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School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Original Article

Sodium hydrogen sulfide may not protect the kidney against ischemia/reperfusion damage in male and female rats

Majid Askaripour[1], Hamid Najafipour[2], Shadan Saberi[3,*], Shahriar Dabiri[4], Maryam Iranpour[4], Abbas Etminan[5,*], and Mehdi Nematbakhsh[6]

[1]*Department of Physiology, School of Medicine, Bam University of Medical Sciences, Bam, I.R. Iran.*
[2]*Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, I.R. Iran.*
[3]*Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, I.R. Iran.*
[4]*Department of Pathology, Pathology and Stem Cell Research Center, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, I.R. Iran.*
[5]*Physiology Research Center, Departments of Nephrology, Urology and Renal Transplantation, Kerman University of Medical Sciences, Kerman, I.R. Iran.*
[6]*Water and Electrolytes Research Center, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.*

Abstract

Background and purpose: Renal ischemia/reperfusion (IR) injury is a pathologic phenomenon that caused to increase risk of mortality. The main objective of this study was to investigate the effect of sodium hydrogen sulfide (NaHS) on renal IR injury in male and female rats.
Experimental approach: Fifty-eight male and female rats were randomized into 4 groups of control, sham, IR, and IR + NaHS. The IR was performed by 45 min of ischemia by vessel clamping followed by 24 h reperfusion. The NaHS (100 µmol/kg) treatment was applied 10 min prior to IR. Finally, after 24 h of reperfusion, the measurements were performed.
Findings/Results: The serum levels of blood urea nitrogen, creatinine, tissue level of malondialdehyde, and kidney tissue damage score (KTDS) were increased by IR. Urine volume, creatinine, and urea clearances decreased by IR. NaHS administration improved some parameters in males but exacerbated KTDS and serum markers related to renal function.
Conclusions and implications: Our data demonstrated that NaHS didn't protect female rats against renal IR injury. In males, it has null effects or just a few protective effects *via* antioxidant activity.

Keywords: Oxidative stress; Renal ischemia-reperfusion injury; Sodium hydrogen sulfide.

INTRODUCTION

Renal ischemia-reperfusion (IR) injury is a pathologic phenomenon, which is characterized by a period of low or lack of blood and oxygen supply to the organ followed by recirculation. Renal IR occurs during renal transplantation, complex heart surgeries, or renal drug intoxication, which causes renal damage and dysfunction and increases the risk of mortality in these clinical conditions (1,2). Ischemia triggers reactive oxygen species (ROS) formation and inflammation, disturbs renal cells and mitochondria, and these disturbances have been exacerbated in the reperfusion phase (3). Physiologically, antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase remove the ROS, but in pathologic conditions like IR they don't act sufficiently, so they imbalance the tissue redox system and levels of oxidative and nitrosative stress products increase include of lipid peroxidation, malondialdehyde (MDA), and the reactive nitrogen species (4-7).

*Corresponding authors:
Sh. Saberi, Tel: +98-9133010291, Fax: +98-3433257671
Email: sh_saberi@kmu.ac.ir
A. Etminan, Tel: +98-9123962708, Fax: +98-3433257671
Email: etminan@kmu.ac.ir

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Hydrogen sulfide (H_2S) is the third known gasotransmitter along with nitric oxide and carbon monoxide, which is synthesized endogenously by cystathionine γ-lyase, cystathionine β-synthase (CBS), and 3-mercaptopyruvate sulfur transferase (3-MST). These enzymes are expressed in several organs including of liver, brain, skin fibroblasts, and kidney (8). Several physiologic roles are explained for H_2S and sodium hydrosulfide (NaHS) as H_2S donors including increasing glomerular filtration rate (GFR), decreasing Na and K excretion and reducing renin release (9-11) and pharmacologic role to protect renal injury *via* increasing renal blood flow (8), anti-inflammatory, antioxidant, and anti-apoptotic effects in renal ischemia injury (12). Although NaHS reduced serum levels of blood urea nitrogen (BUN), creatinine (Cr), kidney tissue MDA, apoptotic cells, and conserved SOD in renal IR injury in male rats (13), the effect of NaHS in female rats is not confirmed and needs to be clarified. On the other hand, previous studies reported gender-related responses in the renal IR rat model (14). Accordingly, this study aimed at identifying the protective effect of NaHS in the IR model in rats and comparing this effect between male and female rats, also the role of free radical scavenging enzymes was investigated.

