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Can Paricalcitol Increase the Effectiveness of N-Acetylcysteine in Contrast Induced Acute Kidney Prophylaxis in Rats? A Biochemical and Histopathological Study

¿Puede el Paricalcitol Aumentar la Eficacia de la N-acetilcisteína en la Profilaxis Renal Aguda Inducida por Contraste en Ratas? Un Estudio Bioquímico e Histopatológico

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SUMMARY: N-Acetylcysteine (NAC) is used for contrast induced acut kidney injury (CI-AKI) prophylaxis because of its antioxidant effects. Paricalcitol, which has reno-protective effects, is likely to provide a more effective prophylaxis when added to NAC treatment. The study was designed based on this hypothesis. The study was organised to include 4 groups each consisting of 7 rats. Group 1 was the control group, and Group 2 included rats with CI-AKI. Rats in Group 3 were administered NAC at a dose of 100 mg/kg via oral gavage once a day for 5 days. Rats in group 4 were administered paricalcitol at a dose of 0.4 mcg/kg once a day for 5 days in addition to NAC. CI-AKI was induced after the treatments in both groups. The study was terminated on the sixth day. Samples were collected from the rats' sera and kidney tissues to study oxidant and antioxidant parameters; kidney function tests were also studied. There were significant differences between the contrast nephropathy group (Group 2) and NAC and NAC+paricalcitol groups with respect to serum urea and creatinine levels. When the same groups were compared regarding oxidant (TOS-MDA) and antioxidant (TAC-Paraoxonase) parameters, we observed that the oxidant parameters increased in serum and kidney tissue samples with NAC use, and that effect was strengthened by the addition of paricalcitol to NAC treatment. However, despite increased antioxidant effectiveness, we observed no decrease in urea and creatinine levels when paricalcitol was added for CI-AKI in rats. There was no significant difference between Group 3 and Group 4. Paricalcitol provides a more potent antioxidant effect in both serum and kidney tissue samples when added to NAC treatment in rats with CI-AKI. Despite increased antioxidant parameters, however, paricalcitol does not provide a significant decrease in urea and creatinine levels.

KEY WORDS: CI-AKI; Paricalcitol; NAC; Oxidative stress; Antioxidants.

INTRODUCTION

Contrast-induced acute kidney injury is a clinical disorder with a usually reversible course, which occurs after radiocontrast agent use. Intravascular administration of iodinated radiocontrast agents has been reported to cause acute renal dysfunction. Even minor changes in renal function have been closely associated with increased morbidity and mortality. For this reason, it is an important reference point for the prevention of radiocontrast nephropathy (Weisbord & Palevsky, 2005). It is more common in hospitalized patients. Contrast-induced nephropathy, a form of acute kidney injury, has been the focus of attention in recent years, with new information on its pathogenesis, proliferation of innovative approaches to its prevention and in recent years. The recognition that contrast-induced nephropathy is associated

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with long-term adverse events has been reported to be an important point that should not be overlooked by clinicians (Solomon *et al*., 2009), In a randomized prospective study, the incidence of contrast nephrotoxicity among non-ionic contrast media, iohexol and ionic contrast media, diatrizoate, was investigated in a large population of both 'low' and 'high risk' patients undergoing cardiac angiography. It can even occur with a lower incidence in patients having no risk factor (Rudnick *et al*., 1995).

