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Article

The effect of lithium tetraborate as a novel cardioprotective agent after renal ischemia-reperfusion injury

Kubra Koc[1], Fatime Geyikoglu[1*], Asli Yilmaz[2,3], Serkan Yildirim[4], Gulsah Yildiz Deniz[5]

[1]Department of Biology, Faculty of Science, Ataturk University, Erzurum, Turkey, [2]Department of Molecular Biology and Genetics, Faculty of Science, Ataturk University, Erzurum, Turkey, [3]East Anatolian High Technology Research and Application Center, Ataturk University, Erzurum, Turkey, [4]Department of Pathology, Faculty of Veterinary, Ataturk University, Erzurum, Turkey, [5]Vocational School of Health Services, Ataturk University, 25240 Erzurum, Turkey

Epidemiological studies suggest that acute kidney injury has certain effect on myocardial function. In this study, for the first time, we tested a boron compound namely lithium tetraborate an act as an anti-oxidant and anti-inflammatory agent in ischemia-reperfusion injury. For this, we employed an *in vivo* rat model with kidney ischemia reperfusion injury to evaluate cardiac injury to clarify the mechanisms of lithium tetraborate. The evaluation of cardiac injury through kidney artery occlusion and reperfusion rat model indicated that lithium tetraborate could (1) reduce oxidative stress-induced endothelial dysfunction; (2) attenuate the inflammatory response of cardiac cells; and (3) alleviate the apoptosis and necrosis of myocytes. In summary, lithium tetraborate demonstrates significant therapeutic properties that contribute to the amelioration of cardiac damage, and it could be a promising candidate for future applications in myocardial dysfunction.

Keywords: Ischaemia-reperfusion. remote organ damage. Boron compounds. cardioprotective agent. Lithium tetraborate.

INTRODUCTION

The blood flow to the kidney is stable under the well-regulated conditions. However, in the case of oxygen deficiency, the blood flow in renal pathobiology is accelerated remarkably. The increment of blood flow leads to the emergence of the reperfusion injury (Menshikh *et al*., 2019). The renal ischemia-reperfusion (I/R) injury results in various acute and chronic conditions. In most cases, the primary failing organ is the heart. Acute myocardial injury due to the renal ischemia and subsequent reperfusion has major effect on myocardial infarction (Zhu *et al*., 2017). Since the myocytes and endothelial cells in the cardiac tissue have very low cell proliferation capabilities (Galdos *et al*., 2017), reperfusion injury creates cell death and cardiac dysfunction. In this respect, reperfusion of the ischemic kidney is crucial for impaired cardiac tissue (Ischia, Bolton, Patel, 2019). Oxidative stress is a common subject of a wide range of cardiovascular disorders including I/R injury (Griendling *et al*., 2003). To eliminate oxidative stress, antioxidants are promising candidates for I/R injury therapy. Thus, it is noteworthy to evaluate the association between the pharmacodynamics effects of antioxidants and I/R injury alleviation (Studneva *et al.,* 2019). Antioxidants inhibit reactive oxygen species (ROS) emission and apoptosis induction (Xiao *et al*., 2016). Besides, the antioxidants as therapeutic agents can target inflammation and improve myocardial function (Lan *et al*., 2019; Zhang *et al*., 2016). However, the cardioprotective effects of protective agents in

***Correspondence:** F. Geyikoglu. Department of Biology. Faculty of Science. Ataturk University, Erzurum, TURKEY. E-mail: geyikogluff@yahoo.com. Orcid: https://orcid.org/0000-0003-2488-1757

clinical settings remain controversial (Kleinbongard *et al*., 2015). Therefore, it is still of importance to find out potential natural and synthetic products as pharmacological postconditioning agents.

