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Original Article

N-acetyl cysteine in combination with forelimbs remote ischemic preconditioning improves the contrast-induced nephropathy: an in-vivo experimental study

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ABSTRACT

Introduction: Given some limitations in the efficacy of N-acetyl cysteine (NAC) or remote ischemic preconditioning (RIPC) to prevent contrast-induced nephropathy (CIN), the present study investigated the beneficial effects of NAC alone or in combination with RIPC on CIN prevention.

Methods: Rats were randomly assigned into five groups of eight animals each. Group 1 was sham-operated controls. In group 2, an experimental model of diatrizoate-induced CIN was induced. In groups 3 and 4, NAC (150 mg/kg orally, 24 h before the CIN induction) or RIPC (3 cycles of 4 min/4 min of ischemia and reperfusion in the forelimbs 24 h before the CIN induction) was applied, and both strategies were applied in group 5. 48 hours after the intervention, serum was collected to assess creatinine (Cr) and blood urea nitrogen (BUN) levels. Kidney tissue samples were also kept to evaluate the histology and measure malondialdehyde (MDA) levels and superoxide dismutase (SOD) activity.

Results: Considerable increases in serum Cr (0.82±0.04 vs 0.53±0.03 mg/dl) and BUN (49.87±2.85 vs 22.93±1.11 mg/dl) levels in the CIN group showed renal functional damages compared to the sham group. The morphological changes (2 vs 0 score), increased renal MDA levels (8.11±1.27 vs 3.12±0.52 µmol/100 mg tissue), and decreased renal SOD activity (2.29±0.65 vs 27.32±0.98 U/g tissue) in the CIN group represent a remarkable renal injury and oxidative stress compared to the sham group. The individual use of NAC (serum Cr levels: 0.59±0.01 mg/dl; serum BUN levels: 27.24±1.01 mg/dl; morphological changes: 1 score; renal MDA levels: 4.35±0.58 µmol/100 mg tissue; renal SOD activity: 17.24±1.48 U/g tissue) and RIPC (serum Cr levels: 0.60±0.03 mg/dl; serum BUN levels: 28.78±1.66 mg/dl; morphological changes: 1 score; renal MDA levels: 5.34±0.53 µmol/100 mg tissue; renal SOD activity: 13.11±1.96 U/g tissue) improved all indices above. However, the combination of NAC and RIPC (serum Cr levels: 0.57±0.01 mg/dl; serum BUN levels: 25.32±1.14 mg/dl; morphological changes: 1 score; renal MDA levels: 3.56±0.52 µmol/100 mg tissue; renal SOD activity: 30.54±2.92 U/g tissue) was more effective than other strategies used alone.

Conclusion: The combined use of NAC and RIPC may be more useful in preventing CIN than the individual use of possible additive effects through reducing oxidative stress.

Keywords:
Blood urea nitrogen
Creatinine
Diatrizoate
Oxidative stress
Renal injury

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Introduction

During the past few decades, the increasing application of medical imaging techniques has led to a significant increase in the use of contrast media. Based on the evidence, half of all annually performed computed tomographic (CT) and magnetic resonance imaging (MRI) scans have used contrast media. Although currently available clinical contrast media are generally regarded as safe, their use is not without adverse effects (Beckett et al., 2015). One of the major complications after contrast media administration is the development of specific type of acute kidney injury (AKI), called contrast-induced nephropathy (CIN) (Haq et al., 2020). In fact, CIN is the third common cause of hospital-acquired AKI, which leads to a longer in-hospital stay, an increase in costs, and high levels of patient morbidity and mortality (Kelemen et al., 2020).

The pathophysiological mechanisms of CIN are complex and not fully understood. However, it can be seen that reduced renal blood flow and resulting hypoxia following contrast media administration may lead to excessive production of free radicals, called oxidative stress status, which causes renal functional and histological damages (Agmon et al., 1994). It is worth noting that experimental models of CIN have helped understand the pathological processes underlying CIN. In this regard, the classic rat CIN model includes inhibition of prostaglandin synthesis by indomethacin, inhibition of vasodilators via inhibition of nitric oxide synthase (NOS) by N-nitro-l-arginine methyl ester (L-NAME), and the administration of high osmolar contrast media (Kiss and Hamar, 2016).

