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Barbaloin attenuates ischemia reperfusion-induced oxidative renal injury via antioxidant and anti-inflammatory effects

Ayhan Tanyeli[1] , Mustafa Can Guler[1], Ersen Eraslan[2], Fazile Nur Ekinci Akdemir[3], Omer Topdagi[4], Elif Polat[5], Tuncer Nacar[1]

[1]Ataturk University, Faculty of Medicine, Department of Physiology, Erzurum, Turkey
[2]Bozok University, Faculty of Medicine, Department of Physiology, Yozgat, Turkey
[3]Agri Ibrahim Cecen University, High School of Health, Department of Nutrition and Dietetics, Agri, Turkey
[4]Ataturk University, Faculty of Medicine, Department of Internal Medicine, Erzurum, Turkey
[5]Ataturk University, Faculty of Medicine, Department of Biochemistry, Erzurum, Turkey

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Abstract
The goal of this research is to find out the protective effects of barbaloin on kidney injury by ischemia-reperfusion. In this research, the rats were allocated into four groups. Study groups are programmed as; sham control, ischemia-reperfusion, ischemia reperfusion+DMSO and ischemia reperfusion+barbaloin. When the study was completed, various oxidative stress parameters like total oxidant status, total antioxidant status, oxidative stress index, myeloperoxidase, and cytokine levels such as tumor necrosis factor-α and interleukin-1β were measured in all groups. Oxidant and inflammatory parameters increased, and antioxidant parameters decreased in the ischemia reperfusion group, but antioxidant parameters increased while oxidant and inflammatory parameters decreased in the treatment group. These results have shown us that barbaloin has a protective effect against oxidative renal injury caused by ischemia-reperfusion.

Keywords: Barbaloin, Ischemia-Reperfusion, Kidney, Oxidative stress, Cytokines

Introduction

Acute kidney injury (AKI) could be induced by various conditions, including kidney ischemia, exposure to toxic substances, obstruction of urinary tracts, and severe inflammation [1]. Renal ischemia-reperfusion (I/R) injury, a widespread reason for AKI [2], may occur due to several surgical operations such as cardiac surgery, renal transplantation and vascular surgery [3,4]. As a widespread clinical syndrome, renal I/R injury results in a high rate of complications and death [5]. Renal, I/R injury pathophysiology mechanisms are complex and involve several signaling pathways that are associated with the interaction of apoptosis-related factors, inflammatory cytokines/chemokines, ROS, and oxidative stress [6,7]. Free radicals induced by oxidative stress play a critical role in I/R pathophysiology [8]. When the mitochondrial respiratory chain is dysfunctional during the ischemic phase, this leads to ROS production, and the reperfusion phase enhances this production [9]. Lipid peroxidation is the most detrimental feature of ROS. Malondialdehyde (MDA), as a lipid peroxidation end-product, much more exacerbates the cell damage [10].

The ratio of total oxidant status (TOS) to total antioxidant status (TAS) is called an oxidative stress index (OSI), and it reflects the balance between oxidative and antioxidative systems [11]. In AKI (induced by I/R), the inception and improvement of kidney dysfunction and tubular injury are associated with infiltrating inflammatory cells [12]. Myeloperoxidase (MPO) is secreted by activated neutrophils and takes the role of catalyzing hypochlorous acid and chloride anion formation. For this reason, MPO activity is preferred for the evaluation of neutrophil activation [13]. Inflammation constitutes a major part of I/R pathogenesis by way of playing a key role for cytokines, particular cells and adhesion molecules [14]. I/R is responsible for the upregulation of inflammatory pathways such as tumor necrosis factor-α

***Coresponding Author:** Ayhan Tanyeli, Ataturk University, Faculty of Medicine, Department of Physiology, Erzurum, Turkey
E-mail: ayhan.tanyeli@atauni.edu.tr

(TNF-α) and interleukin-1β (IL-1β) [15,16]. Although important developments about understanding ischemic AKI pathogenesis, in the last decades, there is still supportive therapy instead of curative approaches [17].

