Kafkas Univ Vet Fak Derg
26 (3): 365-370, 2020
DOI: 10.9775/kvfd.2019.23250

Kafkas Universitesi Veteriner Fakultesi Dergisi
ISSN: 1300-6045 e-ISSN: 1309-2251
Journal Home-Page: http://vetdergikafkas.org
Online Submission: http://submit.vetdergikafkas.org

Research Article

Higenamine Decreased Oxidative Kidney Damage Induced By Ischemia Reperfusion in Rats

Mustafa Can GÜLER [1,a] Ayhan TANYELİ [1,b] Ersen ERASLAN [2,c]
Fazile Nur EKİNCİ AKDEMİR [3,d] Tuncer NACAR [1,e] Ömer TOPDAĞI [4,f]

[1] Department of Physiology, Faculty of Medicine, Atatürk University, TR-25240 Erzurum - TURKEY
[2] Department of Physiology, Faculty of Medicine, Bozok University, TR-66900 Yozgat - TURKEY
[3] Department of Nutrition and Dietetics, High School of Health, Ağrı İbrahim Çeçen University, TR-04100 Ağrı - TURKEY
[4] Department of Internal Medicine, Faculty of Medicine, Atatürk University, TR-25240 Erzurum - TURKEY
[a] ORCID: 0000-0001-8588-1035; [b] ORCID: 0000-0002-0095-0917; [c] ORCID: 0000-0003-2424-2269; [d] ORCID: 0000-0001-9585-3169
[e] ORCID: 0000-0002-9287-7170; [f] ORCID: 0000-0002-9690-4447

Article ID: KVFD-2019-23250 Received: 25.08.2019 Accepted: 23.12.2019 Published Online: 23.12.2019

How to Cite This Article

Güler MC, Tanyeli A, Eraslan E, Akdemir FNE, Nacar T, Top Ö: Higenamine decreased oxidative kidney damage induced by ischemia reperfusion in rats. *Kafkas Univ Vet Fak Derg,* 26 (3): 365,370, 2020. DOI: 10.9775/kvfd.2019.23250

Abstract

The aim of this research is to determine protective effects of higenamine on kidney tissue injury caused by ischemia reperfusion. In this study, 24 Sprague Dawley female rats were divided into 3 groups. The groups were designed as follows; control, ischemia reperfusion, and ischemia reperfusion + higenamine. Some oxidant, antioxidant and inflammatory parameters were evaluated in kidney tissues at the end of the experimental procedure. It was confirmed that the oxidant and inflammatory parameters of kidney tissue increased and antioxidant parameters decreased in ischemia reperfusion group compared to control group. Antioxidant parameters increased while oxidant and inflammatory parameters decreased in the ischemia reperfusion + higenamine group compared to ischemia reperfusion group. These results have demonstrated that higenamine administration as single dose is effective against oxidative kidney damage originating from ischemia reperfusion.

Keywords: *Ischemia reperfusion, Higenamine, Kidney, Oxidative stress, Inflammation, Rat*

Higenamin Ratlarda İskemi Reperfüzyonunun Neden Olduğu Oksidatif Böbrek Hasarını Azaltır

Öz

Bu araştırmanın amacı, higenaminin, iskemi reperfüzyonunun neden olduğu böbrek dokusu hasarı üzerine koruyucu etkilerini belirlemektir. Bu araştırmada 24 adet Sprague Dawley dişi sıçan üç gruba ayrıldı. Bu çalışmanın grupları aşağıdaki şekilde tasarlanmıştır; kontrol, iskemi reperfüzyon ve iskemi reperfüzyon + higenamin grupları. Deney sonunda elde edilen böbrek dokularındaki bazı oksidan, antioksidan ve inflamatuvar parametreler değerlendirildi. İskemi reperfüzyon grubu kontrol grubu ile kıyaslandığında, böbrek dokusundaki oksidan ve inflamatuvar parametrelerin arttığı fakat antioksidan parametrelerin azaldığı belirlendi. Tedavi grubu (iskemi reperfüzyon + higenamin) yalnızca iskemi reperfüzyon grubu ile kıyaslandığında antioksidan parametreler artarken, oksidan ve inflamatuvar parametreler azaldı. Bu sonuçlar, tek doz higenamin uygulamasının, iskemi reperfüzyon kaynaklı oksidatif böbrek hasarına karşı etkili olduğunu göstermiştir.