Due to the critical involvement of oxidative agents in CIN pathogenesis, research on antioxidants has attracted much attention and became a hotspot (Zhang et al., 2020). Currently, N-acetylcysteine (NAC) is considered an important therapeutic strategy for CIN prevention as it presents various beneficial properties including interfering with the production of free radicals, detoxifying these radicals, and increasing intracellular antioxidant capacity (Shetty et al., 2019). Furthermore, remote ischemic preconditioning (RIPC) is recently emerged as a novel approach for CIN prevention based on the concept that inducing brief episodes of ischemia-reperfusion in a non-target organ protects against the target organ damage by different mechanisms such as activation of the endogenous antioxidant system (Bafna and Shah, 2020; Damasceno et al., 2020).

The present study investigated the beneficial effects of NAC alone or in combination with RIPC of the forelimbs in an experimental model of CIN in rats through analysis of renal functional, histological, and oxidative stress markers.

Material and methods

Animals

All animal protocols were approved by the Animal Ethics Community of Tehran University of Medical Sciences, Iran (Ethical approved ID: 9311344005). The experiments in this study were performed on adult male Wistar rats weighing 300 ± 20 g received from the Department of Physiology, Tehran University of Medical Sciences. The rats had access to food and water *ad libitum* and were housed in plastic cages at a temperature of 21 ± 2 °C with a 12/12 h light/dark cycle.

Experimental design

To make the kidneys sensitive to contrast media, the rats in all groups were deprived of water for 72 h. Then, to make the kidneys more sensitive, after anesthetizing the animals with ketamine (100 mg/kg, intraperitoneally (ip)) and xylazine (10 mg/kg, ip), they received a tail vein injection of indomethacin (10 mg/kg) and L-NAME (10 mg/kg, twice at 15 and 30 min). Next, to induce the CIN model, they received a tail vein injection of high osmolar contrast media diatrizoate (6 ml/kg) (Kedrah et al., 2012; Kurtoglu et al., 2015). Forty rats were randomly divided into five groups (n = 8). Sham group: the rats were administered indomethacin and L-NAME but not diatrizoate; CIN group: the rats were subjected to the CIN model; NAC group: the rats were orally administered NAC (150 mg/kg) 24 h before the induction of CIN (Aboubakr et al., 2019); RIPC group: the rats anesthetized with ketamine and xylazine underwent RIPC in the right and left forelimbs using a blood pressure cuff. The cuff was inflated to 300 mmHg to block blood flow to both forelimbs for 4 min (ischemia) and then deflated for 4 min (reperfusion). The RIPC protocol consisted of three cycles of 4 min of ischemia followed by 4 min of reperfusion 24 h before the induction of CIN (Johnsen et al., 2016); NAC+RIPC group: the CIN model was induced to the rats as the CIN group, administered NAC as the NAC group and underwent RIPC as the RIPC group. The animals were then allowed to recover for 48

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h in their cages. After re-anesthetizing the rats, blood samples were collected from the inferior vena cava, centrifuged at 3500 g for 10 min at 4 °C, and the serum was frozen at -70 °C until analysis for renal functional markers. For histological examination, the right kidney tissues were fixed in 10% formalin. To assess oxidative stress markers, the left kidney tissues were snap-frozen in liquid nitrogen quickly and stored at -70 °C until further study.

Renal oxidative stress assessment

Malondialdehyde (MDA) levels were evaluated using the Esterbauer and Cheeseman method. According to this method, MDA reacts with thiobarbituric acid (TBA) to generate a pink pigment with maximum absorption at 532 nm (Esterbauer et al., 1991).

Superoxide dismutase (SOD) activity was determined based on the Paoletti and Mocali method. In this assay, superoxide anion is produced from molecular oxygen, and oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) is linked to the availability of superoxide anions in the tissue samples that are monitored at 340 nm (Paoletti and Mocali, 1988).