Barbaloin(10-β-D-glucopyranosyl-1,8-dihydroxy3-(hydroxymethyl)-9(10H)-anthracenone), the primary active ingredient in aloe has gained increasing attention [18]. Barbaloin is a specific extract of aloe and has been determined to have several pharmacological effects such as anti-inflammatory, free radical scavenging, antiviral, and antibacterial properties [18-22]. Barbaloin attenuated inflammation, oxidative stress and thus prevented liver injury induced by alcohol in mice experimental models [23]. Different agents with anti-inflammatory, antioxidant and radical scavenging properties have been reported in alleviation or elimination of I/R injuries [24-26]. We searched the effects of barbaloin on several cytokine levels and oxidative stress parameters in bilateral renal I/R applied rats.

Material and Methods

Laboratory conditions and Drugs

This study was fulfilled in Atatürk University Experimental Animal Research and Application Center, Atatürk University Faculty of Medicine Department of Physiology. The present work has also been confirmed by Atatürk University Experimental Animals Local Ethics Committee. All rats were kept in a laboratory environment a 12-night/12-day, with a humidity of 55 % and a mean temperature of 21 degrees. Experimental animals were fed with standard pellet feed and water. However, all rats were starved before 12 hours from the experiment. For sacrification, 10 mg/kg i.p. xylazine hydrochloride (Rompun®, Bayer, Istanbul) and 60 mg/kg, i.p. ketamine (Ketalar®, Pfizer, Istanbul) were used. Barbaloin was supplied by Sigma-Aldrich Co, USA.

Groups and Ischemia-Reperfusion Model

In the present study, 32 Wistar albino male rats were weighed (220-240 g) and randomly divided into four groups. In group I, the back region was shaved and cleaned. Also, the back region was opened with an incision under the anesthesia and closed again without the I/R model and any medication application. In group II, the incision area was cleaned with povidone-iodine. Bilateral renal arteria and veins were held with atraumatic microvascular clamp for 1 hour. Later, allowing blood circulation for 24 hours by opening the clamps in the reperfusion period. Incision closed with silk 3/0 suture. When the reperfusion ended, renal tissues were removed. In group III, DMSO purchased from Sigma Aldrich Co. DMSO was administered by oral gavage for one week before the experiment and the latest dose was applied 30 minutes before reperfusion. In group IV (I/R + 20 mg/kg barbaloin), barbaloin was performed to rats via oral gavage for one week before the experiment, and the latest dose was applied 30 minutes before reperfusion as mentioned in the previous study [27]. Later, as described in group II, the I/R model was established. All procedures were performed under anesthesia of xylazine hydrochloride and ketamine. Finally, when the experiment ended, renal tissues were washed and kept frozen until the biochemical analysis.

Biochemical Analysis of Renal Tissues

After the tissues have been homogenized, all biochemical analyses were made in the homogenized tissues. In renal tissue samples, MDA level to define lipid peroxidation status due to the method presented by Ohkawa et al, were measured [28]. The results were given as μmol/g protein. It was analysed using the superoxide dismutase (SOD) activity specification protocol detected by Sun et al [29]. SOD activity results of tissue samples were given as U/mg protein. MPO activity of the kidney tissue was measured using a method improved by Bradley et al [30]. The results of MPO activity tissue were presented as U/g protein. TOS measurement was made with commercially available kit (Rel Assay Diagnostics). TAS value was evaluated with the commercial kit (Rel Assay Diagnostics, Gaziantep, Turkey). TAS and TOS results were presented as nmol/L. The ratio of TOS to TAS was accepted as the OSI. OSI value was detected as follows: OSI = [(TOS, μmol H_2O_2 equivalent/L)/(TAS, mmol Trolox equivalent/L) × 10]. OSI has been proposed. TNF-α and IL-1β levels were determined with the commercially available kit (Elabscience, Wuhan, China). Following bilateral renal I/R, proinflammatory cytokine levels obtained from renal homogenate were determined by enzyme-linked immunosorbent assay (ELISA, BioTEK Powerwave XS Winooski, UK).