Anahtar sözcükler: *İskemi reperfüzyon, Higenamin, Böbrek, Oksidatif stres, İnflamasyon, Sıçan*

INTRODUCTION

Decreasing the blood flow, reperfusion and systemic inflammatory response may lead to kidney ischemia reperfusion (I/R) injury [1]. Acute kidney injury (AKI) is related to a severe mortality, great economic, and social burdens, particularly in critically ill cases [2-4]. In the long term, AKI may cause chronic kidney disease and end-stage kidney disease [5]. Reactive oxygen species (ROS), are related to the early phase of inflammation, necrosis and apoptosis in kidney I/R injury [6]. It has been suggested that increased ROS production during kidney I/R is one of the most important reasons of kidney damage with extensive interstitial edema, tubular flattening with brush border

İletişim (Correspondence)
+90 507 3631654
ayhan.tanyeli@atauni.edu.tr

microvilli loss, tubular dilatation, brush border shedding, casts and obstruction [7,8]. Elevated malondialdehyde (MDA) levels were shown due to I/R injury and activities of antioxidants (ROS scavenger) such as catalase (CAT) and superoxide dismutase (SOD) were determined to be essential to prevent the toxic effects of MDA [9]. MDA is a lipid peroxidation product and it is used to evaluate the oxidative stress levels in *in vitro* and *in vivo* conditions [10]. Linas et al.[11] indicated that kidney I/R injury was aggravated by activated neutrophils. Neutrophil activation is related with myeloperoxidase (MPO). Furthermore, proinflammatory cytokine and ROS production is associated with active neutrophils [12]. I/R injury aggregates inflammatory cells, releases inflammatory factors (TNF-α, IL-8, and IL-6, etc.) and increases adhesion molecules [13,14]. Up to day, there has been no efficient therapy against kidney I/R injury [15,16].

Higenamine (Hig) (1-[(4-hydroxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol) is an alkaloid and was first derived from Aconitum [17]. As a source for Hig, *Aconicum japonicum* Thunb has been used for collapse, tumor, bronchial asthma, rheumatic fever, edema, painful joint, and syncope treatment for centuries in China and Japan [18]. In 1976, aconite root was used for the first isolation of Hig [19]. Hig has pharmacological features including immunomodulatory, antiapopitotic, anti-inflammatory and antithrombotic effects [17]. This research was planned to detect the protective effect of Hig against kidney oxidative damage induced by I/R.

MATERIAL and METHODS

This study was initiated with approval (2019-69) of Atatürk University Experimental Animals Local Ethics Committee. Experimental phase of the present research was performed at Atatürk University Experimental Animal Research and Application Center and the animals were supplied from the same place. Animals were kept in standard cages in laboratory environment provided with humidity, 20-22°C temperature and 12 h light/dark cycle control. They were fed with standard pellet feed and water. They were fasted 12 h before the experiment to prevent anesthesia complications.

Groups and Ischemia Reperfusion Model

All procedures were performed under anesthesia of 10 mg/kg i.p xylazine hydrochloride (Rompun®, Bayer, Istanbul) and 60 mg/kg i.p ketamine (Ketalar®, Pfizer, Istanbul). The number of animals and there should be at least 8 animals in each group if the animals were divided into 3 groups were determined by 5% deviation, type 1 error (α) 0.05 and type 2 error (β) (Power = 0.80) power analysis. Three groups each containing 8 Sprague Dawley female rats (240±10 g) were set. Control group; the back region was shaved, cleaned and opened with an incision under anesthesia and then closed without I/R model or a medication. I/R group; the incision area was cleaned with povidone iodine, opened with an incision under anesthesia and then, bilateral kidney arteria and veins were blocked with an atraumatic microvascular clamp for 1 h. In reperfusion period, blood circulation was allowed for 24 h by opening the clamps. Incision closed with silk 3/0 suture. I/R + Hig group; Hig was administered to rats intraperitoneally at a dose of 10 mg/kg 30 min before reperfusion. Later as described in I/R group, the I/R model was created. At the end of the experiment, the right kidneys of all decapitated rats were collected with capsules. Finally, when the experiment ended, the kidney tissues were washed and kept frozen until the biochemical analysis. Hig was purchased from Sigma Aldrich (Missouri, USA).