It has been stated that the prevalence of increased oxidative stress and acute phase inflammation in patients with chronic kidney disease has not been fully investigated. Few prevalence studies have been reported to examine biomarkers of oxidative stress and inflammation in the larger patient population with chronic kidney disease. Given the high prevalence of cardiovascular disease in the chronic kidney disease population, it was hypothesized that this population would show an increase in inflammation and oxidative stress biomarkers, and these biomarkers would be inversely proportional to glomerular filtration rate. Therefore, commonly used biomarkers of acute phase inflammation and oxidative stress status in a cohort of patients with stage 3-5 chronic kidney disease not receiving renal replacement therapy were examined (Oberg *et al*., 2004). It has also been reported that there is an increase in oxidative stress parameters due to uremia in chronic renal failure (Himmelfarb & McMonagle, 2001). It was concluded that AdipoRon, an agonist of adiponectin receptors, benefits many organs, including the kidney. AdipoRon (50 mg/kg) was found to significantly reverse serum creatinine, blood urea nitrogen, creatinine clearance, and urinary kidney injury molecule-1 levels induced by iopromide in Sprague-Dawley rats. They found that preservation of AdipoRon was accompanied by enhanced activated protein kinase (AMPK) phosphorylation. Both in vivo and in vitro studies concluded that compound c, an AMPK inhibitor, reversed AdipoRon-mediated development in the contrast-induced nephropathy model (Gu *et al*., 2020).

Izquierdo *et al*. (2012) observed that the initial levels of oxidation markers MDA, nitric oxide and protein carbonyl groups decreased significantly after three months of paricalcitol treatment, while the levels of GSH, thioredoxin, catalase and SOD activity increased significantly. It has been reported that after paricalcitol treatment, the levels of inflammatory markers CRP, TNF-a, IL-6 and IL-18 were significantly decreased in serum and the level of the anti-inflammatory cytokine IL-10 increased. It has been suggested that paricalcitol-induced reduction in albuminuria and inflammation may be mediated independently of its effects on hemodynamics or parathyroid hormone suppression. They stated that long-term randomized, controlled studies are needed to confirm these benefits of vitamin D analogues. Despite the use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers, it has been reported that patients with chronic kidney disease show no improvement in endothelial function within 1 month of treatment with paricalcitol, but a reduction in inflammation and albuminuria (Alborzi *et al*., 2008).

The aim of this experimental study was investigated based on the hypothesis whether a further level of kidney function protection could be achieved by adding paricalcitol therapy to NAC to treat contrast induced acut kidney injury in rats.

MATERIAL AND METHOD

This study was approved by Dicle University Prof. Dr. Sabahattin PAYZIN Health Sciences Research and Practice Center Experimental Animals Ethics Committee and conducted in Dicle University Prof. Dr. Sabahattin PAYZIN Health Sciences Research and Practice Center. Biochemical analyses were performed in University of Dicle, Faculty of Medicine Biochemistry Department Central Laboratory, and histopathological studies in University of Dicle Veterinary Faculty Department of Histology and Embryology Research Laboratory. Our experimental study was funded by Scientific Research Project Unit of Dicle University (Project No: 13-TF 90).

Experimental protocol and groups. The study was conducted with a total of 28 adult Wistar Albino rats that were allocated equally into 4 groups. The rats had a mean weight of 200-250 grams. The animals were fed on ad libitum and water under standard conditions for 5 days in the DUSAM. The study was designed with 28 rats allocated equally into four groups.

1. Group (Control group) : No agent administered.

2. Group (Contrast nephropathy group): Diatrizoate (urografin 76 %, Schering AG, Germany) was administered at a dose of 6 ml/kg via the tail vein under ether anesthesia on day 5 to create experimental contrast agent nephropathy (n=7) (Fig. 1).

3. Group (Contrast nephropathy + NAC group): The rats were administered 100 mg/kg NAC (Asist ampoule, Bilim Ilac, Turkey) via oral gavage once a day for 5 days. Contrast nephropathy was induced by administering 6 ml/kg diatrizoate (Urografin 76 %, Schering AG, Germany) via the tail vein under ether anesthesia on day 5 (n=7) (Fig. 1).

4. Group (Contrast nephropathy+ Paricalcitol + NAC group): The rats were administered 0.4 mcg/kg paricalcitol (Zemplar ampoule, Abbott USA) once a day and 100 mg/kg NAC (Asist ampoule, Bilim Ilac Turkey) via oral gavage for 5 days. Contrast nephropathy was induced by administering 6 ml/kg diatrizoate (Urografin 76 %, Schering AG, Germany) via the tail vein under ether anesthesia on day 5 (n=7) (Fig. 1).