Renal functional assessment

Serum levels of creatinine (Cr) and blood urea nitrogen (BUN) were measured using colorimetric methods by a commercial kit and a Hitachi 704 autoanalyzer.

Renal histological assessment

The fixed tissues in 10% formalin were embedded in paraffin, cut into 4-µm-thick sections, and stained by hematoxylin and eosin (H&E). Biopsies were then assessed for the presence of tissue destruction, cellular degeneration, tubular obstruction, and formation of luminal casts (Kianian et al., 2019). The scoring scale used was: 0 = no or minimal lesion; 1 = less than 25% of tubules are involved; 2 = 25-50% of tubules are involved, and 3 = more than 50% of tubules are involved.

Statistical Analysis

Quantitative comparisons among groups were performed using one-way analysis of variance (ANOVA) and Tukey's post-hoc test, and results were expressed as mean ± standard error of the mean (SEM). Kruskal-Wallis analysis of variance with Bonferroni post-hoc test was used to analyze renal histopathological score, and results were expressed as median values. $P<0.05$ was considered significant.

Results

Effects of the treatments on renal oxidative stress status

As shown in Figure 1A, a significant rise in renal MDA levels was observed in the CIN group in comparison with the sham group ($P<0.001$). The use of NAC and RIPC, alone or together, markedly reduced renal MDA levels compared to the CIN group ($P<0.001$, $P<0.01$, and $P<0.001$, respectively) (Figure 1A). In addition, renal MDA levels in the NAC+RIPC group were significantly lower than the RIPC group ($P<0.05$) (Figure 1A).

As shown in Figure 1B, a significant decline in renal SOD activity was observed in the CIN group in comparison with the sham group ($P<0.001$). The use of NAC

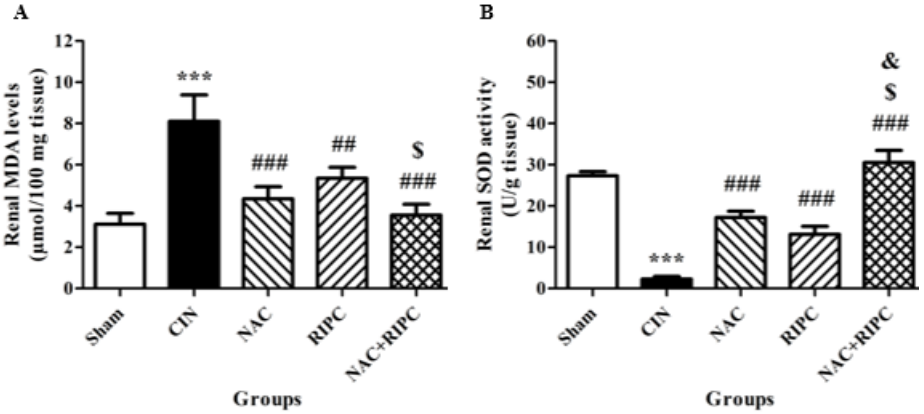

FIGURE 1. MDA levels (A) and SOD activity (B) in the kidney tissue samples in different groups. The data are expressed as mean ± SEM. $^{***}P<0.001$ compared to the sham group. $^{\#\#}P<0.01$ and $^{\#\#\#}P<0.001$ compared to the CIN group. $^{\&}P<0.05$ compared to the NAC group. $^{\$}P<0.05$ compared to the RIPC group. CIN: contrast-induced nephropathy; NAC: N-acetyl cysteine; RIPC: remote ischemic preconditioning.

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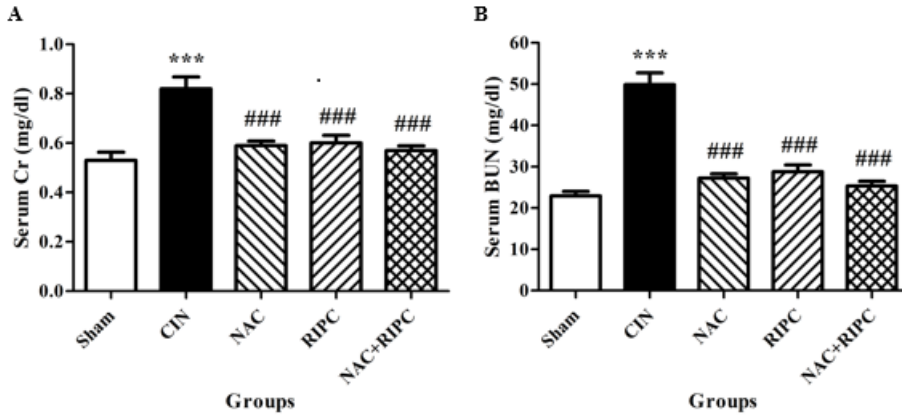

