An Investigation into the Biochemical Effects of Barbaloin on Renal Tissue in Cecal Ligation and Puncture–Induced Polymicrobial Sepsis Model in Rats

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ABSTRACT

Objective: The present study aims to examine the protective effects of barbaloin on renal injured by cecal ligation and puncture (CLP) model.

Methods: In our study, animals were divided into four groups. Study groups were designed as follows: sham, CLP, DMSO+CLP and 20 mg/kg barbaloin+CLP. Oxidative stress and cytokines were evaluated in renal tissues obtained at the end of the experiment.

Results: The findings showed that the TOS, OSI, MPO, MDA, TNF-α and IL-1β increased and TAS and SOD decreased in the CLP group, but in the treatment group, molecule concentrations changed significantly.

Conclusion: Our results have demonstrated that of barbaloin is effective against kidney injury caused by CLP-induced polymicrobial sepsis model.

INTRODUCTION

Sepsis, due to multiorgan failure,[1,2] causes death in intensive care units as high as 20% worldwide[3–5] because mortality rates are extremely high and it is important to investigate the sepsis with appropriate experimental models. The most commonly used model for experimental sepsis is the cecal ligation and puncture (CLP) model.[6,7] Inflammation plays an important role in the etiology and prognosis of sepsis. With the release of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), the severity of the inflammatory response increases.[8,9] With cytokines and leukocyte activation, inflammatory responses are exacerbated, and organ damage occurs. The most important role in tissue damage is the releasing of oxidative molecules.[10]

Because of the oxidative stress, tissue damage occurs due to the decrease of antioxidant molecules that arise from increased reactive oxygen species (ROS) and nitrogen.[11] An increase in ROS causes lipid and protein peroxidation to enhance malondialdehyde (MDA), the fatty acid peroxidation product.[12,13] Myeloperoxidase (MPO) is an indicator of neutrophils concentration in damaged tissues.[14] While the total antioxidant level (TAS) is used as an indicator of total antioxidant activity, total oxidant status (TOS) is a strong marker to determine total oxidant status. Oxidative stress index (OSI) is a value indicating the balance in the current oxidative status.[15,16]

Barbaloin is a molecule derived from Aloe vera. According to the literature, barbaloin has many pharmacological effects, including antioxidant, anti-inflammatory and antitumor properties.[17] In the present study, we aimed to

evaluate the effects of barbaloin, which has various biological properties, such as antioxidant, anti-inflammatory on renal tissue, to alleviate the oxidative damage in the CLP-induced polymicrobial sepsis in rats.

MATERIALS AND METHODS

Laboratory conditions and drugs

The present study was carried out in our University Experimental Animal Research and Application Center, our University Faculty of Medicine, Department of Physiology. This study has also been approved by our university Experimental Animals Local Ethics Committee (no. 28.03.2019/59). All rats were kept in the 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. Ketamine (from Ketalar®, Pfizer, Istanbul), Xylazine (from Rompun®, Bayer, Istanbul) were used during the sacrifice. Barbaloin was supplied by Sigma-Aldrich Co, USA.

Experimental animals and experimental design

In this study, 32 healthy Sprague Dawley male rats (230-260 gr) were used. The rats were randomly divided into four groups. The formation of groups and the applications were as follows. Group 1 (Sham control group, n=8): We reached the peritoneum with a 2 cm incision from the abdominal area of the rats, and they were closed with a suture without any procedure and treatment. Group 2 (CLP group, n=8): The cecum was isolated by reaching the peritoneum with a 2 cm incision from the abdominal area of the rat, and the ileocecal valve was ligated up to 2 cm distal, then, it was pierced by 18-gauge needle (4 holes), the cecum was put back the abdomen and abdomen was closed with 3.0 silk suture. Group 3 (DMSO + CLP group, n=8): Surgical procedures were performed as in Group 2. The DMSO was administered by oral gavage for five days. The final application was performed just before the CLP model. Group 4 (20 mg/kg barbaloin + CLP group, n=8): Surgical procedures were performed as in Group 2. Barbaloin was administered by oral gavage for five days. The final application was performed just before the CLP model. In all groups the abdominal region was washed with povidone-iodine after being shaved. Analgesic lidocaine solution was applied to the suture areas of the rats to remove the error margin that might be caused by pain stress. The rats were deprived of food postoperatively but had free access to water for 18 hours until they were sacrificed.