In recent years, biologically active boron compounds have been considered as therapeutic agents in various applications (Fernandes, Denny, Dos Santos, 2019). Recent studies enabled the construction of significant background on boron-based molecules. Despite the numerous studies, the mechanism behind the biochemical effects of various boron compounds has not been fully understood (Romero-Aguilar *et al*., 2019). Specifically, lithium tetraborate compounds are very effective in the elimination of oxidative stress and provide significant antioxidant activity. Also, it was reported that lithium tetraborate was employed as an advanced application in eye lens dosimetry (Charubala *et al*. 2019). However, the protective or therapeutic efficiency of lithium borate is still limited. Recently, Yildirim *et al*. (2018) investigated the protective effects of lithium borate against Cd toxicity. Yet the underlying mechanisms behind the protective effect of this boron compound in organ injury have not been explored. In the present study, for the first time, we aimed to investigate the therapeutic effect of lithium tetraborate as a boron compound against cardiac injury following acute renal I/R in rats. It was detected that lithium tetraborate provided significant potential in the development of therapeutic tools to modulate ischemic organ damages.

MATERIAL AND METHODS

Animals

Sprague Dawley rats (280 to 300 g) purchased from Medical Experimental Application and Research Center, Atatürk University, Erzurum, Turkey, and housed in standard conditions (12 hr light/day cycle with 20 to 22°C temperature and 40 to 50% humidity). A standard pellet diet was available with drinking water ad libitum. All efforts were made to minimize the potential suffering of the animals, and the study was performed according to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication No. 85-23, revised 1996). All experimental procedures in this study were approved by the Atatürk University Local Ethics Committee for Animal Experiments (No. 66, 22.03.2018).

Experimental scheme

All rats were anesthetized with sevofluran, and randomly assigned to three groups (n = 6 each): I) sham-operated control; II) renal I/R; III) oral administration of lithium tetraborate 50 mg/kg 50 min before ischemia. Lithium borate was purchased from Sigma-Aldrich Chemical Company (St. Louis, MO, USA) and dissolved in 100 ml distilled water. The dose of lithium tetraborate was chosen from selected according to the literature data (Yildirim *et al.,* 2018). Renal I/RI was induced by bilateral renal pedicle clamping for 50 min and sham-operated rats underwent identical operation protocols except for the clamping as reported previously. At the end of 3 hrs reperfusion, rats were sacrificed by an overdose of sevofluran, and their hearts were quickly removed and then directly fixed with 10% buffered formalin phosphate for histology assessment. For biochemical and inflammation measurements, heart samples were immersed in liquid nitrogen and stored at –80° C until analysis.

Estimation of antioxidant enzymes, lipid peroxidation and cytokines

Frozen tissue taken from each group was ground in liquid nitrogen. Before each test, 2 gr of tissue samples were weighed and homogenized into 1 mL of PBS. They were centrifuged at 10,000 g for 10 min at 4°C, and the supernatants were collected. The supernatant aliquots were assayed for superoxide dismutase (SOD) and glutathione (GSH), malondialdehyde (MDA) and myeloperoxidase (MPO), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and endothelial nitric oxide synthase (eNOS) levels in rat heart tissue using enzyme-linked immunosorbent assay (ELISA) kits (SunLong Biotech Co., China) in accordance with the manufacturer's manuals.

Histopathological and immunohistochemical assessments

The fixed heart tissues were dehydrated and embedded in paraffin for staining. Tissue samples were sectioned at 5 µm for staining with hematoxylin and eosin (H&E) and Periodic acid–Schiff (PAS), and at a thickness of 4 µm for immunostainings by specific monoclonal antibodies of 8-OHdG and Bax. The sections were deparaffinized and applied Diaminobenzidine (DAB) as chromogen, slides were counterstained with hematoxylin, dehydrated, and covered by coverslips. Immunohistochemical stainings of Bax and 8-OHdG were performed using anti-Bax and anti–8-hydroxydeoxyguanosine (8-OHdG) antibodies (Santa Cruz; 1:2500 dilution) with a Novolink Polymer Detection kit (Leica Microsystems Pte Ltd, Taipei, Taiwan), following the manufacturer's instructions. Analysis of the sections was performed by the same pathologist blindly using a light microscope (Leica DM 1000, Germany). The pathologists continuously observed at least 10 high-power fields (×200) for each slice.