The rats were administered xylazine (10 mg/kg) and ketamine HCl (70 mg/kg) via intramuscular (I.M) route prior to the surgical procedure on the final study day. The rats were fixed in the supine position under general anesthesia; a midline section was made on the anterior abdominal wall for histopathological and biochemical studies. The right kidney of each animal was removed for histopathological study. A piece of kidney tissue samples put into 10 % neutral formaline for further histopathological investigation. Another piece of kidney tissue samples taken for biochemical study were placed into aluminum foils. Then, a 5-ml blood sample was collected from the heart after sternotomy for biochemical study. This step was also used to sacrifice the animals. Blood samples collected on the first and sixth days were used for biochemical analysis.

Evaluation of renal function. AEROSET c8000 analyzer was used for measurement of serum urea and creatinine.

Biochemical analysis: Tissue samples were weighed and homogenized. Both serum and kidney tissue specimen were examined for oxidant malondialdehyde (MDA), total oxidant status (TOS) and antioxidant parameters paraoxonase and total antioxidant capacity (TAC) were measured. MDA were determined with the thiobarbituric acid method. TOS and TAC were determined through use of a new measurement method developed by Erel (2004, 2005). Paraoxonase was measured by employing kits available.

Histopathological evaluation. Histopathological evaluations were performed under a light microscope. The kidneys were fixed in 10 % neutral formaline, embedded into paraffin. Four-five mm sample sections were obtained and stained with periodic acid-Schiff as well as hematoxylin and eosin. The following histological parameters were examined with respect to morphological kidney damage: tubular necrosis and atrophy, hydropic degeneration, regenerative atypia, interstitial fibrosis, and loss of brush margin. The analysis was performed with the sum of the individual scores (0 to 3); no histopathological alterations (0), mild histopathological alterations (1), moderate histopathological alterations (2), severe histopathological alterations (3) for evaluation of kidney injury by Aydın *et al*. (2020).

Statistical Analyses. Statistical Package for Social Sciences (SPSS), Version 18.0 for Windows was employed to perform data analyses. All the data were reported with mean ± standard deviation. One-way analysis of variance (ANOVA) with a post-hoc Bonferroni correction was performed for multiple group comparison. $P < 0.05$ was considered statistically significant.

RESULTS

The comparison of the control group and the CI-AKI group showed a significant difference between the serum urea and creatinine levels of both groups. The same difference was also found when the groups that developed CI-AKI after NAC and NAC+paricalcitol were administered (groups 3-4). When compared with groups 3 and 4, CI-AKI group (group 2) showed significant reduction in serum urea and creatinine levels. We interpreted this finding as the clinical effectiveness of NAC and NAC+Paricalcitol.