Analysis of Biochemical Parameters

The kidney samples (right kidney samples with capsules, each sample 100 mg) were homogenized with phosphate buffer (2 mL). The homogenized kidney tissues were centrifuged at 5000 rpm at +4°C for 20 min; and the supernatants obtained in this way were transferred to microcentrifuge tubes. Kidney tissue samples were processed for MDA assay to determine lipid peroxidation status as described by Ohkawa et al.[20]. The results were given in µmol/g protein. SOD activity was measured as defined by Sun et al.[21]. The results were presented in U/mg protein. We also quantified kidney injuries by measuring tissue MPO activity, using a protocol developed by Bradley et al.[22]. The results of MPO activity in tissue samples were presented in U/g protein. The total antioxidant status (TAS) value was evaluated with a commercially available kit (Rel Assay Diagnostics). Total oxidant status (TOS) measurement was done with a commercially available kit (Rel Assay Diagnostics). TAS and TOS results were presented as nmol/L. TOS to TAS ratio was accepted as the oxidative stress index (OSI). OSI level was detected as follows: OSI = [(TOS, µmol H_2O_2 equivalent/L)/(TAS, mmol Trolox equivalent/L) × 10]. OSI has been proposed to be better in demonstrating the oxidative state more precisely compared to TOS value [23].

Statistical Analysis

Statistical analysis was performed using IBM SPSS Package Program (version 22.0). Experimental results were reported as mean ± standard deviation. The normality assumption was confirmed by the Kolmogorov Smirnov test. One-way ANOVA was used to compare the experimental groups with the control. Multiple comparisons were made using the Post hoc Tukey test.

RESULTS

While TAS value decreased significantly, TOS and OSI levels increased in I/R group compared to control group. TOS and OSI values decreased but TAS level increased in I/R + Hig group compared to group I/R (*Table 1*, $P<0.05$).

Table 1. *TAS (mmol/L), TOS (μmol/L) and OSI values of control, I/R and I/R+Hig groups*

Groups/Parameters	Control	I/R	I/R+Hig
TAS (mmol/L)	2.60±0.15	1.39±0.15[a]	2.53±0.15[b]
TOS (μmol /L)	7.09±0.53	10.05±0.93[a]	7.50±0.68[b]
OSI	0.27±.02	0.72±0.10[a]	0.29±0.03[b]

The results are presented as mean ± SD (n=8). [a] P<0.05 versus to control group, [b] P<0.05 versus to I/R group