Statistical Analysis

All data were expressed as mean±standard error of the mean (SEM) of 6 rats per experimental group. The comparisons were done by a one-way analysis of variance (ANOVA) test followed by Graphpad prism 5.0 statistics software (GraphPad, La Jolla, CA, USA). Tukey's test was used as a post hoc. $p<0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

Lithium tetraborate protects the heart from renal I/R injury

To assess whether lithium tetraborate pretreatment has a protective role on heart injury with renal I/R, we assessed the degree of oxidative stress by measuring the levels of MDA and GSH, and the activity of SOD in rat heart tissues. As shown in Figures 1, levels of SOD and GSH on the heart were reduced in the renal I/R group as compared to sham group rats ($p<0.0001$). These levels were reverted by lithium tetraborate (50 mg/kg) pretreatment ($p<0.0001$). On the other hand, MDA levels on the heart were significantly increased in the I/R group as compared with the sham group. However, pretreatment of lithium tetraborate significantly reduced MDA levels compared to the renal I/R group ($p<0.0001$).

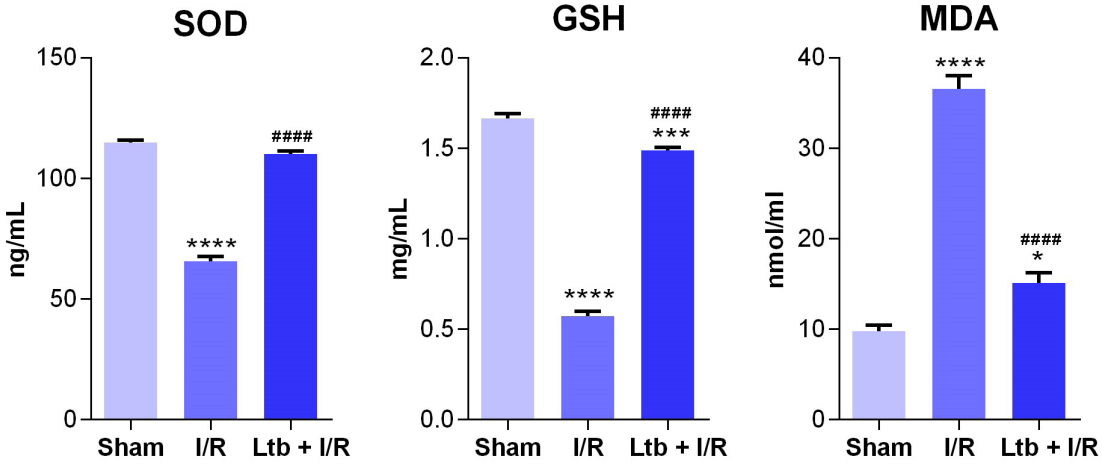

FIGURE 1 - The effects of lithium tetraborate the SOD, GSH and MDA levels on heart after I/R injury. Data are presented as mean ± SEM (n=7). * denotes significant differences between other studied groups and sham (*: $p<0.05$, ****: $p<0.0001$), # denotes significant differences between other studied groups and I/R group (####: $p<0.0001$) by Tukey's multiple range tests. Abbreviation used: I/R: Ischaemia/Reperfusion, Ltb: Lithium tetraborate.

Lithium tetraborate alleviates inflammatory responses on heart during renal I/R injury

To explore the role of lithium tetraborate as a potential cardiac inflammatory mediator in renal I/R, we examined the levels of MPO, TNF-α, IL-6, and eNOS in rat heart. As shown in Figures 2, in comparison with the sham group, the indicators of cardiac inflammation production augmented evidently in the renal I/R group ($p<0.0001$). However, lithium tetraborate (50 mg/kg) pretreatment resulted in significantly decreased cardiac inflammation levels compared with the renal I/R group ($p<0.0001$). In addition, TNF-α and IL-6 levels were significantly increased and eNOS level on the heart was considerably reduced in the renal I/R group as compared to the sham group. However, pretreatment of lithium tetraborate significantly reduced TNF-α and IL-6 levels as compared to the renal I/R group ($p<0.0001$). The level of eNOS on heart was significantly elevated in the lithium tetraborate pretreated group compared to renal I/R group ($p<0.0001$). These findings clearly demonstrated that lithium tetraborate pretreatment alleviates the inflammatory responses on heart following renal I/R treatment.

