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Research Paper

Protective Effects of Vitamin C Concomitant Treatment on Deferasirox-induced Renal Toxicity in Rats

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ABSTRACT

Background and Aim Deferasirox (Exjade) is an iron-chelating drug used in patients with beta-thalassemia major. Oxidative stress is among f the major causes of nephrotoxicity and its progression. Deferasirox, due to oxidative stress and increased cell apoptosis causes the dysfunction of renal tubules and renal toxicity. According to its antioxidant and anti-inflammatory properties, the present study explored the effect of vitamin C on deferasirox-induced kidney damage.

Methods & Materials This study was performed on 30 Wistar rats in 3 groups of control, deferasirox, and deferasirox plus vitamin C. To induce the nephrotoxicity, the intra-peritoneum injection of deferasirox (75 mg/kg/day) was used. After taking plasma from the blood samples of the explored rats, we determined the values of Cr, Na+, K+, Mg+, osmolality, and BUN in the obtained plasma and urine samples. The creatinine clearance, as well as the relative and absolute excretion of sodium and potassium, were also calculated. After separating the two kidneys, they were used for the histologic study with Hematoxylin and Eosin (H&E) staining, as well as Malondialdehyde (MDA) and Ferric Reducing Antioxidant Power (FRAP) biochemical studies.

Ethical Considerations This study was approved by the Research Ethics Committee of Arak University of Medical Sciences (Code: IR.ARAKMU.REC.1396.309).

Results Cotreatment with deferasirox and vitamin C reduced renal tissue MDA and relative and absolute Na and K excretion and urine osmolarity; this method also increased creatinine clearance and renal tissue FRAP.

Conclusion The co-administration of vitamin C presented a significant protective effect on the renal toxicity induced by deferasirox. The protective property of deferasirox is because of the antioxidant impacts of vitamin C in reducing oxidative stress and lipid peroxidation.

Extended Abstract

1. Introduction

Acute renal failure is a sudden decrease in renal function due to renal toxicity [2, 3]. Deferasirox or oxide can generate acute renal failure due to the oxidative stress and dysfunction of the renal tubules by increasing cell apoptosis.

Deferasirox is a selective iron chelator. It is used to treat chronic iron overload conditions caused by repeated blood transfusions in patients with beta-thalassemia major [5, 6].

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Vitamin C, as an essential coenzyme and antioxidant, prevents cell membrane damage caused by oxidative radicals [7]. Therefore, using antioxidants, like vitamin C can be effective for the treatment or prevention of deferasirox-induced kidney damage. This study investigated the effect of the concomitant use of vitamin C on the renal toxicity of deferasirox.

2. Materials and Methods

This experimental study was performed on 30 rats of Wistar breed in 3 groups of control, deferasirox, and deferasirox plus vitamin C. Deferasirox (75 mg/kg/day) was intraperitoneally injected for 8 days to induce renal toxicity. In the concomitant treatment group, in addition to deferasirox (75 mg/kg/day), vitamin C 200 mg/kg /day was intraperitoneally injected for 8 days. On the eighth day, the explored animals were placed in a metabolic cage for 6 hours; after collecting urine samples, they were anesthetized. Then, the required blood sample was obtained from the aorta using a heparin syringe.

After plasma extraction from the rat blood samples, the concentrations of Cr, + Na, + K, + Mg, osmolality, and BUN in plasma and urine samples were determined. Accordingly, renal creatinine clearance (Cr), as well as the absolute and relative excretion of sodium and potassium were calculated. Kidney tissue was stained by Hematoxylin and Eosin (H&E) staining for histological study; antioxidant capacity was measured by FRAP and lipid peroxidation by MDA for biochemical study [12, 13].

The percentage of damage caused by the pathologist was determined and graded as follows: The lack of damage equivalent to zero degrees; damage between 1% to 25% equivalent to grade 1; damage between 25% to 50% equivalent to grade 2; damage between 50% to 75% equivalent to grade 3, and damage between 75% to 100% equivalent to grade 4 [15].

3. Results

The present research results revealed that creatinine clearance in the group treated with vitamin C (1.63±0.1 mL/min/kg) was significantly different, compared to that in the deferasirox group (0.59±0.1 mL/min /kg, P<0.001) (Figure 1).