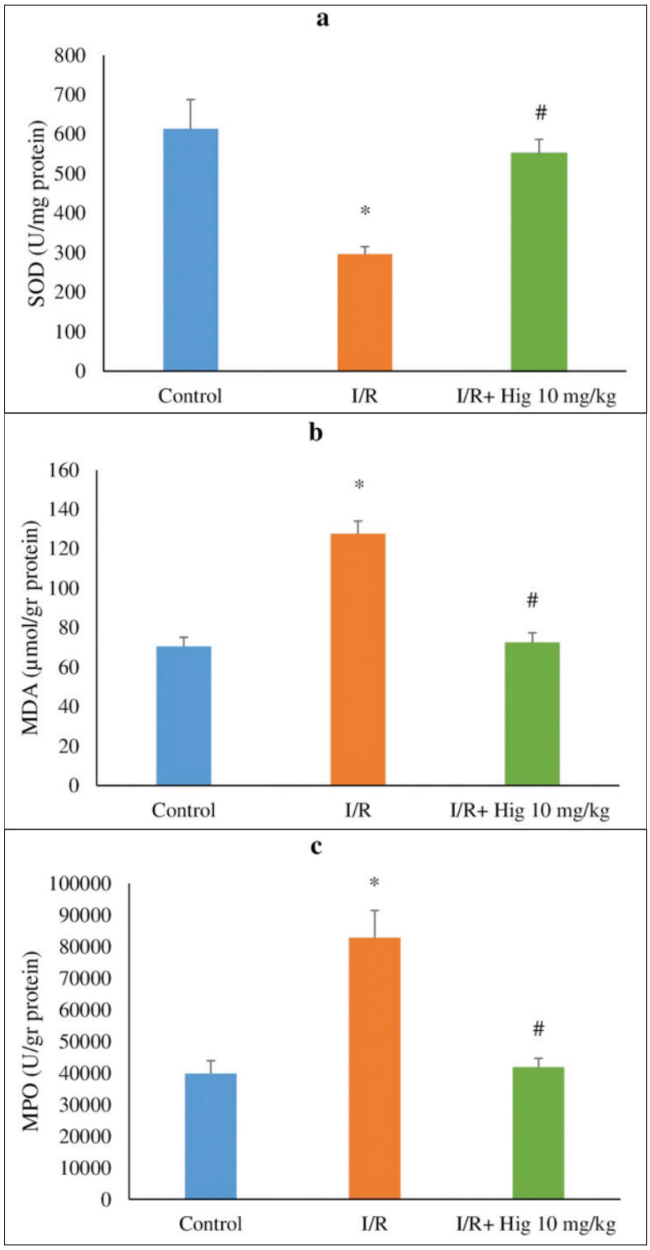

Fig 1. Biochemical parameters in kidney tissue. **a-** SOD levels, **b-** MDA levels and **c-** MPO activity. Data are expressed as mean ± SD; * P<0.05 versus to control group, # P<0.05 versus to I/R groups

Superoxide dismutase enzyme activity increased in I/R + Hig group compared to I/R group. The antioxidant and anti-inflammatory properties and protective effects of Hig against I/R-induced kidney injury have been demonstrated by biochemical results (as shown in *Fig. 1-a)*. However, MPO activity *(Fig. 1-b)*, MDA *(Fig. 1-c)*, TNF-α *(Fig. 2-a)* and IL-1β *(Fig. 2-b)* levels increased in I/R group compared to control group and decreased in I/R + Hig group compared to IR group (P<0.05).

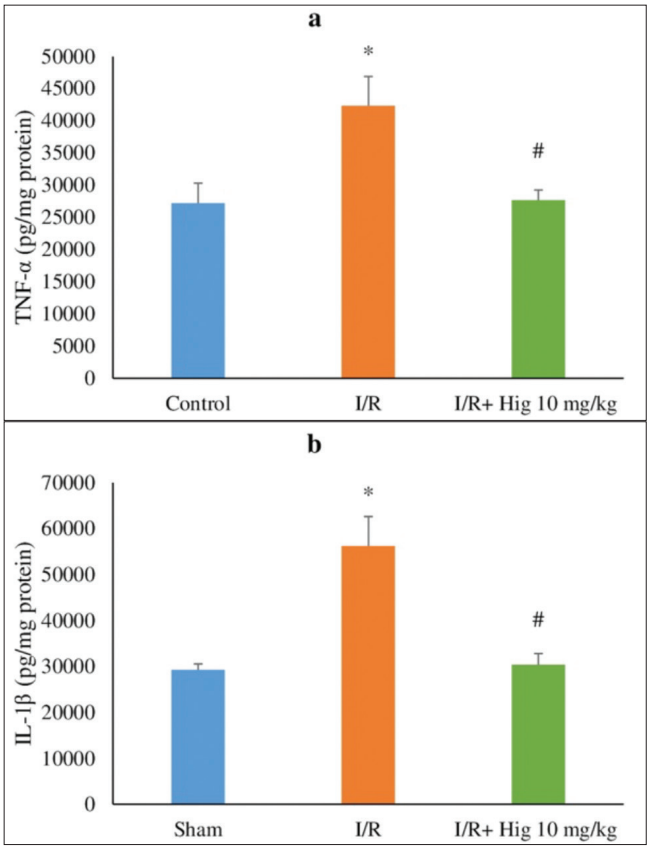

Fig 2. Inflammatory markers in kidney. **a-** TNF-α levels and **b-** IL-1β levels. Data are expressed as mean ± SD (n=8). * P<0.05 versus to control group, # P<0.05 versus to I/R groups

DISCUSSION

Acute kidney injury, especially in developing countries, is related to mortality and morbidity [24]. AKI usually occurs due to I/R injury [25]. Kidney I/R injury is a major reason for AKI with various origins such as kidney transplantation, shock and low cardiac output [26]. Kidney injury following kidney transplantation may also lead to kidney I/R injury [27]. In the reperfusion phase, oxygen derived free radicals occur [28]. Tissue injury induced by I/R is based on oxidative stress and this condition is supported with a strong body of evidence [29]. To remove toxic ROS, cells have several

natural defense systems, including SOD enzyme. Increased ROS that is generated during I/R may cause endogenous antioxidant depletion [30]. The protecting enzymes (SOD, CAT) perform against the devastating actions of ROS and these molecules comprise TAS. TAS measurement provides the evaluating of all antioxidant levels in a biological sample [31]. TOS to TAS ratio is confirmed as OSI, which is an indication of oxidative stress [32]. Reaction between ROS and lipids causes lipid peroxidation in biological membranes during kidney I/R injury [33] and ultimately, enzymatic actions like ion pump activity (plays role on inhibition of DNA transcription and repair) is affected. If an uncontrolled lipid peroxidation continues, it may end with cell death [34,35]. MDA, bioproducts of lipid peroxidation, indicates oxidative stress. CAT and SOD indirectly show free radical generation ability. These are positive and negative markers for oxidative stress level [36]. MDA was clearly increased in a kidney I/R model in rats [37].