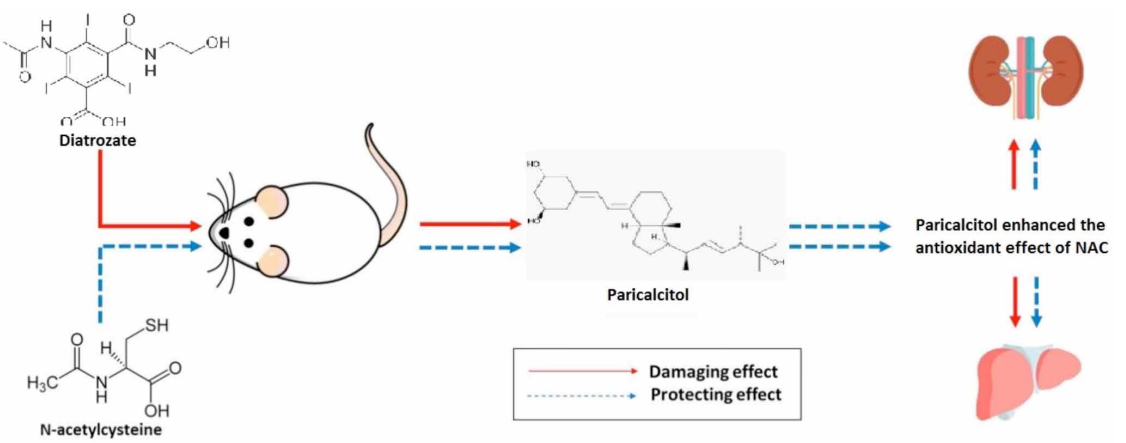

Fig. 1. Schematic diagram of the experimental study hypothesis.

However, there was no significant difference between group 3 and group 4 with respect to serum urea and creatinine levels (Table I).

The comparison of the oxidant (TOS-MDA) and antioxidant (TAC-paraoxonase) parameters in the serum and kidney samples of the control group (group 1) and the CI-AKI group (group 2) showed a significant increase in the oxidant parameters and a drop in antioxidant parameters. When the groups that developed CI-AKI after being treated with NAC and NAC+ Paricalcitol (group 3 and group 4) were compared with the contrast nephropathy group, a significant increase in antioxidant parameters and a significant decrease on oxidant parameters were observed. The comparison of group 3 and group 4 with each other with respect to antioxidant and oxidant parameters revealed that adding paricalcitol to NAC treatment showed statistical significance unlike serum creatinine and urea levels. Addition of paricalcitol increased antioxidant effect and significantly reduced oxidant parameters (Table II).

In the evaluation of the control group sections, normal histologic view has been observed (Fig. 2a). Strong tubular necrosis and atrophy were seen in CI-AKI group sections (Fig. 2b). Tubular necrosis and atrophy levels were decreased in CI-AKI+NAC (Fig. 2c) and CI-AKI+NAC+Paricalcitol (Fig. 2d) as compared to CI-AKI group sections. The histopathological comparison of the groups has been shown in Table III.

The examination of kidney tissue samples demonstrated that the histopathological changes were more severe in the CI-AKI group than the CI-AKI+NAC and CI-AKI+NAC+Paricalcitol groups.

Table I. Renal function tests in rats of the groups.

Parameters	Control (n=7)	CIN (n=7)	CIN+NAC (n=7)	CIN+NAC+Paricalcitol (n=7)
Serum				
Urea (mg/dl)	36,29±5,85	98,29±5,56[a]	74,57±3,41[a,b]	71±6,56[a,b]
Creatinine (mg/dl)	0,67±0,04	1,09±0,8[a]	0,76±0,41[d,b]	0,78±0.04[d,b]

a p<0.001 in comparison with the control group. b p<0.001 in comparison with the CIN group. c p<0.001 in comparison with CIN+NAC. d p<0.05 in comparison with the control group.

Table II. Oxidant and antioxidant parameters of serum and kidney tissue in the study groups.

Parameters	Control (n=7)	CIN (n=7)	CIN+NAC (n=7)	CIN+NAC+Paricalcitol (n=7)
Serum				
MDA (mmol/ml)	4,44±0,47	32,59±3,28[d]	20,4±2,13[d,e]	16,81±1,5[d,e,c]
TOS (µmol /L)	42,4±2,16	281,21±15,72[d]	132,63±5,4[d,e,]	119,6±6,41[d,e]
TAC (mmol /L)	0,85±0,12	0,96±0,13	1,96±0,28[d,e]	2,02±0,16[d,e]
Paraoxonase (U/L)	93,6±7,62	158,43±39,28	195,03±24,72	212,45±16,02
Kidney Tissue				
MDA (mmol/ml)	16,73±3,58	38,90±5,17[d]	34,35±3,22[d]	29,28±2,68[d,e]
TOS (µmol /L)	81,79±4,63	205,8±19,97[d]	129,71±9,37[d,e]	123,15±9,23[d,e]
TAC (mmol /L)	4,92±0,87	3,21±0,34[d]	4,03±0,24[a,b]	4,26±0,38[b]
Paraoxonase (U/L)	51,97±2,19	44,34±3,13[a]	106,66±5,82[d,e]	124,07±4,53[d,e,f]

