury (Figure I C and D), including tubular dilatation (*) and necrosis (arrow), indicative of significant renal injury (Figure 2). Kidneys of group 2 exhibited significantly less histopathological damage compared to group 1 (Figure 2 E and F). The reduction in tubular dilatation and necrosis suggests that saroglitazar has a protective effect against CLP-induced kidney injury (Figure 2).

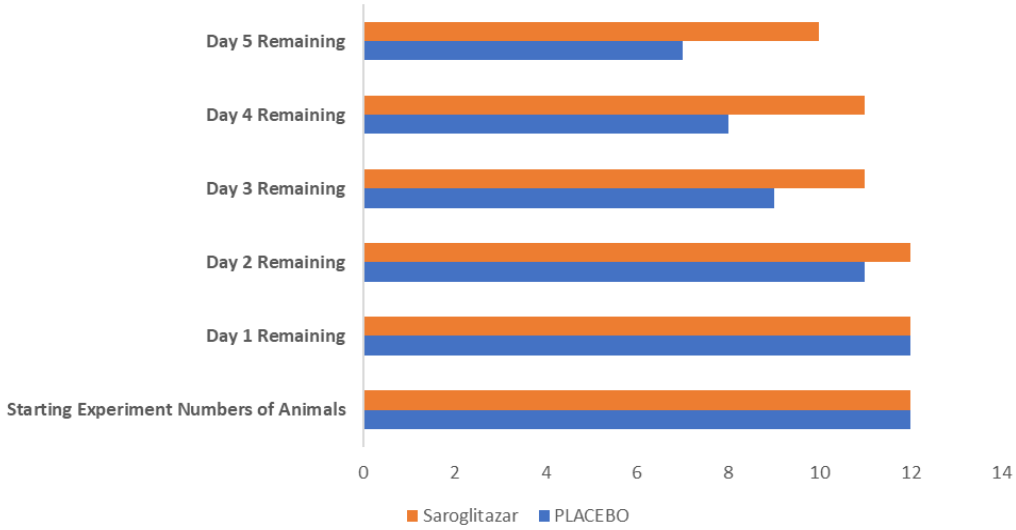

Figure 1: Mortality and Survival numbers of the rats during the experiment

Table 1: Results of biochemical markers in the 3 groups (mean ± SEM)

Parameter	Control	Study group	
		Group 1	*Group 2*
Plasma MDA (nM)	50.1±3.5	148.2±8.2**	105.3±7.4$^{\#}$
Plasma TNF alfa (pg/mL)	17.8±2.2	96.4±9.5*	67.3±3.6$^{\#}$
Plasma NETs (ng/mL)	1.21±0.3	3.42±0.3**	2.9±0.1$^{\#}$
Plasma IGFBP-7 (ng/mL)	0.23±0.06	0.94±0.1*	0.58±0.1$^{\#}$
Plasma BUN (mg/dL)	20.8±0.5	37.2±2.03*	25.8±1.9$^{\#}$
Plasma Creatinin (mg/dL)	0.27±0.03	0.68±0.1**	0.36±0.09$^{\#\#}$
Kidney NLRP3 (pg/mg protein)	0.95±0.0.08	16.4±2.7**	11.5±1.6$^{\#}$
Kidney Neuropilin-1 (pg/mg protein)	24.5±4.1	39.8±3.9*	56.2±6.5$^{\#}$

*$P < 0.01$, **$p < 0.0001$ vs control, $^{\#}p < 0.05$, $^{\#\#}p < 0.001$ vs Group 1

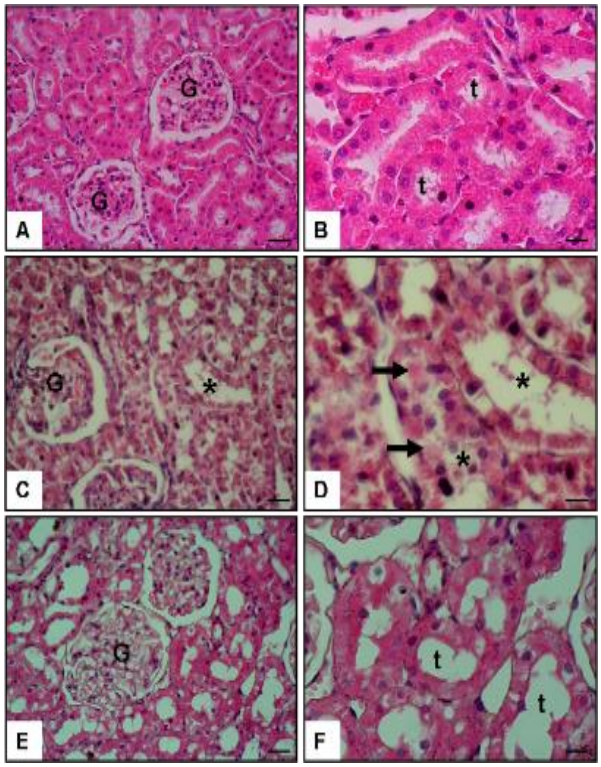

Figure 2: Kidney histopathology using H and E stain (magnification x10 and x 20). A-B: Control group kidney, renal tubules (t), Glomerulus (G); C-D: Group 1 showed severe histopathologic alteration related to tubular injury including dilatation (*) and necrosis (arrow), E-F: Group 2 showed decreased injury

Histopathological grading

Saroglitazar significantly decreased tubular epithelial necrosis, luminal necrotic debris, tubular dilatation, amount of bleeding, and interstitial inflammation compared to normal saline and control groups ($p < 0.05$; Table 2).