The inflammatory response is another important part of the pathophysiology implicated in kidney I/R injury [38]. Some proinflammatory cytokines such as IL-2, IL-6, TNF-α and IL-1β are released during kidney I/R injury [39,40]. TNF-α takes an important part in the beginning and continuation of the inflammatory response. Further, TNF-α could lead to endothelial damage, apoptosis and even kidney failure [41]. IL-1 is a proinflammatory cytokine involved in several inflammatory processes [42]. When the inflammatory response is regulated at the early stage effectively, this presents a vital step for prevention and treatment of kidney injury [43,44].

There are several studies showing the antioxidant and anti-inflammatory properties of Hig that support the results of this study. In the present study, reduction of IL-1β and TNF-α levels in kidney I/R model in rats by Hig, suggesting that Hig decreased IR-induced kidney injury. In a rat model of cerebral I/R, Hig improved functional state of nerves and significantly stopped the increase in TNF-α, IL1, and IL-6 levels while decreasing the axonal nerve degeneration [45]. Induction of ROS and MDA production, and SOD activity inhibition arising from neuronal cell injury triggered by oxygen-glucose deprivation/reperfusion were attenuated by Hig [46]. Hig increased antioxidant level and reduced MDA, TNF-α and IL-1β levels in a collagen-induced arthritis study [47]. According to published reports, Hig possesses a variety of pharmacological properties, including dilatation of blood vessels and bronchi, immunomodulatory, anti-inflammatory, antiapoptocic and antioxidation features [18]. In parallel with these studies, in the present study anti-oxidant and antiinflammatory properties of Hig have been shown in kidney I/R model in rats. In I/R group, TAS and SOD values decreased while TOS, OSI, MDA, MPO, TNF-α, and IL-1β levels increased compared to control group and Hig treatment reversed these levels.

Oxidative stress in kidney tissue was assessed to determine the possible mechanisms of the protective effect of Hig against I/R-induced kidney injury and it was observed that oxidative stress decreased with Hig. 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 suppression of inflammation and oxidative stress can provide significant contributions to I/R treatment. In the present study, inflammation and oxidative stress pathways are suppressed by Hig and this promises hope in the treatment of I/R.

Hig provides a protection against I/R-induced kidney injury with its antioxidant and anti-inflammatory properties. We have indicated that treatment with Hig reduces kidney injury in experimental animals exposed to I/R model. Moreover, further researches are necessarry to explain the other protective mechanisms in I/R-induced kidney tissue injury.

Conflict of Interest Statement

None.

Acknowledgement

There is no financial support organization in the implementation of this study. We would like to thank all participants for contributing in the present study and also thanks to Kardelen Erdoğan and Yaylagülü Yaman, undergraduates of Atatürk University Nursing Faculty, for their effort, help and support during the experiment.

REFERENCES

1. Mole DJ, Olabi B, Robinson V, Garden OJ, Parks RW: Incidence of individual organ dysfunction in fatal acute pancreatitis: Analysis of 1024 death records. *HPB,* 11 (2): 166-170, 2009. DOI: 10.1111/j.1477-2574.2009.00038.x

2. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW: Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol,* 16 (11): 3365-3370, 2005. DOI: 10.1681/asn.2004090740

3. Deng Y, Yuan J, Chi R, Ye H, Zhou D, Wang S, Mai C, Nie Z, Wang L, Zhai Y, Gao L, Zhang D, Hu L, Deng Y, Chen C: The Incidence, risk factors and outcomes of postoperative acute kidney injury in neurosurgical critically ill patients. *Sci Rep,* 7:4245, 2017. DOI: 10.1038/s41598-017-04627-3