Biochemical analysis of renal tissues

After the tissues were homogenized, all biochemical analyses were carried out in supernatants from homogenized tissues. In renal tissue samples, the MDA level to define lipid peroxidation status according to the method presented by Ohkawa et al.,[18] were measured. The results were given as μmol/g protein. the MDA level was analyzed using the superoxide dismutase (SOD) activity specification protocol detected by Sun et al.[19] SOD activity results of tissue samples were given as U/mg protein. MPO activity of the renal tissue was measured using a method improved by Bradley et al.[20] The results of MPO activity were presented as U/g protein. TOS measurement was performed with a commercially available kit (Rel Assay Diagnostics). TAS value was evaluated with commercial kit (Rel Assay Diagnostics). 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]. TNF-α and interleukin-1β (IL-1β) levels were determined with a commercially available kit (Elabscience, Wuhan, China).

Statistical analysis

The results obtained from the experiments were given as mean±standard deviation (S.D.). P-values below 0.05 were considered statistically significant. The comparisons between groups were made according to One-Way ANOVA and Bonferroni test.

RESULTS

There has been no morbidity or mortality in rats during experimental applications. When CLP group compared to sham control group, TAS (from 261.917±24.628 to 160.309±30.273, p=0.000) level decreased, whereas TOS (from 96.542±13.268 to 167.174±17.454, p=0.000), OSI (from 0.037±0.006 to 0.108±0.027, p=0.000) levels increased. When barbaloin treatment group compared to CLP group, TAS (from 160.309±30.273 to 254.709±11.107, p=0.000) level increased, while TOS (from 167.174±17.454 to 97.327±7.205, p=0.000), OSI (from 0.108±0.027 to 0.038±0.003, p=0.000) levels decreased. There was no statistically significant difference between CLP and DMSO + CLP groups in terms of TAS, TOS and OSI.

When the CLP group compared to sham control group, SOD (from 2.432±0.094 to 0.728±0.072, p=0.000) level decreased, while MPO (from 6.079±0.519 to 10.015±0.980, p=0.000), MDA (from 0.233±0.043 to 1.312±0.213, p=0.000), TNF-α (from 17715.030±732.057 to 76336.300±5007.314, p=0.002), and IL-1β (from 22440.471±1277.683 to 88671.906±5321.605, p=0.002) levels increased. When barbaloin treatment group compared to CLP group, while the level of SOD (from 0.728±0.072 to 2.495±0.360, p=0.003) increased, MPO (from 10.015±0.980 to 6.406±1.095, p=0.000), MDA (from 1.312±0.213 to 0.247±0.057, p=0.000), TNF-α (from 17715.030±732.057 to 21186.340±1585.869, p=0.000), and IL-1β (from 88671.906±5321.605 to 24554.486±1590.800, p=0.000) levels decreased. There was no statistically significant difference between CLP and DMSO + CLP groups concerning SOD, MPO, MDA, TNF-α and IL-1β. When the results are evaluated, a great

Table 1. Comparisons of TAS, TOS and OSI levels among the experimental groups

Experimental groups (n=8)	TAS (nmol/L)	TOS (nmol/L)	OSI (arbitrary unit)
Sham control (1)	261.917±24.628	96.542±13.268	0.037±0.006
CLP (2)	160.309±30.273	167.174±17.454	0.108±0.027
DMSO+CLP (3)	153.063±6.316	169.096±17.049	0.110±0.011
Barbaloin 20 mg/kg +CLP (4)	254.709±11.107	97.327±7.205	0.038±0.003
P-value (Meaningful intergroup comparisons)	0.000 (1–2)	0.000 (1–2)	0.000 (1–2)
	0.000 (1–3)	0.000 (1–3)	0.000 (1–3)
	0.000 (2–4)	0.000 (2–4)	0.000 (2–4)
	0.000 (3–4)	0.000 (3–4)	0.000 (3–4)

TAS: Total Antioxidant Status; TOS: Total Oxidant Status; OSI: Oxidative Stress Index. Data are presented as mean±SD.