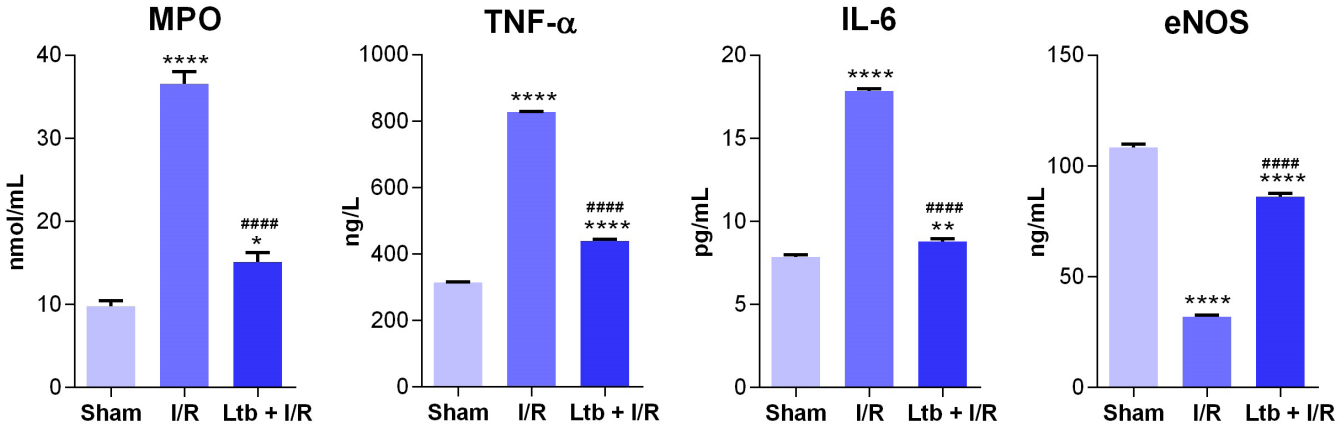

FIGURE 2 - The effects of lithium tetraborate the MPO, TNF-α, IL-6 and eNOS levels on heart after I/R injury. Data are presented as mean ± SEM (n=7). * denotes significant differences between other studied groups and sham (*: $p<0.05$, **: $p<0.01$, ****: $p<0.0001$), # denotes significant differences between other studied groups and I/R group (####: $p<0.0001$) by Tukey's multiple range tests. Abbreviation used: I/R: Ischaemia/Reperfusion, Ltb: Lithium tetraborate.

Lithium tetraborate reduces myocyte apoptosis and DNA damage in renal I/R injury

As renal I/R injury is associated with heart apoptosis, we assessed the apoptosis amount in the heart by Bax immunostaining. In addition, we assessed the DNA damage amount in the heart by 8-OHdG immunostainings. As shown in Figures 3, Bax immunoreactivity on heart tissue was markedly increased in the renal I/R group as compared to sham group rats. In contrast, reduced Bax immunoreactivity was detected in the heart treated with Lithium tetraborate before renal I/R. Therefore, these results clearly demonstrated that Lithium tetraborate protects the cardiac cell against renal I/R induced apoptosis. Although renal I/R led to the marked 8-OHdG formation in the renal I/R group compared with the control rat, the lithium tetraborate pretreated group displayed significantly reduced 8-OHdG formation in the heart (Figure 3).