FIGURE 2. Serum creatinine (Cr) (A) and blood urea nitrogen (BUN) (B) in different groups. The data are expressed as mean ± SEM. $^{***}P<0.001$ compared to the sham group. $^{###}P<0.001$ compared to the CIN group. CIN: contrast-induced nephropathy; NAC: N-acetyl cysteine; RIPC: remote ischemic preconditioning.

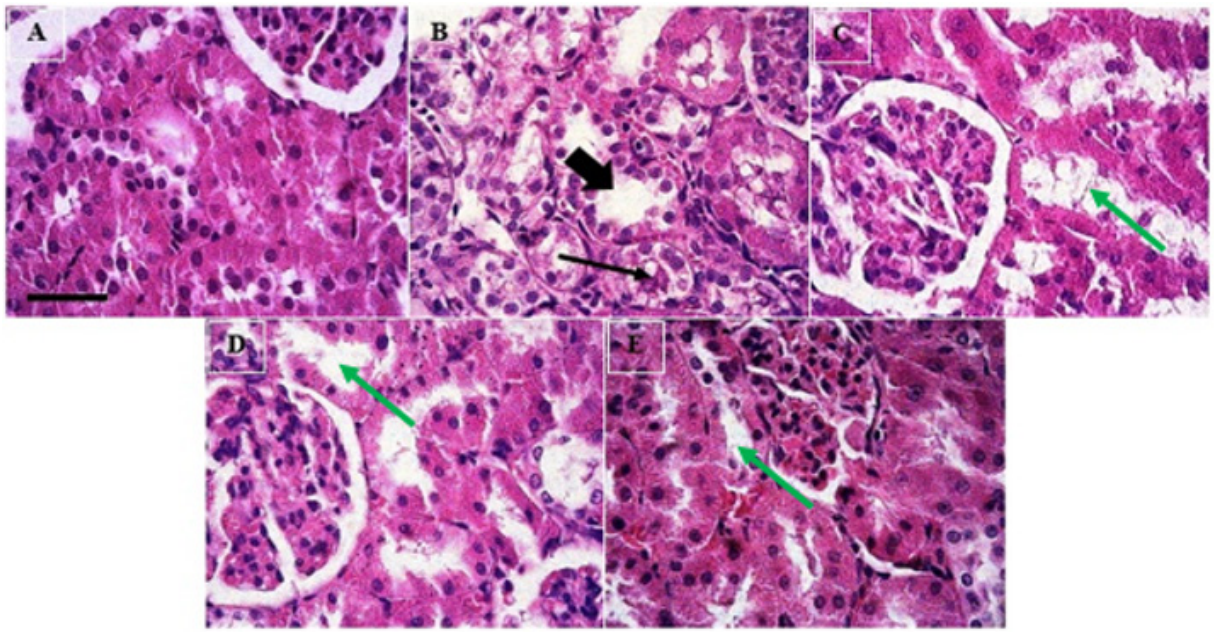

FIGURE 3. Histological changes in kidney tissues (by light microscopy, magnification 400 ×) in different groups: (A) sham group; (B) CIN group; (C) NAC group; (D) RIPC group; (E) NAC+RIPC group. In the sham group, no kidney tissue damage was detectable. In the CIN group, several histological changes were observed such as cast formation and tubular obstruction (long black arrow) and flattening of the tubular cells (thick arrow). The use of NAC and RIPC, alone or together, decreased the extent of renal histological damage including cast formation and tubular obstruction (long green arrow). Bar: 100 µm. CIN: contrast-induced nephropathy; NAC: N-acetyl cysteine; RIPC: remote ischemic preconditioning.

and RIPC, alone or together, markedly increased renal SOD activity compared to the CIN group ($P<0.001$, all) (Figure 1B). In addition, renal SOD activity in the NAC+RIPC group was significantly higher than the groups of NAC and RIPC ($P<0.05$, both) (Figure 1B).