MDA: Malondialdehit, TOS: Total oxidant status, TAC: Total antioxidant capacity, NO: Nitric oxide. a: p<0.05 in comparison with the control group. d: p<0.001 in comparison with the control group. b: p<0.05 in comparison with the CIN group. e: p<0.001 in comparison with the CIN group. c:p<0.05 in comparison with CIN+NAC. f: p<0.001 in comparison with CIN+NAC.

Table III. Comparison of histopathological parameters of all experimental groups.

Histopathological Findings	Control (n=7)	CI-AKI (n=7)	CI-AKI+NAC (n=7)	CI-AKI+NAC +Paricalcitol (n=7)
Tubular necrosis	0	2.86 ± 0.38[c]	1.71 ± 0.49[b,c]	1.57 ± 0.78[c,d]
Tubular atrophy	0	2.71 ± 0.49[c]	1.72 ± 0.76[b,c]	1.55 ± 0.60[b,c]
Regenerative atypia	0	0	0	0
Hydropic degeneration	0	2.85 ± 0.38[c]	1.71 ± 0.49[b,c]	1.57± 0.79[c,d]
Interstitial fibrosis	0	0	0	0
Loss of brush margin	0	2.85 ± 0.37[c]	1.85 ± 0.69[b,c]	1.71 ± 0.95[b,c]

a: p < 0.05 in comparison with control group. b: p < 0.05 in comparison with CI-AKI group. c: p < 0.001 in comparison with control group. d: p < 0.001 in comparison with CI-AKI group