Statistical Analysis

All results were presented as mean ± SD. The statistical significance was analyzed using the Student's t-test. The difference was considered statistically significant at $P < 0.05$. The statistical analyses were performed using the SPSS 20 Program.

Results

It was determined that TOS and OSI values increased while TAS values decreased in I/R and I/R+DMSO groups compared to the sham group. However, it has been observed that TAS value increased, but TOS and OSI values decreased significantly due to barbaloin treatment (Table 1; $p<0.05$). MDA and MPO levels were increased, whereas SOD activity was significantly decreased in I/R and I/R+DMSO groups compared to the sham group.

Table 1. Mean±SD results of TAS (mmol/L), TOS (μmol /L) and OSI activities all experiment groups

Parameters/Groups	TAS (mmol/L)	TOS (μmol /L)	OSI
Sham	2.70±0.19 [a]	6.11±0.50 [a]	0.22±0.02 [a]
I/R	1.43±0.14 [a,b]	8.44±0.91 [a,b]	0.59±0.08 [a,b]
I/R+DMSO	1.38±0.13 [a,b]	8.52±0.77 [a,b]	0.61±0.06 [a,b]
I/R+Barbaloin	2.53±0.19 [b]	6.59±0.67 [b]	0.26±0.02 [b]

[a,b]: The significance relationship at the level of $p<0.05$, represents a meaningful relationship between groups with the same letters

Table 2. Mean ± SD results of MDA (μmol/g protein), MPO (U/g protein) and SOD (U / mg protein) activities of all experimental groups

Groups/ Parameters	MPO (U/g protein)	MDA (μmol/g protein)	SOD (U/ mg protein)
Sham	39068.98±4602.39 [a]	73.07±5.62 [a]	615.94±68.28 [a]
I/R	81058.63±7297.27 [a,b]	131.15±7.30 [a,b]	302.18±17.79 [a,b]
I/R+DMSO	83375.31±8366.29 [a,b]	132.91±8.47 [a,b]	298.09±16.54 [a,b]
I/R+Barbaloin	41259.91±1846.15 [b]	76.77±4.16 [b]	552.68±33.92 [b]

[a,b]: The significance relationship at the level of $p<0.05$, represents a meaningful relationship between groups with the same letters

On the contrary, it was observed that these results changed significantly due to barbaloin treatment (Table 2; $p<0.05$). It was also found that TNF-α and IL-1β levels increased in I/R and I/R+DMSO groups and decreased significantly with barbaloin treatment. (Table 3; $p<0.05$).

Table 3. Mean ± SD results of TNF-α (pg/mg protein) and IL-1β (pg/mg protein) levels of all experimental groups

Parameters/Groups	TNF-α (pg/mg protein)	IL-1β (pg/mg protein)
Sham	22061.77±1967.07 [a]	24241.29±2701.64 [a]
I/R	43504.51±4249.33 [a,b]	59772.61±3840.21 [a,b]
I/R+ DMSO	43704.82±3380.27 [a,b]	61645.57±4383.07 [a,b]
I/R+ Barbaloin	22608.58±1918.31 [b]	25695.86±2397.31 [b]

[a,b]: The significance relationship at the level of $p<0.05$, represents a meaningful relationship between groups with the same letters

Discussion

Renal I/R injury has a key role in ischemic acute renal failure (ARF). ARF may occur after kidney transplantation and shock. It may lead to morbidity and also mortality with a high rate [31]. Oxidative stress is indispensable for the inception and improvement of renal I/R injury [32]. Many antioxidant enzymes, including SOD and glutathione peroxidase (GPx), have ROS scavenging properties that provide protection against renal I/R injury [33]. GPx, SOD, glutathione reductase and catalase (CAT) perform against ROS and its destructive effects. All these protective molecules form TAS [34]. As described by Erel, we preferred to measure serum TOS value instead of seperately measurement of oxidant molecules [35]. OSI much more reflects oxidative status than TOS or TAS level [36]. When there is an overaccumulation of oxidative agents, renal detoxification capacity may be insufficiant. This situation results in lipid peroxidation and cellular membrane damage [37]. Reperfusion phase increases MPO and MDA levels. This much more injures renal tissue and decreases antioxidant levels [38]. During I/R injury response, neutrophil accumulates and inflammation occurs. MPO may demonstrate neutrophil activity and accumulation [39]. Inflammation exacerbates tubular necrosis and inflammation arises from the inflammatory mediators produced by damaged tubular cells [40].