4. Deng Y, Chi R, Chen S, Ye H, Yuan J, Wang L, Zhai Y, Gao L, Zhang D, Hu L, Lv B, Long Y, Sun C, Yang X, Zou X, Chen C: Evaluation of clinically available renal biomarkers in critically ill adults: A prospective multicenter observational study. *Crit Care,* 21:46, 2017. DOI: 10.1186/s13054-017-1626-0

5. Negi S, Koreeda D, Kobayashi S, Yano T, Tatsuta K, Mima T, Shigematsu T, Ohya M: Acute kidney injury: Epidemiology, outcomes, complications, and therapeutic strategies. *Semin Dial,* 31 (5): 519-527, 2018. DOI: 10.1111/sdi.12705

6. Chen H, Xing B, Liu X, Zhan B, Zhou J, Zhu H, Chen Z: Similarities between ozone oxidative preconditioning and ischemic preconditioning in renal ischemia/reperfusion injury. *Arch Med Res,* 39 (2): 169-178, 2008. DOI: 10.1016/j.arcmed.2007.09.005

7. Kim J, Jang HS, Park KM: Reactive oxygen species generated by renal ischemia and reperfusion trigger protection against subsequent renal ischemia and reperfusion injury in mice. *Am J Physiol Renal Physiol,* 298 (1): F158-F166, 2010. DOI: 10.1152/ajprenal.00474.2009

8. Shanley PF, Rosen MD, Brezis M, Silva P, Epstein FH, Rosen S: Topography of focal proximal tubular necrosis after ischemia with reflow in the rat kidney. *Am J Pathol,* 122 (3): 462-468, 1986.

9. Kaleli B, Aktan E, Gezer S, Kirkali G: Reperfusion injury after detorsion of unilateral ovarian torsion in rabbits. *Eur J Obstet Gynecol Reprod Biol,* 110 (1): 99-101, 2003.

10. Del Rio D, Stewart AJ, Pellegrini N: A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. *Nutr Metab Cardiovasc Dis,* 15 (4): 316-328, 2005. DOI: 10.1016/j.numecd.2005.05.003

11. Linas SL, Shanley PF, Whittenburg D, Berger E, Repine JE: Neutrophils accentuate ischemia-reperfusion injury in isolated perfused rat kidneys. *Am J Physiol,* 255 (4): F728-F735, 1988. DOI: 10.1152/ajprenal.1988.255.4.F728

12. Wang L, Shan Y, Chen L, Lin B, Xiong X, Lin L, Jin L: Colchicine protects rat skeletal muscle from ischemia/reperfusion injury by suppressing oxidative stress and inflammation. *Iran J Basic Med Sci,* 19 (6): 670-675, 2016.

13. Hashmp SF, Sattar MZA, Rathore HA, Ahmadi A, Johns EJ: A critical review on pharmacological significance of hydrogen sulfide (H_2S) on NF-κB concentration and icam-1 expression in renal ischemia reperfusion injury. *Acta Pol Pharm,* 74 (3): 747-752, 2017.

14. Peng J, Ren X, Lan T, Chen Y, Shao Z, Yang C: Renoprotective effects of ursolic acid on ischemia/reperfusioninduced acute kidney injury through oxidative stress, inflammation and the inhibition of STAT3 and NFkappaB activities. *Mol Med Rep,* 14 (4): 3397-3402, 2016. DOI: 10.3892/mmr.2016.5654

15. Schrier RW, Wang W, Poole B, Mitra A: Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. *J Clin Invest,* 114 (1): 5-14, 2004. DOI: 10.1172/JCI22353

16. Andreucci M, Faga T, Pisani A, Sabbatini M, Michael A: Acute kidney injury by radiographic contrast media: Pathogenesis and prevention. *Biomed Res Int,* 2014:362725, 2014. DOI: 10.1155/2014/362725

17. Zhang N, Lian Z, Peng X, Li Z, Zhu H: Applications of higenamine in pharmacology and medicine. *J Ethnopharmacol,* 196, 242-252, 2017. DOI: 10.1016/j.jep.2016.12.033

18. Singhuber J, Zhu M, Prinz S, Kopp B: *Aconitum* in traditional Chinese medicine: A valuable drug or an unpredictable risk? *J Ethnopharmacol,* 126 (1): 18-30, 2009. DOI: 10.1016/j.jep.2009.07.031

19. Kosuge T, Yokota M: Studies on cardiac principle of aconite root. *Chem Pharm Bull (Tokyo),* 24 (1): 176-178, 1976. DOI: 10.1248/cpb.24.176

20. Ohkawa H, Ohishi N, Yagi K: Assay for lipid peroxides in animal-tissues by thiobarbituric acid reaction. *Anal Biochem,* 95 (2): 351-358, 1979.