Table 2. Comparisons of other oxidative markers and cytokines among experimental groups

Experimental groups (n=8)	SOD (U/mg protein)	MPO (U/g protein)	MDA (µmol/g protein)	TNF-α (pg/mg protein)	IL-1β (pg/mg protein)
Sham control (1)	2.432±0.094	6.079±0.519	0.233±0.043	17715.030±732.057	22440.471±1277.683
CLP (2)	0.728±0.072	10.015±0.980	1.312±0.213	76336.300±5007.314	88671.906±5321.605
DMSO+CLP (3)	0.771±0.064	10.019±1.218	1.326±0.208	79309.087±2867.281	91450.243±4135.841
Barbaloin 20 mg/kg + CLP (4)	2.495±0.360	6.406±1.095	0.247±0.057	21186.340±1585.869	24554.486±1590.800
P value (Meaningful intergroup comparisons)	0.000 (1–2)	0.000 (1–2)	0.000 (1–2)	0.000 (1–2)	0.000 (1–2)
	0.000 (1–3)	0.000 (1–3)	0.000 (1–3)	0.000 (1–3)	0.000 (1–3)
	0.000 (2–4)	0.000 (2–4)	0.000 (2–4)	0.019 (1–4)	0.011 (1–4)
	0.000 (3–4)	0.000 (3–4)	0.000 (3–4)	0.000 (2–4)	0.000 (2–4)
				0.000 (3–4)	0.000 (3–4)

SOD: Superoxide Dismutase; MPO: Myeloperoxidase; MDA: Malondialdehyde; TNF-α: Tumor necrosis factor α; IL-1β: Interleukin-1beta. Data are presented as mean±SD.

similarity is observed between the sham control and barbaloin treatment group.

DISCUSSION

Sepsis is a host inflammatory reaction to infection leading to life-threatening multiorgan dysfunctions with high mortality rates (28% to 50%), and there are few options for its cure.[21–23] World surgeons have been dealing with intraabdominal infections following gastrointestinal perforation complicating abdominal surgery.[24] The sepsis has mortal complications, including septic shock, multiple organ dysfunction syndromes.[25,26] Septic shock does progressive damage to lots of vital organs, including the liver, kidneys and heart, easily causing mortality in intensive care units.[21,27–29] The experimental and clinical data also reported that sepsis induces vital inflammation, such as acute kidney injury.[30,31] TNF-α initiates the upregulation of cytokines and chemokines in an inflammatory cascade with its upstream role, but IL-1β and IL-6 are downstream molecules impairing the renal cells.[32] CLP in rodents is told by researches as the 'gold standard' in the investigation of sepsis in a single animal model creating polymicrobial peritonitis.[7,33]

ROS attacks and does damages to macromolecules, such as membrane lipids, nucleic acids, carbohydrates, and proteins. TAS and TOS reflect the redox balance between oxidants and antioxidants. Measurement of the TAS indicates the activity of all antioxidants, while TOS is an indicator of ROS.[15,16] In our study, these molecules changed in favor of antioxidation enzymes, such as SOD, protect tissue against oxidative damage.[34] SOD is the most potent enzyme that scavenges superoxide anions. SOD and TAS decreased in CLP and DMSO+CLP group compared to sham control group in our study. MDA, reflecting the level of ROS produced by lipid oxidation, is the major product of the peroxidation process. To evaluate the level of oxidative stress, MDA and SOD are usually analyzed simultaneously.[35] An oxidant parameter MDA is a toxic product generated during oxidation of the cellular membrane lipids by free oxygen radicals.[36,37] Oxidized lipids and proteins and damaging cell membranes are associated with septic mortality.[38] Antioxidant systems prevent oxidative damage in tissues dominated by oxidant mechanisms leading to lipid peroxidation through scavenging ROS.[39] MDA in high levels exerts an increasing burden on urogenital system leading to renal function decline.[40] MPO is an indicator of neutrophils that leak into tissue. TNF-α and IL-1β, which are released by the infiltrated neutrophils,[41,42] are pro-inflammatory cytokines of this complex systemic inflammatory response.[43,44] According