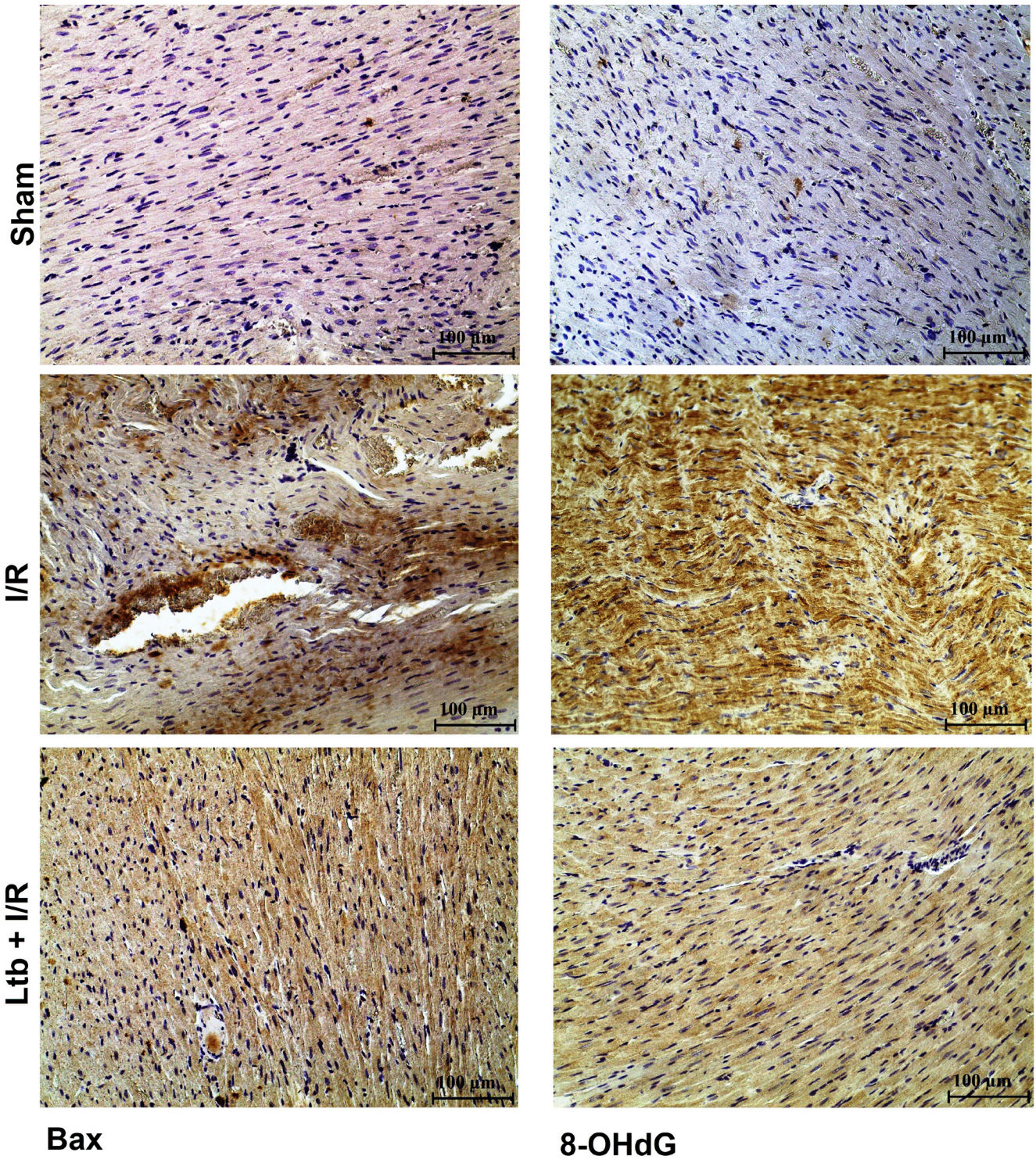

FIGURE 3 - The effects of lithium tetraborate the Bax and 8-OHdG expression levels on heart after I/R injury. **Sham**; Bax and 8-OHdG negative, **I/R**; severe Bax and 8-OHdG expression, **Ltb + I/R**; weak Bax and 8-OHdG immunoreactivity.