Following renal I/R, leukocyte infiltration to parenchyma is observed. Inflammatory mediators such as TNF-α, interleukin-1 (IL-1), interleukin-8 (IL-8) and interleukin-6 (IL-6) allows targeting and adhesion of leukocytes to related damaged blood vessel endothelium. Leukocytes play role in ROS production, raise in vascular wall permeability and lysosomal enzyme secretion [41]. TNF-α is well known as one of the key cytokines mediating inflammatory responses [42]. TNF-α is an initiator factor for inflammatory response. IL-6 and IL-1 are major inflammatory factors take action on tissue damage mediating [43]. During I/R-induced renal injury, IL-1α levels are at maximum level in 24 h [44]. Therefore, we preferred ischemia (1 hour)/reperfusion (24 hours) model to guarantee the damage model. Even with progresses in diagnosis and treatment methods, ischemic acute renal failure is a major and common clinical problem [45].

In literature reviews, there is no study about barbaloin in renal I/R and our study is of original quality. However, there are several studies showing the antioxidant and anti-inflammatory properties of barbaloin that support the results of this study. In the present study, reduction of TNF-α, IL-1β levels in renal I/R model in rats by barbaloin, suggesting that barbaloin decreased I/R-induced renal injury. Barbaloin has been reported to have a myocardial protective effect in a rat model of myocardial I/R injury [27]. Barbaloin has been reported to reduce the levels of intracellular ROS and proinflammatory cytokines (TNF-α, IL-1β and IL-6) and prevented lipopolysaccharide-induced acute lung injury [46]. Barbaloin pretreatment has been shown to alleviate myocardial ischemia reperfusion injury by antioxidant and antiinflammatory effects [47].

Barbaloin has been reported to have antiviral activity [20] and anti-inflammatory [48] property and may be used as a potential candidate for an alternative for antimicrobial. Barbaloin demonstrated protection against liver injury induced by alcohol throughout alleviation of oxidative stress and inflammation [23]. In parallel with these studies, in our study, antioxidant and anti-inflammatory properties of barbaloin have been shown in renal I/R model in rats. In I/R group, SOD and TAS decreased while OSI, MDA, MPO, TOS, TNF-α and IL-1β levels increased and barbaloin treatment reversed these levels.

We assessed oxidative stress in the renal tissue to investigate the possible mechanisms of the protective effect of barbaloin against I/R-induced renal injury and observed oxidative stress decreased with barbaloin.

To make effective changes in the clinical management of I/R, the pathogenesis of I/R-induced organ damage should be better understood for the development of therapeutic strategies. Clearly observed in I/R studies is that inflammation, oxidative stress suppression can provide significant contributions to the treatment of I/R. In current study, inflammation, oxidative stress pathways are suppressed by barbaloin and this promise hope in the treatment of I/R.

Conclusion

Barbaloin protects against I/R-induced renal injury with its antioxidants and anti-inflammatory properties. We have indicated that treatment with barbaloin reduces renal damage in experimental animals exposed to I/R model. Moreover, further researches are necessary for explaining the other protective mechanism on I/R-induced renal tissue damage.

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Competing interests
The authors declare that they have no competing interest.

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Ethical approval
Ethical permission related to the study was obtained from the Ataturk University Experimental Animals Local Ethics Committee with the decision number 60 on 25.03.2019

Ayhan Tanyeli ORCID: 0000-0002-0095-0917
Mustafa Can Guler ORCID: 0000-0001-8588-1035
Ersen Eraslan ORCID: 0000-0003-2424-2269

Fazile Nur Ekinci Akdemir ORCID: 0000-0001-9585-3169
Omer Topdagi ORCID: 0000-0002-9690-4447
Elif Polat ORCID: 0000-0003-0042-4084
Tuncer Nacar ORCID: 0000-0002-9287-7170

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