to our results, these cytokines increased. There may be an inflammatory response in the pathogenesis of sepsis and associated with excessive production of cytokines. TNF-α plays a major role in the pathogenesis of an early phase of shock.[45,46] Many barbaloin-related studies are available in the literature supporting the results of our study. In our study, reduction of levels of proinflammatory and oxidant parameters in septic rats by barbaloin, suggesting that barbaloin alleviated CLP-induced renal injury. Barbaloin has been demonstrated as protective of ischemic myocardial tissue in a rat model.[47] Barbaloin has been reported to reduce the levels of intracellular ROS and inflammatory cytokines prevented lipopolysaccharide-induced acute lung injury.[48] Barbaloin pretreatment has been shown to alleviate myocardial ischemia-reperfusion injury by antioxidant and anti-inflammatory effects.[17] Barbaloin has been reported to have antiviral activity[49] and anti-inflammatory[50] property and may be used as a potential candidate for an alternative for antimicrobial therapy. Barbaloin has been shown to reduce inflammation and ROS formation in alcohol-mediated liver injury.[51] In parallel with these studies, in our study, antioxidant and anti-inflammatory properties of barbaloin have been shown in CLP-induced polymicrobial sepsis model in rats. In the CLP group, TAS and SOD decreased while MDA, MPO, TNF-α, IL-1β, TOS and OSI levels increased and barbaloin treatment reversed these levels. These data increase the potential of the drug to be used in the treatment of polymicrobial sepsis in the future to make effective changes in the clinical treatment of sepsis, the pathogenesis of cellular damage should be better understood. Clearly observed in sepsis studies is that inflammation, oxidative stress suppression can provide significant contributions to the treatment of sepsis. In the present study, inflammation, oxidative stress pathways are suppressed by barbaloin and this promises hope in the treatment of sepsis.

CONCLUSION

Barbaloin provides protection against renal damage by CLP-induced sepsis with its antioxidants and anti-inflammatory properties. We have indicated that treatment with barbaloin reduces renal damage in experimental animals exposed to CLP-induced polymicrobial sepsis model. Moreover, further studies are necessary to explain the other protective mechanism on CLP-induced renal tissue damage.

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Sıçanlarda Çekal Ligasyon ve Ponksiyon Kaynaklı Polimikrobiyal Sepsis Modelinde Barbaloinin Renal Doku Üzerindeki Biyokimyasal Etkilerinin İncelenmesi

Amaç: Bu araştırmanın amacı barbaloinin çekal ligasyon ve ponksiyon (CLP) modeliyle böbrek üzerindeki yaralanmaya karşı koruyucu etkisini incelemektir.

Gereç ve Yöntem: Çalışmamızda hayvanlar dört gruba ayrıldı. Çalışma grupları şöyle tasarlandı; sham, CLP, DMSO+CLP ve 20 mg/kg barbaloin + CLP. Oksidatif stres ve sitokinler, deney sonunda elde edilen renal dokularda değerlendirildi.

Bulgular: CLP grubunda TOS, OSI, MPO, MDA, TNF-α ve IL-1β'nin arttığı, TAS ve SOD'un azaldığı, ancak tedavi grubundaki değerlerin anlamlı olarak değiştiği bulundu.

Sonuç: Sonuçlarımız, barbaloinin CLP'nin neden olduğu polimikrobiyal sepsis modelinin neden olduğu böbrek hasarına karşı etkili olduğunu göstermiştir.

Anahtar Sözcükler: Barbaloin; böbrek; çekal ligasyon ve ponksiyon; enflamasyon; oksidatif stres; sıçan.