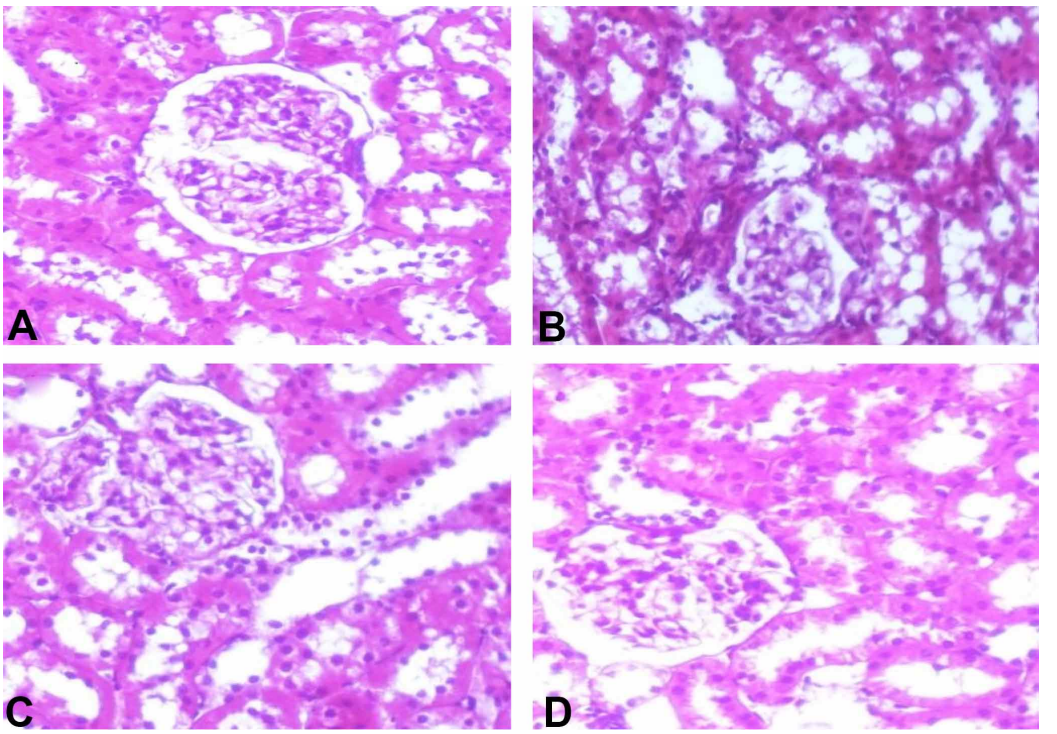

Fig. 2 (A-D). Kidney histopathological findings of the study groups (Haematoxylin and Eosin staining, original magnification, × 200). (A) Group 1 (control); (B) Group 2 (CI-AKI); (C) Group 3 (CI-AKI+NAC); (D) Group 4 (CI-AKI+NAC+Paricalcitol).

DISCUSSION

Diagnosis of many clinical conditions is only possible with radiological studies. Thus, contrast agent use is required in an increasingly higher number of diagnostic and therapeutic procedures. This causes a higher incidence of acute kidney injury due to contrast agent use. Therefore, hospital admissions due to acute kidney injury after contrast agent use are the third most common cause of acute kidney failure (Nash *et al*., 2002). CI-AKI also causes prolonged hospital stay and increased hospital costs (Rihal *et al*., 2002). Because of all these reasons, CI-AKI prophylaxis is greatly important.

Medullary ischemia caused by vasoconstriction in the renovascular bed and the toxic effects of increased reactive oxygen species secondary to contrast agent use are the most likely causes of CI-AKI (Murphy *et al*., 2000). However, direct renal tubular toxicity may be another important cause (Tumlin *et al*., 2006). It is known that there occurs an increase in oxidant parameters and oxidative stress with the progression of acute kidney injury (Himmelfarb & McMonagle, 2001). MDA and TBARS are the end products of the peroxidation of membrane polyunsaturated fatty acids by free oxygen radicals; they are markers of oxidative injury. It is known that these metabolites increase in experimental CI-AKI models (Cetin *et al*., 2008; Devrim *et al*., 2009). In accordance with the literature, our study demonstrated an increase in oxidant MDA and TAC levels in both tissue and serum samples (Table II). All these studies indicate that the variability of oxidant and antioxidant parameters in CI-AKI may be important for determining clinical injury and the benefits of preventive measures. Our study investigated the results of paricalcitol treatment in addition to NAC treatment in rats with CIN. N-acetylcysteine is the precursor of glutathione synthesis; it clears free oxygen radicals (Shalansky *et al*., 2005a). The use of NAC is associated with increased levels of antioxidants (Quintavalle *et al*., 2011). A handicap of the drug is its rapid metabolism in its hepatic first pass, which reduces its bioavailability (Olsson *et al*., 1988). Therefore, it is widely accepted that its high-dose use via intravenous route may be more effective for preventing CI-AKI (Shalansky *et al*., 2005b). In our study, the comparison of the contrast nephropathy group (group 2) and the group with induced contrast nephropathy after being treated with NAC (group 3) showed that the oxidant parameters MDA and TOS were reduced in serum and kidney tissue samples. There occurred a significant increase in

antioxidant parameters TAC and paraoxonase in group 3 compared with group 2. In our study it is evident that NAC administration reduces oxidative stress. The comparison of serum urea and creatinine levels of group 2 and group 3 revealed that NAC administration was effective. There are many studies on the use of NAC in CI-AKI prophylaxis. In some of them, the beneficial effects of prophylactic use of NAC have been shown.

Tepel *et al*. (2000) showed that the risk of CI-AKI was reduced by 90.5 % and Shyu *et al*. (2002) by 86.6 % after NAC use. Our results are in parallel with the literature data. However, there are also several studies that have shown that NAC is ineffective on CI-AKI. Although Boccalandro *et al*. (2003), NAC dose is debated, the study by Vallero *et al*. (2002), represents this group of studies. Another important point is that whether NAC is effective in patients with increased serum creatinine levels. Durham *et al*. (2002) showed that NAC was ineffective in this group of patients (serum creatinine >1.7 mg/dl). The main rationale of our study was to test whether adding another drug with reno-protective properties and known antioxidant effects would provide a more effective CI-AKI prophylaxis.