MATERIALS AND METHODS

Animals

Fifty-six Wistar rats half female and half male (220 ± 20g) were purchased from Kerman University Animal House. Animals were treated in accordance with the Canadian Council on Animal Care (CCAC). During the experiment, the animal kept in an animal room at 23 ℃ temperature, in a 12/12-h light/dark cycle, and they had free asses to standard chow and water. All the experiments were approved by the Kerman University of Medical Sciences Ethics Committee (Ethic No. 1398.038).

Study design and surgical preparation

Animals of each gender were randomly divided into 4 groups (n = 7) of the experiment including the control group: no intervention was performed on the animals in this group; sham-operated group: the rats were anesthetized by ketamine/xylazine (80/8 mg/kg) (15) intraperitoneally, then underwent surgery without clamping renal vessels; IR group: the rats in this group received 45 min bilateral ischemia followed by 24-h reperfusion; IR + NaHS group: the animals in this group were subjected to IR but they received NaHS (100 μmol/kg) (16) 10 min before the release of the vessel clamp. After recovery, the animals were put in metabolic cages individually to collect 24-h urine samples. Blood sampling was done by heart puncture in anesthetized rats, the kidney was harvested and weighed immediately, and the right kidneys were fixed in 10% formalin for histology analysis. The left kidneys and serum were stored in a -80 ℃ freezer until measurements.

Measurements

The serum levels of BUN and Cr and urine albumin were measured by an auto-analyzer (Selectra-XL, Vital Science, Netherlands) using commercial kits (Pars Azmoon, Tehran, Iran). Kidney MDA levels were measured by the thiobarbituric acid method, and renal SOD and GPX activities were determined by special ELIZA kits (Navand Salamat, Iran). The clearance of Cr and urea and urine volume was determined. Cr clearance was reported as an index of GFR which is calculated by the equation below (17):

$$\mathrm{GFR} = \frac{\mathrm{uCr} \times \mathrm{UV}}{\mathrm{sCr}}$$

where uCr stands for urine creatinine concentration, UV for urine volume, and sCr is serum creatinine concentration.

Tissue samples were stained by hematoxylin and eosin (H&E) and Masson's trichrome staining and scored by a pathologist who was blind to the protocol of the study.

Statistical analysis

The data were compared by two-way analysis of variance (ANOVA) followed by LSD test with Bonferroni correction as post hoc of two-way. The non-parametric data were compared by the Kruskal-Wallis H and followed by Mann-Whitney tests as post hoc. All data were represented as mean ± SEM and $P < 0.05$ was considered statistically significant.

RESULTS

The serum levels of BUN and Cr and urine albumin

No significant differences were detected in serum levels of BUN and Cr, and urine albumin between the control and sham groups. This finding revealed no toxic effect for NaHS. The induced renal IR increased the serum level of BUN and Cr in both sexes. NaHS treatment raised these parameters noticeably just in females in comparison with the IR group (Fig. 1A and B).

Urine volume and Cr and urea clearance

A significant increase of urine volume in females was seen followed by renal IR which was reduced followed by NaHS treatment (Fig. 1D). The result also showed a decrement in GFR calculated by Cr clearance (ClCr) in IR groups compared to control groups. NaHS increased GFR and didn't alter urea Cl in males, a reduction was seen in these factors in NaHS-treated female rats which were remarkable in comparison to sham and control groups but not with IR groups (Fig. 1E and F).