Abbreviation used: I/R: Ischaemia/Reperfusion, Ltb: Lithium tetraborate.

Lithium tetraborate reduces the heart injury induced by renal I/R

Histopathological examination by H&E staining of tissue sections revealed normal histology of the heart in the sham group (Figure 4). Compared with normal heart, renal I/R induced a significant heart injury that featured remarkable cell infiltration and apoptosis, and diffuse necrosis, and severe congestion and haemorrhage. However, the treatment with lithium tetraborate before renal I/R significantly reduced heart injury as indicated by the reduction in the number of histopathological changes. Moreover, taking into account the PAS staining which showed the abnormal distribution of glycogen in the heart after renal I/R (Figure 4). In the lithium tetraborate 50 mg/kg group heart glycogen content was similar with the sham group.

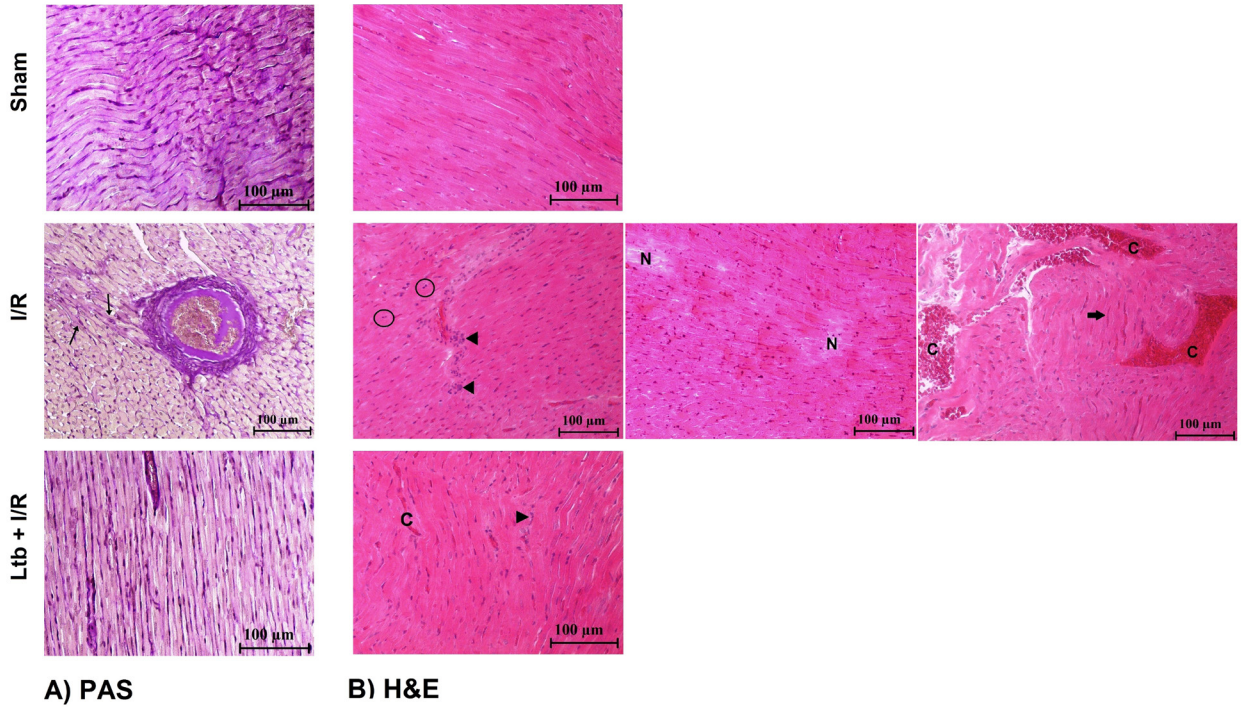

FIGURE 4 - A) PAS staining of rat heart. **Sham**; Sham, normal structure of heart,
I/R; I/R group; Thin arrow: abnormal distribution of glycogen,
Ltb + I/R; glycogen content was similar with sham group.
B) H&E staining of rat heart. **Sham**; Sham, normal structure of heart,
I/R; I/R group; extensive infiltration and apoptosis, Arrow heads: infiltration, Circle: apoptosis,
Diffuse necrosis, N: necrosis,
Extensive congestion and haemorrhage, C: congestion, Arrow: haemorrhage
Ltb + I/R; decreased congestion and infiltration
Abbreviation used: I/R: Ischaemia/Reperfusion, Ltb: Lithium tetraborate.

Renal I/R demonstrates sequential events with marked biochemical and pathological alterations in vital organs (Nakazawa *et al*., 2017). However, there has been limited evaluation of the effects of the acute renal I/R injury in experimental animal models. The renal malfunction during I/R leads to myocardial infarction (Ronco *et al.,* 2008). To attain the cardiac tissue healthy, the renal tissue substantially must be kept sustained as well. The present study highlights the alterations in cardiac tissue after the renal I/R and also the action of lithium tetraborate against injury.