Paricalcitol is an active vitamin D analog that has non-hypercalcemic effects. Paricalcitol use in hemodialysis patients is associated with as much increase in antioxidant parameters as with active vitamin D (Yeter *et al*., 2021).

Antioxidant parameters were higher in both serum and kidney tissue in group 4, which was treated with paricalcitol, than the contrast nephropathy group (group 2) and CI-AKI+ NAC group (group 2). These results agree with the literature data. There are other studies indicating paricalcitol's pleiotropic effects. It is known to prevent cyclosporine-induced nephrotoxicity in rats (Park *et al*., 2010) and to reduce proteinuria in diabetic patients (de Zeeuw *et al*., 2010). Paricalcitol also has antifibrotic effects (Piao *et al*., 2012). Bae *et al*. (2020) showed that paricalcitol with known reno-protective effects mitigated mitochondrial injury in tissue samples with contrast nephropathy.

CONCLUSIONS

In accordance with the literature data, we observed no statistically significant reduction in serum urea and creatinine levels despite an increase in antioxidant parameters when we added paricalcitol to NAC treatment. Paricalcitol shows a more potent antioxidant effectiveness when added to NAC in CI-AKI prophylaxis. However, paricalcitol provides no additional benefit in kidney function over NAC treatment.

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RESUMEN: Debido a sus efectos atioxidantes la N-acetilcisteína (NAC) se usa para la profilaxis de la lesión renal aguda inducida por contraste (CI-AKI). Es probable que el paricalcitol, que tiene efectos renoprotectores, proporcione una profilaxis más eficaz cuando se agrega al tratamiento con NAC. En base a esta hipótesis el estudio fue diseñado para incluir cuatro grupos cada uno compuesto por siete ratas. El grupo 1 fue el grupo control y el grupo 2 incluyó ratas con CI-AKI. A las ratas del Grupo 3 se les administró NAC con una dosis de 100 mg/kg por sonda oral una vez al día, durante 5 días. A las ratas del grupo 4 se les administró paricalcitol a una dosis de 0,4 mcg/kg una vez al día durante 5 días, además de NAC. Se indujo CI-AKI después de los tratamientos en ambos grupos. El estudio finalizó el sexto día. Se recolectaron muestras de suero y tejidos renales de ratas para estudiar los parámetros oxidantes y antioxidantes; También se estudiaron las pruebas de función renal. Hubo diferencias significativas entre el grupo de nefropatía por contraste (Grupo 2) y los grupos NAC y NAC+paricalcitol con respecto a los niveles séricos de urea y creatinina. Cuando se compararon los mismos grupos con respecto a los parámetros oxidantes (TOS-MDA) y antioxidantes (TAC-Paraoxonase), observamos que los parámetros oxidantes aumentaron en muestras de suero y tejido renal con el uso de NAC, y ese efecto se vio reforzado por la adición de paricalcitol a tratamiento NAC. Sin embargo, a pesar de una mayor eficacia antioxidante, no observamos una disminución en los niveles de urea y creatinina cuando se agregó paricalcitol para CI-AKI en ratas. No hubo diferencias significativas entre el Grupo 3 y el Grupo 4. El paricalcitol proporciona un efecto antioxidante más potente tanto en muestras de suero como de tejido renal cuando se agrega al tratamiento con NAC en ratas con CI-AKI. Sin embargo, a pesar del aumento de los parámetros antioxidantes, el paricalcitol no proporciona una disminución significativa en los niveles de urea y creatinina.

PALABRAS CLAVE: CI-AKI; Paricalcitol; NAC; Estrés oxidativo; Antioxidantes.

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