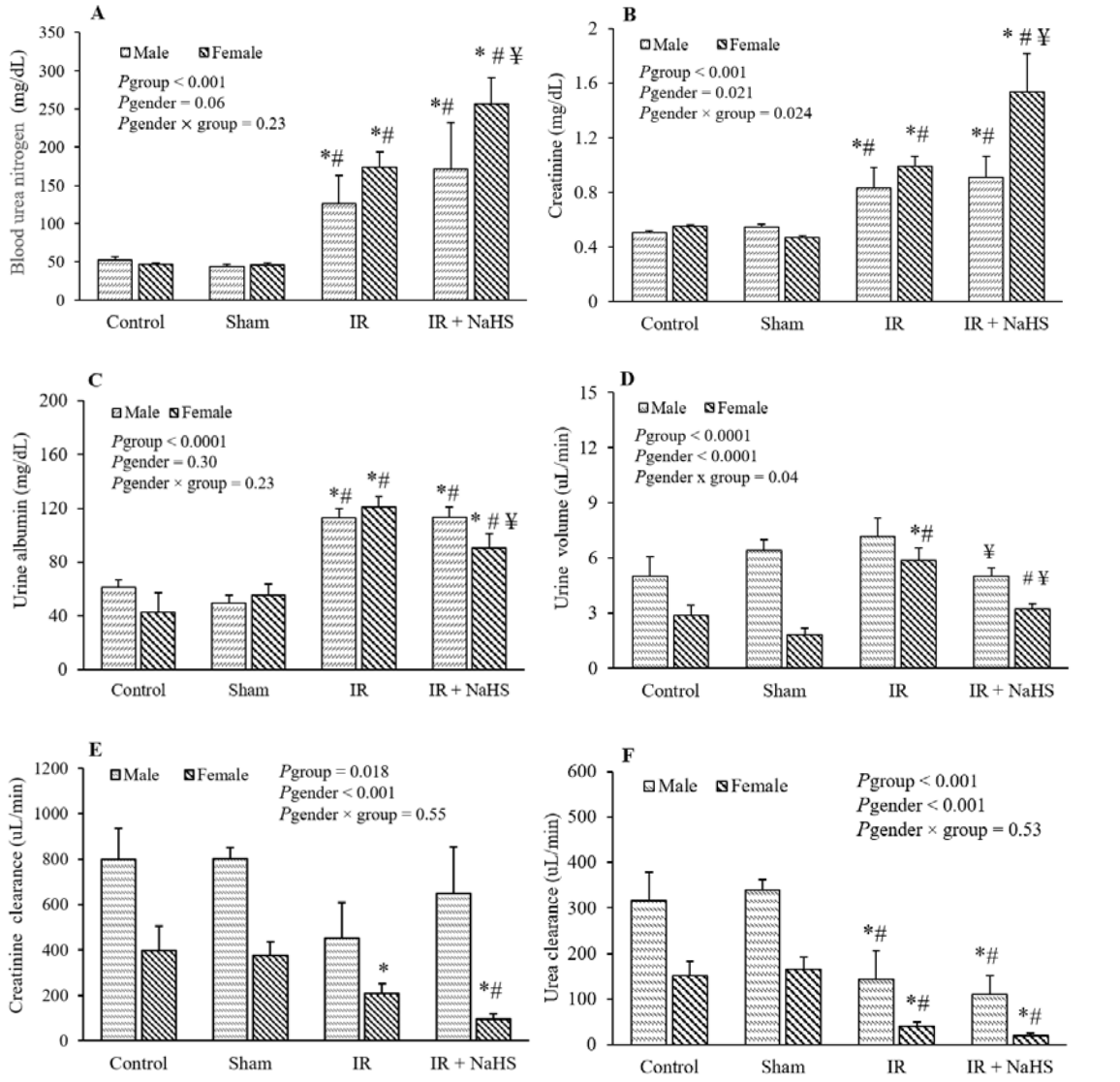

Fig. 1. The serum levels of blood urea nitrogen and creatinine; urine level of albumin and volume, and creatinine and urine clearances in control, sham, IR, and IR + NaHS groups. *$P < 0.05$ Represents significant differences in comparison with control, $^{\#}P < 0.05$ versus sham, and $^{¥}P < 0.05$ in contrast with the IR group. IR, Ischemia/reperfusion; IR + NaHS, IR treated with sodium hydrogen sulfide.

Renal MDA and SOD and GPX levels

MDA levels in IR groups increased in comparison with control and sham groups, which confirms IR injury-induced oxidative stress and lipid peroxidation in the kidney. Treatment with NaHS significantly decreased renal MDA in female rats compared to the IR group, the decrement observed in males was insignificant (Fig. 2A).

The result showed a decrement in SOD activity by IR compared with control and sham groups, NaHS administration elevated enzyme activity in both genders and it was significant in males. The same trend was seen in GPX levels in IR groups compared to the sham groups, and NaHS treatment increased GPX, but total alterations in GPX were not prominent in both genders (Fig. 2B and C).