Effects of the treatments on renal function

As shown in Figure 2A, a significant rise in serum Cr levels was observed in the CIN group in comparison with the sham group ($P<0.001$). The use of NAC and RIPC, alone or together, markedly reduced serum Cr levels compared to the CIN group ($P<0.001$, all) (Figure 2A). However, there were no significant differences in serum Cr levels between all treatment groups (Figure 2A).

As shown in Figure 2B, a significant rise in serum BUN levels was observed in the CIN group in comparison with the sham group ($P<0.001$). The use of NAC and RIPC, alone or together, markedly reduced serum BUN levels compared to the CIN group ($P<0.001$, all)

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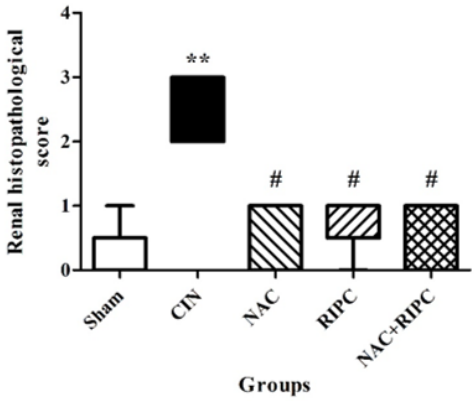

FIGURE 4. Renal histopathological score in different groups. The data are expressed as median values. $^{**}P<0.01$ compared to the sham group. $^{\#}P<0.05$ compared to the CIN group. CIN: contrast-induced nephropathy; NAC: N-acetyl cysteine; RIPC: remote ischemic preconditioning.

(Figure 2B). However, there were no significant differences in serum BUN levels between all treatment groups (Figure 2B).

Effects of the treatments on renal histology

As shown in Figures 3B and 4, severe changes (e.g., flattening, disintegration, and destruction of the tubular cells as well as cast formation and tubular obstruction) were observed in the CIN group in comparison with the sham group ($P<0.01$). The use of NAC and RIPC, alone or together, markedly reduced the extent of renal histological damage compared to the CIN group (Figures 3C, 3D, and 3E, respectively, and Figure 4, $P<0.05$, all).

Discussion

CIN ranks third in the causes of hospital-acquired AKI and is associated with significant morbidity and mortality (Kelemen et al., 2020). With the rapid increase in the use of contrast-related technologies in recent years, CIN has attracted considerable attention from researchers and clinicians (Liu et al., 2017).

A critical event following most of the pathologic conditions and tissue injuries is excessive production of free radicals (e.g., reactive oxygen species [ROS]), which exceeds the antioxidant reserve of the patient body and thus causes oxidative stress (Honda et al., 2019). Excess ROS formation can lead to membrane lipid peroxidation, intracellular protein degeneration, and deoxyribonucleic acid (DNA) breakdown, resulting in extensive renal morphological abnormalities such as tubular flattening with loss of the brush border microvilli, shedding of brush border, and cast formation (Zhang et al., 2020). Based on the important involvement of oxidative stress in CIN pathogenesis, we evaluated the levels of MDA, a valuable indicator of lipid peroxidation, and the activity of SOD, the most powerful intracellular antioxidant, in the kidney tissue samples (Ighodaro and Akinloye, 2018; Kianian et al., 2020). Our results showed an increase in the MDA levels and a decrease in the SOD activity in the kidney of rats subjected to CIN.

Another finding of this study was that the induction of CIN in the rats led to significant damage in function (i.e., the increased serum levels of Cr and BUN) and histology of the kidneys. Decreased renal blood flow and subsequent hypoxia after contrast media administration may contribute to renal functional and histological changes observed in CIN as the study of Agmon et al. found that a reduction in medullary blood flow with CIN induction was associated with decreased Cr clearance and renal histological damage (Agmon et al., 1994). In fact, it is indicated that hypoxia caused by decreased renal blood flow leads to impaired water and electrolyte homeostasis by reducing the glomerular filtration rate (GFR) (Ow et al., 2018).