It was observed that lithium tetraborate showed significant function in the protection of the heart due to kidney injury. This observation is consistent with the research by Yildirim *et al*. which is on liver and kidney damage as a result of acute Cadmium toxicity (Yildirim *et al*., 2018). At present anti-oxidant effects of lithium tetraborate are still unknown both *in vitro* and *in vivo* conditions. In this study, we detected an excellent agreement between the oxidative stress and antioxidant parameters in cardiac tissue. The pretreatment of lithium tetraborate reversed the significant increase in MDA level and the reduction in SOD and GSH levels induced by renal I/R. We also observed that concomitant activation of important antioxidant scavengers such as SOD and GSH was adequate to scavenge the oxidant burden. SOD is considered to be the primary enzyme to reduce multiple organ failure and acute kidney injury (Jung *et al.,* 2019). The cardiomyocyte contains abundant mitochondria and ROS under oxidative stress mainly produced by mitochondria. Indeed, SOD scavenges ROS and protects the function of mitochondria (Liu, Chen, 2017). Further, enzyme activity tests showed that renal I/R increased the 8-OHdG amount, suggesting the induction of oxidative stress during renal I/R which led to oxidative DNA damage in cardiac cells. The excess ROS production in mtDNA results in aggregation of 8-OHdG due to ischemia, and excessive intracellular ROS generation could trigger extensive mitochondrial oxidative damage (Tan *et al.,* 2017). MDA, a key indicator of oxidative balance, directly reflects the amount of ROS (Türkoğlu *et al.,* 2017). Undoubtedly, the upregulation of GSH can effectively scavenge the overproduction of MDA and may play a key role to decrease heart dysfunction due to I/R injury (Shan *et al.,* 2019). Here, we report that lithium tetraborate could inhibit myocardial oxidative stress after kidney damage. Also, it is revealed that lithium tetraborate pretreatment could attenuate MDA production and this effect was mediated by eNOS-dependent cardioprotection. It was indicated that the cardiac complications interacted with the vascular eNOS/NO pathway and MDA down-regulated (Ding *et al*., 2019). In an experimental study, the *in vitro* induction of angiogenesis by boron-incorporated calcium silicate coating extract appeared to involve oxidative stress-induced nitrosative stress (Li *et al*., 2019). According to our results, lithium tetraborate might be a promising therapeutic agent for the treatment of cardiac damages caused by I/R in the future.