21. Sun Y, Oberley LW, Li Y: A Simple method for clinical assay of superoxide-dismutase. *Clin Chem,* 34 (3): 497-500, 1988.

22. Bradley PP, Priebat DA, Christensen RD, Rothstein G: Measurement of cutaneous inflammation: Estimation of neutrophil content with an enzyme marker. *J Invest Dermatol,* 78 (3): 206-209, 1982.

23. Eraslan E, Tanyeli A, Polat E, Yetim Z: Evodiamine alleviates kidney ischemia reperfusion injury in rats: A biochemical and histo-pathological study. *J Cell Biochem,* 120 (10): 17159-17166, 2019. DOI: 10.1002 /jcb.28976

24. Zuk A, Bonventre JV: Acute kidney injury. *Annu Rev Med,* 67, 293-307, 2016. DOI: 10.1146/annurev-med-050214-013407

25. Lameire N, Van Biesen W, Vanholder R: The changing epidemiology of acute renal failure. *Nat Clin Pract Nephrol,* 2, 364-377, 2006. DOI: 10.1038/ncpneph0218

26. Oliveira RC, Brito MV, Ribeiro RFJ, Oliveira LO, Monteiro AM, Brandao FM, Cavalcante LC, Gouveia EH, Henriques HY: Influence of remote ischemic conditioning and tramadol hydrochloride on oxidative stress in kidney ischemia/reperfusion injury in rats. *Acta Cir Bras,* 32 (3): 229-235, 2017. DOI: 10.1590/s0102-865020170030000007

27. Sheashaa H, Lotfy A, Elhusseini F, Aziz AA, Baiomy A, Awad S, Alsayed A, El-Gilany AH, Saad MA, Mahmoud K, Zahran F, Salem DA, Sarhan A, Ghaffar HA, Sobh M: Protective effect of adipose-derived mesenchymal stem cells against acute kidney injury induced by ischemia-reperfusion in Sprague-Dawley rats. *Exp Ther Med,* 11 (5): 1573-1580, 2016. DOI: 10.3892/etm.2016.3109

28. Noiri E, Nakao A, Uchida K, Tsukahara H, Ohno M, Fujita T, Brodsky S, Goligorsky MS: Oxidative and nitrosative stress in acute renal ischemia. *Am J Physiol Renal Physiol,* 281 (5): F948-F957, 2001.

29. Aragno M, Cutrin JC, Mastrocola R, Perrelli MG, Restivo F, Poli G, Danni O, Boccuzzi G: Oxidative stress and kidney dysfunction due to ischemia/reperfusion in rat: Attenuation by dehydroepiandrosterone. *Kidney Int,* 64 (3): 836-843, 2003. DOI: 10.1046/j.1523-1755.2003.00152.x

30. Sedaghat Z, Kadkhodaee M, Seifi B, Salehi E, Najafi A, Dargahi L: Remote preconditioning reduces oxidative stress, downregulates cyclo-oxygenase-2 expression and attenuates ischaemia-reperfusion-induced acute kidney injury. *Clin Exp Pharmacol Physiol,* 40 (2): 97-103, 2013. DOI: 10.1111/1440-1681.12044

31. Kusano C, Ferrari C: Total antioxidant capacity: A biomarker in biomedical and nutritional studies. *J Cell Mol Biol* 7, 1-15, 2008.

32. Keith ES, Powers JJ: Effect of phenolic acids and esters on respiration and reproduction of bacteria in urine. *Appl Microbiol,* 13, 308-313, 1965.

33. Vaghasiya J, Sheth N, Bhalodia Y, Manek R: Sitagliptin protects renal ischemia reperfusion induced renal damage in diabetes. *Regul Pept,* 166 (1-3): 48-54, 2011. DOI: 10.1016/j.regpep.2010.08.007

34. Molitoris BA, Sutton TA: Endothelial injury and dysfunction: Role in the extension phase of acute renal failure. *Kidney Int,* 66 (2): 496-499, 2004. DOI: 10.1111/j.1523-1755.2004.761_5.x