NAC is a precursor to the amino acid cysteine, which has a variety of biological activities, including interfering with the production of free radicals, detoxifying free radicals, increasing intracellular antioxidant capacity, and preventing DNA damage (Shetty et al., 2019). In addition to these beneficial activities, NAC has also received widespread attention because it is tolerable, inexpensive, ready, and easy to administer (Mokhtari et al., 2017). Thus, it is not surprising that many experimental and clinical studies have investigated the protective effects of NAC in the context of different diseases (Faghfouri et al., 2020; Ommati et al., 2021). Along with these

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studies, we evaluated the effects of NAC in the rats subjected to CIN and found that the administration of this drug markedly reduced the serum levels of Cr and BUN and improved renal histological damage. Similar to our results, a couple of studies reported that NAC administration attenuated deterioration of renal function and pathological manifestations of renal injury in comparison with the CIN group (Wang et al., 2008; Li et al., 2016). Furthermore, in the present study, the administration of NAC was able to decrease the MDA levels and increase the SOD activity in the kidney tissues. Our findings are in agreement with another study showing the attenuation of renal oxidative stress with NAC administration (Li et al. 2016).

RIPC, initiated before contrast media administration, is a new, simple, harmless, and virtually cost-free strategy, which has been extensively used in different animal models and human clinical trials (Zagidullin et al., 2017; Damasceno et al., 2020). RIPC depends on a hypothesis that multiple short intermittent periods of ischemia-reperfusion applied to a non-target organ may protect against the target organ damage (Bafna and Shah, 2020). In the case of CIN, Er et al. for the first time demonstrated that RICP could prevent this disease in 100 high-risk patients undergoing coronary angiography (Er et al., 2012). In this line, our study found that the use of RIPC considerably attenuated the increases in serum levels of Cr and BUN and renal histological damage. Emerging reports from various studies indicate that the underlying mechanisms of RIPC-induced protection against CIN can include activating the endogenous antioxidant defense system which ameliorates oxidative stress (Dugbartey and Redington, 2018). In the current study, we also showed that the RIPC group had significantly lower MDA levels and higher SOD activity in the kidney tissues of rats subjected to CIN. These results are consistent with the study of Wang et al. that reported attenuation of contrast media-induced oxidative stress with the use of RIPC (Wang et al., 2016).

As mentioned above, while NAC and RIPC are both of academic interest, the efficacy of these strategies is limited in the context of CIN (Gomes et al., 2005; Deng et al., 2020). Therefore, we wished to examine whether the administration of NAC in combination with RIPC, as a result of additive or synergistic effects, may be more effective than the individuals in preventing CIN. Based on our results, although no significant differences were detected in the renal functional markers and renal histopathological score between the individual and combined use of NAC and RIPC, the administration of NAC in combination with RIPC improved renal function. We also interestingly found that the combined use of NAC and RIPC was markedly more effective in attenuating renal oxidative stress than the individual use. One possible explanation for these findings is the involvement of various pathophysiological mechanisms in CIN, all of which ultimately cause renal functional and histological damage (Geenen et al., 2013). In this regard, it could be understood that oxidative stress is only one of the factors involved in the pathophysiology of CIN. Therefore, considering the mechanism of action of both NAC and RIPC, which is the reduction of oxidative stress (Dugbartey and Redington, 2018; Shetty et al., 2019), it is not surprising that the combination of these two therapies had a better effect on improving renal oxidative stress than renal function.

Conclusion

The current study demonstrates that although the individual use of NAC and RIPC and their combined use can improve renal functional and histological damages by the same degrees, the combined use more effectively attenuates renal oxidative stress possibly due to additive effects. Therefore, this study suggests that consideration should be given to the combined use of NACA and RIPC as a result of its superior renoprotective properties compared to individual use.

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Conflict of interest

The authors declare that they have no conflict of interest.

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