Inflammation and apoptosis in addition to oxidative stress are involved in the pathogenesis of I/R (Ma *et al*., 2019). The immune response is characterized by the activity of classical cells belonging to the immune system, such as neutrophils, macrophages, lymphocytes, and also endothelial cells (Jackaman *et al*., 2017). Our study revealed that the cardiac tissue of the model group compared with the control group was seriously damaged, presenting severe inflammation. After renal I/R, the cardiac tissue was exposed to congestion. Inflammation in remote organs is an important process, participating in the pathogenesis of injurious response, caused by I/R (Shen *et al*., 2018). The increased inflammation may promote intimal thickening and plaque formation which narrows the vascular lumen and compromises blood flow in the heart (D'Onofrio, Servillo, 2018). Recently, potential pharmacological approaches which decrease MPO activity, a neutrophil enzyme marker, and antagonize mechanisms downstream of activated inflammatory cells are discussed (de Almeida *et al*., 2017). In our study, lithium tetraborate treatment significantly attenuated cardiac tissue MPO activity and macrophage-induced inflammatory factors (TNF-α and IL-6) in a rat model of renal I/R. For the first time, we observed an aggravated inflammatory response and inhibition of the eNOS in cardiac tissue of ischemic rats, both of which were improved by lithium tetraborate treatment. Nitric oxide (NO•) is of the most important ROS generated by inflammatory cells and markedly increases in heart failure. However, the bioavailability of NO, which is generated by constitutive eNOS in endothelial cells by inflammatory cytokines such as TNF-α and IL-6 can be reduced (Wang *et al.,* 2019). The above characteristics are fully reflected in our ischemic rat model, indicating that the treatment of the lithium tetraborate is successful. Thus, our results showed that lithium tetraborate downregulated the levels of pro-inflammatory factors by suppressing ischemia and reperfusion-induced oxidative stress. Nowadays, the immunomodulatory role of antioxidant substances is emphasized as promising in the treatment of organ injuries after I/R (Ghoreyshi *et al*., 2019). Boric acid reduces

oxidative stress in postischemic reperfusion injury of rat kidney (Kar *et al.,* 2019) and also presents useful effects against carbon tetrachloride-induced hepatotoxicity in mice (Ince *et al*., 2012). However, boron nitride as a drug carrier has been proved to cause various *in vivo* toxicities or inflammations in previous reports (Liu *et al.,* 2012).

As an important mediator of pro-apoptosis, the Bax is the executive and its down-regulating is noted in the ischemic organ (Guo *et al*., 2008). Our study showed that renal I/R was associated with a significant increase in cardiac Bax protein value compared to the control group and this was in agreement with others (Liu *et al.,* 2007). Previous studies suggested that oxidative stress and subsequent inflammation have an important role in magnifying the apoptosis in the ischemic organ and distant organ damages (Baraldi *et al*., 2017). In our study, lithium tetraborate could ameliorate myocardial apoptosis via positive regulation of antioxidant defense and negative regulation of inflammation/oxidative stress signaling pathways. Also, this positive effect was strongly supported by the reduction of the histopathological lesions. The significant increase in ROS production damages the myocyte cells and leads to activation of the apoptotic process (Chistiakov *et al.,* 2018). Conversely, the substances with antioxidant properties can decrease ROS formation and inhibit apoptosis under I/R conditions (Mattera *et al*., 2017). Recently, it has been suggested that boron inhibits apoptosis by stabilizing the mitochondrial membrane structure (Routray, Ali, 2019). In fact, the mechanisms of boric acid actions (source of boron) on various organs were well documented (Bahadoran *et al.,* 2016; Khaliq *et al*., 2018). Despite these promising outcomes, additional investigations are strictly needed to elucidate possible mechanisms of the other boron compounds as therapeutic agents. In this context, our study provided a clear association between myocardial damage and suggested mechanisms for lithium tetraborate.

CONCLUSION

In the current study, for the first time, we employed *in vivo* biological evaluation of the lithium tetraborate on heart damage due to renal I/R. We revealed that lithium tetraborate could alleviate myocardial injury via the anti-oxidant, anti-inflammatory, and anti-apoptotic mechanisms pathway. We noticed that lithium tetraborate has a distinctive protective effect against acute myocardial infarction due to renal ischemia-reperfusion.

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