35. Erdogan H, Fadillioglu E, Yagmurca M, Ucar M, Irmak MK: Protein oxidation and lipid peroxidation after renal ischemia-reperfusion injury: Protective effects of erdosteine and N-acetylcysteine. *Urol Res,* 34 (1): 41-46, 2006. DOI: 10.1007/s00240-005-0031-3

36. Wang F, Yu G, Liu SY, Li JB, Wang JF, Bo LL, Qian LR, Sun XJ, Deng XM: Hydrogen-rich saline protects against renal ischemia/reperfusion injury in rats. *J Surg Res,* 167 (2): e339-e344, 2011. DOI: 10.1016/j.jss.2010.11.005

37. Shen X, Hu B, Xu G, Chen F, Ma R, Zhang N, Liu J, Ma X, Zhu J, Wu Y, Shen R: Activation of Nrf2/HO-1 pathway by glycogen synthase kinase-3β ınhibition attenuates renal ischemia/reperfusion ınjury in diabetic rats. *Kidney Blood Press Res,* 42 (2): 369-378, 2017. DOI: 10.1159/000477947

38. Zhang Y, Hu F, Wen J, Wei X, Zeng Y, Sun Y, Luo S, Sun L: Effects of sevoflurane on NF-κB and TNF-α expression in renal ischemia-reperfusion diabetic rats. *Inflamm Res,* 66 (10): 901-910, 2017. DOI: 10.1007/s00011-017-1071-1

39. Munoz M, Lopez-Oliva ME, Pinilla E, Martinez MP, Sanchez A, Rodriguez C, Garcia-Sacristan A, Hernandez M, Rivera L, Prieto D: CYP epoxygenase-derived H_2O_2 is involved in the endothelium-derived hyperpolarization (EDH) and relaxation of intrarenal arteries. *Free Radic Biol Med,* 106, 168-183, 2017. DOI: 10.1016/j.freeradbiomed.2017.02.031

40. Huang R, Zhou Q, Veeraragoo P, Yu H, Xiao Z: Notch2/Hes-1 pathway plays an important role in renal ischemia and reperfusion injury-associated inflammation and apoptosis and the γ-secretase inhibitor DAPT has a nephroprotective effect. *Ren Fail,* 33 (2): 207-216, 2011. DOI: 10.3109/0886022x.2011.553979

41. Xing B, Chen H, Wang L, Weng X, Chen Z, Li X: Ozone oxidative preconditioning protects the rat kidney from reperfusion injury via modulation of the TLR4-NF-κB pathway. *Acta Cir Bras,* 30 (1): 60-66, 2015. DOI: 10.1590/s0102-86502015001000008

42. Dinarello CA: Biologic basis for interleukin-1 in disease. *Blood,* 87 (6): 2095-2147, 1996.

43. Bai M, Zhang L, Fu B, Bai J, Zhang Y, Cai G, Bai X, Feng Z, Sun S, Chen X: IL-17A improves the efficacy of mesenchymal stem cells in ischemic-reperfusion renal injury by increasing Treg percentages by the

COX-2/PGE2 pathway. *Kidney Int,* 93 (4): 814-825, 2018. DOI: 10.1016/j.kint.2017.08.030

44. Nishikawa H, Taniguchi Y, Matsumoto T, Arima N, Masaki M, Shimamura Y, Inoue K, Horino T, Fujimoto S, Ohko K, Komatsu T, Udaka K, Sano S, Terada Y: Knockout of the interleukin-36 receptor protects against renal ischemia-reperfusion injury by reduction of proinflammatory cytokines. *Kidney Int,* 93 (3): 599-614, 2018. DOI: 10.1016/j.kint.2017.09.017

45. Wang X, Li X, Jingfen W, Fei D, Mei P: Higenamine alleviates cerebral ischemia-reperfusion injury in rats. *Front Biosci,* 24, 859-869, 2019.

46. Zhang Y, Zhang J, Wu C, Guo S, Su J, Zhao W, Xing H: Higenamine protects neuronal cells from oxygen-glucose deprivation/reoxygenation-induced injury. *J Cell Biochem,* 120 (3): 3757-3764, 2019. DOI: 10.1002/jcb.27656

47. Duan W, Chen J, Wu Y, Zhang Y, Xu Y: Protective effect of higenamine ameliorates collagen-induced arthritis through heme oxygenase-1 and PI3K/Akt/Nrf-2 signaling pathways. *Exp Ther Med,* 12 (5): 3107-3112, 2016. DOI: 10.3892/etm.2016.3730