Histopathological assessments

The result of tissue sections that were stained by H&E and Masson's trichrome were shown in Table 1. The mean score of tissue alterations include of tubulointerstitial damage, glomerulosclerosis, tubular inflammation, congestion, bleeding, degeneration, necrosis, and fibrosis are calculated as KTDS which totally demonstrated significant tissue damage in IR groups compared to sham groups (Table 1 and Fig. 3). NaHS aggravated renal damage in female rats compared to IR group. Renal tissue images of experimental groups are demonstrated in Fig. 4A and B.

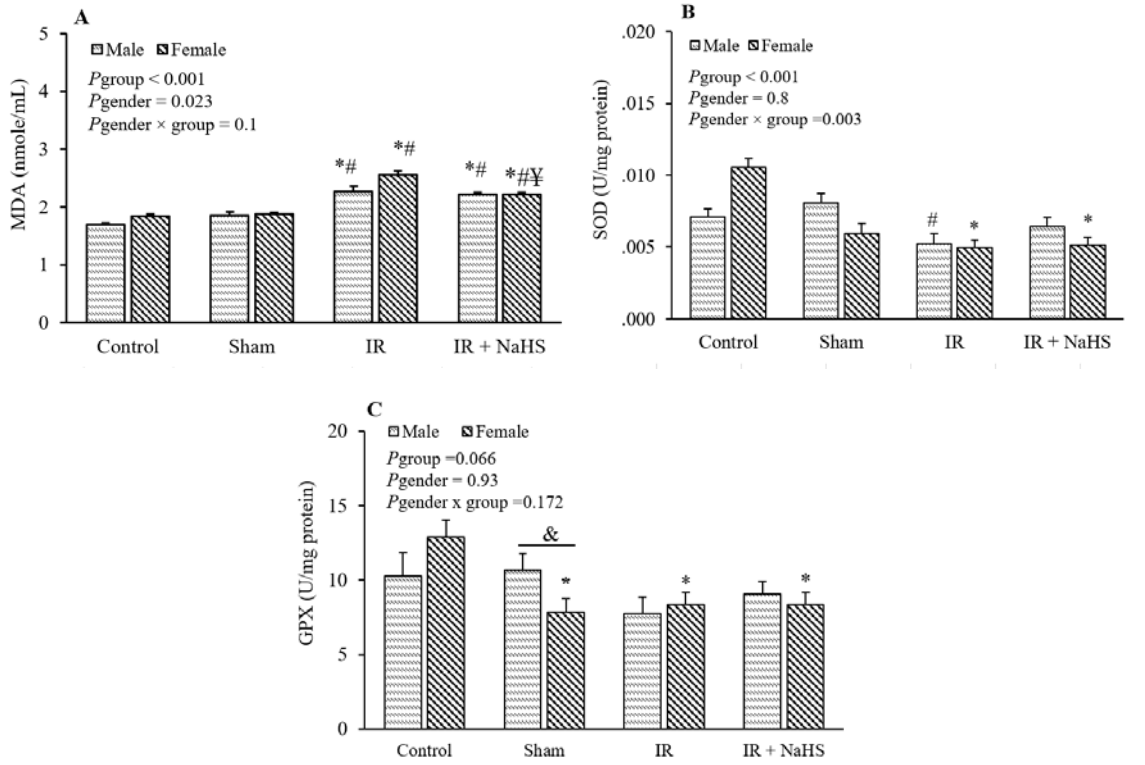

Fig. 2. The kidney tissue antioxidant activity enzymes and malondialdehyde level. Kidney activity of SOD, GPX, and MDA levels in control, sham, IR, and IR + NaHS groups. $^{*}P < 0.05$ Represents significant differences in comparison with control, and $^{\&}P < 0.05$ between the indicated groups, $^{\#}P < 0.05$ versus sham, and $^{¥}P < 0.05$ in contrast with the IR group. SOD, Superoxide dismutase; GPX, glutathione peroxidase; MDA, malondialdehyde; IR, Ischemia/reperfusion; IR + NaHS, IR treated with sodium hydrogen sulfide

Table 1. The mean grade of tubulointerstitial damage, glomerulosclerosis, inflammation, congestion, bleeding, degeneration, necrosis, and fibrosis clearance in control, sham, IR, and IR + NaHS groups.