DISCUSSION

This is the first study that investigated the effect of saroglitazar on S-AKI. The outcomes of rat tests showed that saroglitazar has both curative and preventive effects on S-AKI. This study showed that MDA levels decreased significantly in saroglitazar-treated group which is in tandem with the results of Adu-Amankwaah *et al* [15]. This suggests that saroglitazar increases antioxidant capacity decreases cellular oxidative stress, and prevents cell damage by combating free radicals. Low levels of MDA significantly reduced cellular lipid peroxidation, thus keeping cellular damage to a minimum. Similarly, the TNF-α level significantly decreased in saroglitazar-treated group. Previous studies have reported that saroglitazar decreased hepatic TNF-α expression [13]. Low levels of TNF-α indicate that the inflammation is under control and inflammatory responses are suppressed. There was a significant reduction in NET levels following saroglitazar treatment consistent with the findings from previous study [16]. This suggests that PPAR agonists stabilize immune responses and reduce tissue damage by regulating the immune system, reducing cellular damage, and decreasing NETs.

Another key protein indicated in this process is the IGFBP-7. This study showed that levels of IGFBP-7 were significantly lower following saroglitazar administration. Low levels of IGFBP-7 indicate low cellular proliferation and apoptotic responses. Previous studies have shown that IGFBP-7 is directly related to AKI and support the findings of this study [6]. This may suggest that saroglitazar positively affects these processes. Reduction in BUN and creatinine levels in the saroglitazar-treated group supports the potential of saroglitazar in protecting renal function. This suggests that saroglitazar reduces kidney damage, and preserves kidney functionality. The decrease in NLRP3 and neuropilin-1 levels indicates that inflammation and apoptotic processes are controlled, cellular damage is reduced, and the integrity of tissues is maintained in saroglitazar treated group. It has been reported in previous studies that saroglitazar decreases NLRP3 levels [17].

To the best of our knowledge, no existing study in the literature shows that saroglitazar directly decreases neuropilin-1 levels. However, a reduction in neuropilin-1 level suggests that saroglitazar suppresses inflammation.

Table 2: Histopathological grading in the 3 groups (mean ± SEM)

Parameter	Control	Study groups	
		Group 1	***Group 2***
Tubular epithelial necrosis	0.1±0.1	4.1±0.3*	0.9±0.2$^{\#\#}$
Luminal necrotic debris	0.1±0.2	3.2±0.4*	1.1±0.2$^{\#\#}$
Tubular Dilatation	0.1±0.1	2.1±0.1*	0.8±0.1$^{\#\#}$
Hemorrhage	0.1±0.2	1.2±0.3*	0.6±0.2$^{\#}$
Interstitial inflammation	0.1±0.1	1.3±0.2*	0.7±0.1$^{\#}$

*$P < 0.0001$ vs control, $^{\#}p < 0.01$, $^{\#\#}p < 0.001$ vs Group 1

This finding may be an essential clue to understanding the potential immunomodulatory effects of saroglitazar. This study showed significant improvement in symptoms, such as bleeding, tubular dilatation, luminal necrotic debris, tubular epithelial necrosis, and interstitial inflammation, in the group treated with saroglitazar following CLP procedure. These findings demonstrate that saroglitazar prevents the occurrence of S-AKI.

Previous studies revealed that saroglitazar effectively inhibits inflammation in rat models [18,19]. Furthermore, endothelial PPARγ facilitates vasodilation and inhibits inflammation and oxidative stress by regulating gene expression in NADPH oxidase, catalase, and superoxide dismutase [20] which is regulated by saroglitazar. The anti-inflammatory effect of saroglitazar may potentially mitigate sepsis-induced inflammation, while its antioxidant characteristics may alleviate oxidative stress. In addition, the vasodilatory effect may potentially improve renal perfusion.

Limitations of the study

This study has some limitations. Since it was conducted only on animal models, relevance to the human body is limited. Furthermore, only the effect of saroglitazar was studied and comparison with other treatments may be required. The limited sample size and brief follow-up time may limit the generalizability of the results and long-term consequences.

CONCLUSION

Saroglitazar prevents kidney injury by reducing sepsis-induced inflammation and alleviating oxidative stress. Therefore, early use of saroglitazar in emergency departments, especially in patients with suspected sepsis or sepsis-related complications should be considered. However, these findings need to be supported by clinical studies, and the efficacy and safety of using saroglitazar in emergency departments should be further investigated.

DECLARATIONS

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Ethical approval

Animal Ethics Committee of Demiroğlu Science University Istanbul, Türkiye (Science University, approved the study (approval no. 06.02.2023./0723120906).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Duygu Burcu Arda, Ejder Saylav Bora, Mustafa Agah Tekindal and Oytun Erbaş contributed equally to the study and made critical revisions related to the relevant intellectual content of the manuscript. Special thanks to Osman Sezer Cinaroglu for his technical help.

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