Gender	Groups	Tubulointerstitial damage	Glomerulo-sclerosis	Inflammation	Congestion	Bleeding	Degeneration	Necrosis	Fibrosis
Male	Control	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Sham	0.0	0.0	0.0	0.0	0.0	0.3	0.0	0.0
	IR	3.0	2.5	1.5	2.5	2.0	2.5	0.5	3.0
	IR + NaHS	2.3	1.0	0.7	2.3	2.0	1.3	0.7	2.0
Female	Control	0.0	0.0	0.3	0.5	0.3	0.3	0.0	0.0
	Sham	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0
	IR	2.0	0.8	0.8	2.3	2.0	1.3	0.0	2.0
	IR + NaHS	3.0	1.6	1.0	3.0	3.0	1.8	0.6	2.6

IR, Ischemia/reperfusion; IR + NaHS, IR treated with sodium hydrogen sulfide.

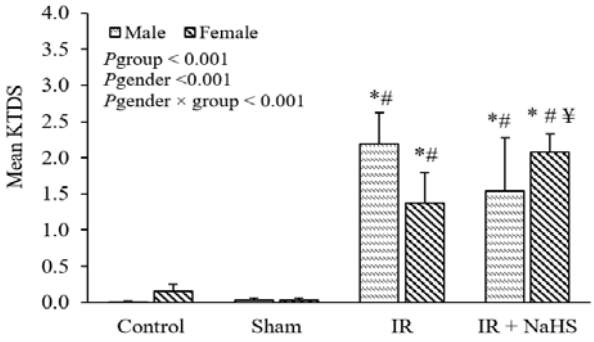

Fig. 3. The mean score obtained from tubulointerstitial damage, glomerulosclerosis, inflammation, congestion, bleeding, degeneration, necrosis, and fibrosis scores in control, sham, IR, and IR + NaHS groups. $^{*}P < 0.05$ Represents significant differences in comparison with control, $^{\#}P < 0.05$ versus sham, and $^{¥}P < 0.05$ in contrast with IR group. IR, Ischemia/reperfusion; IR + NaHS, IR treated with sodium hydrogen sulfide.

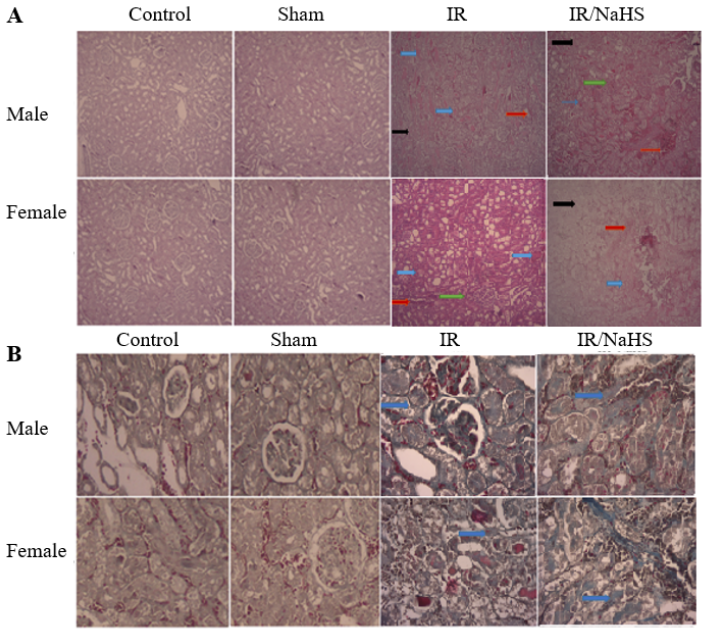

Fig. 4. (A) The hematoxylin and eosin staining of the kidney in control, sham, IR, and IR + NaHS groups. Blue arrows indicate tubular cast, red: congestion, black: necrosis, and green: inflammation. Blue arrows in (B) Masson's trichrome-stained renal sections represents fibrosis. Original magnification ×100 for H&E and ×400 for Masson's trichrome; n = 6 for each group. IR, Ischemia/reperfusion; IR + NaHS, IR treated with sodium hydrogen sulfide.

DISCUSSION

This study demonstrated that 45 min ischemia followed by a 24 h reperfusion, induced renal tissue damage and dysfunction, in male and female rats. An improvement trend was seen by NaHS treatment in the pathological assay, urine volume, and CrCl. Unexpectedly, NaHS aggravated IR injury in female rats. Lipid peroxidation was decreased as MDA levels were lower in animals treated with NaHS, which is consistent with other studies (16).

H_2S, the third gasotransmitter has bronchodilatory, vasodilatory, cytoprotective, and renoprotective effects (18-20). Intravenous injection of H_2S 10 min before clamp release in female pigs induced renal ischemia, reduced serum Cr levels, and preserved glomerular function (21). Azizi *et al*. demonstrated that NaHS protects renal IR injury through antioxidant activity (13). In this study, NaHS was administered 10 min before reperfusion to reduce tissue oxygen demand and just at the onset of reperfusion to decrease ROS production. Intracellular prevention of ROS production by special mitochondrial H_2S donors reduced renal injury induced by glucose oxidase in rats (22). However, our results didn't confirm the renoprotective effect of NaHS. It could be discussed by the concentration-dependent effect of NaHS. Long-term administration of NaHS in several doses from 2.8 to 5.6 mg/Kg in heart ischemia showed a dose-dependent effect, while low doses didn't have beneficial effects, the medium one was the best crucial dose. Although high doses were harmful and increased MDA level, infarct size, and inflammatory biomarkers, in addition, high doses diminished ROS scavenging enzyme activity, and total antioxidant capacity (23). Low NaHS concentration is reported to increase SOD while a high dose decreased GPX activity and ROS production (24-26). The same report is available for the effect of pro-inflammatory or anti-inflammatory of NaHS in the literature (26) and explains the unexpected results of this study which increased BUN, Cr, histopathological alterations, and decreased ROS scavenging enzymes. Another study reported the useful effect of NaHS in a dose of 100 (μmol/kg) in renal IR but the animals they use were mice and the time of NaHS administration was 30 min before the reperfusion and 6h into the reperfusion phase which was different from our study (27). In our results, we observed a gender difference in response to NaHS treatment, although the trend mostly is the same in males but prominently responded in females. For example, the serum levels of BUN and Cr which increased by IR didn't alter in males but enhanced more in females. Also, pathological assay revealed that NaHS exacerbated tissue injury in females. CrCl and urea didn't change by the NaHS administration. However, albuminuria and urine volume were lowered in females by NaHS treatment. The protective effect of NaHS in myocardial IR in both sexes is reported (28). The expression of enzymes that involves in H_2S formation is different in males and females, and they are regulated by sexual hormones (29). Moreover, the effects of H_2S are organ-dependent and different in health and disease conditions (29). CBS enzyme activity is higher in female rats and human kidney tissue whereas, the enzyme activity is higher in male mice which reduced after castration and confirmed the role of testosterone in CBS activity (30,31). Furthermore, a diminution of CBS activity was reported in the renal IR model in rats that increased renal and serum levels of homocysteine and oxidative stress causing renal injury and dysfunction (32). A gender difference was observed in the reduction of H_2S plasma level in rats after left coronary artery ischemia while, NaHS improved microcirculation in both male and female animals (33). As mentioned above the discrepancy observed in the result of this study could explain by several differences in our method regarding animal species, the time NaHS was administered, gender difference, and the most important dose of NaHS was used. As it is known that the effects of NaHS are time- and dose-dependent and a "U" shape manner is reported for its biological function (34,23).

CONCLUSION

Our data indicated that IR induced renal injury *via* stress oxidative and altering antioxidant enzyme activity. NaHS as a

bioactive molecule was shown a null effect in renal IR male rats and against females in the dose of 100 µmol/kg since NaHS effects are dose-dependent.

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Conflict of interest statement

The authors declared no conflict of interest in this study.

Authors' contributions

S. Saberi participated in the design and coordination of the study, drafting of the manuscript, statistical analysis, and interpretation of the findings; M. Askaripour participated in the experimental procedures and drafting; H. Najafipour participated in the design and coordination of the study; S. Dabiri and M. Iranpour participated in pathology scoring; A. Etminan participated in the design and drafting; M. Nematbakhsh participated in the drafting the manuscript, statistical analysis, and interpreting the findings. All authors read and approved the final manuscript.

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