The relative excretion of sodium and potassium was significantly different, compared with the deferasirox group (P<0.001). The absolute excretion of sodium was significantly different in the concomitant treatment group with vitamin C (2.46 ± 0.087 mmol/min/kg), compared with the deferasirox group (001.15±0.04 mmol/min/kg, P<0.7). The absolute excretion of potassium was significantly higher in the deferasirox group (13.41±0.098 mmol/min/kg,) compared with the vitamin C group (2.986±0.163 mmol/mi / kg) (P<0.001).

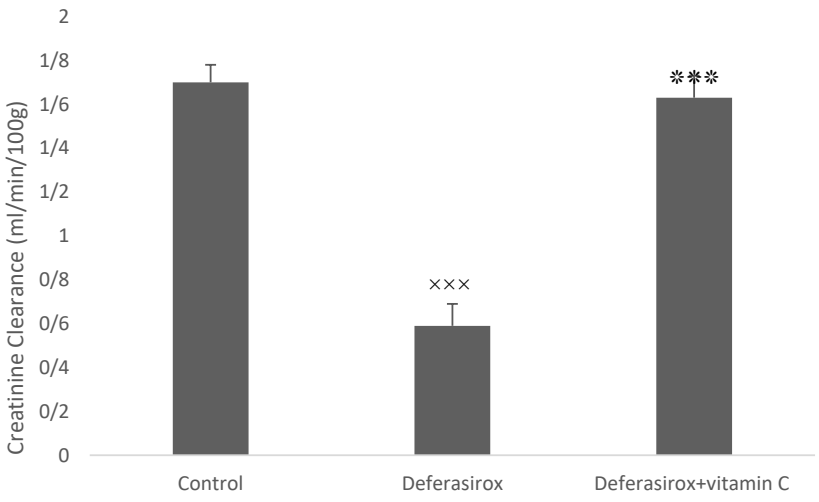

Figure 1. Comparing creatinine clearance between the research groups

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××× P<0.001 compared to the control group; ***P<0.001 compared to the deferasirox group, one-way Analysis of Variance (ANOVA) and Tukey's test (Mean±SEM). N=10, compared with the control group, creatinine clearance was significantly lower in the deferasirox group (P<0.001). There was a significant difference between the concomitant treatment group with vitamin C and the deferasirox group (P<0.001).

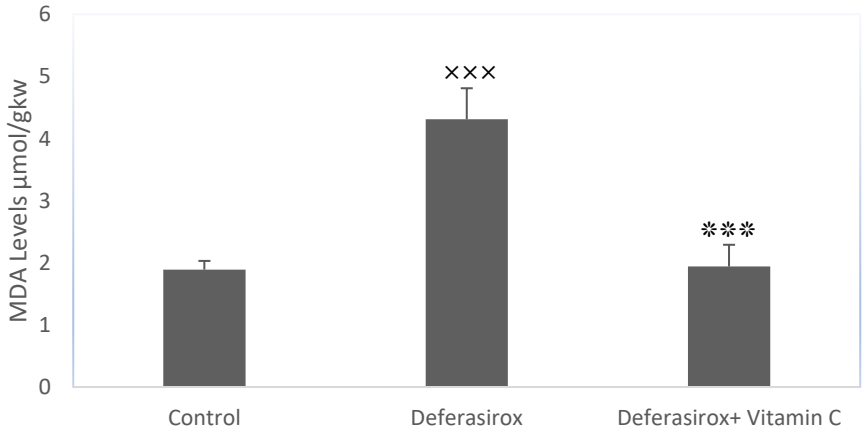

Figure 2. Comparing renal tissue MDA levels between the study groups

×××P<0.001 compared with the control group; ***P<0.001 compared with the deferasirox group. One-way ANOVA and Tukey's test (Mean±SEM) (n=10) were significantly higher in the deferasirox group, compared to the control group (P<0.001). There was a significant difference between the vitamin C treatment groups, compared to the deferasirox group (P<0.001).

The obtained data revealed that urinary creatinine concentration in the deferasirox group (32.7±1.55 mg/dL) was significantly lower than that of the concomitant treatment group with vitamin C (69.8±6.7 mg/dL) (P<0.001). Urinary urea concentration in the concomitant treatment group with vitamin C (137±3.82 mg/dL) was significantly increased, compared to the deferasirox group (72±0.14 mg/dL) (P<0.001). Urinary sodium concentration signified that the concomitant treatment group with vitamin C (127.4±3.1 µmol/mL) had lower values than the deferasirox group (220.4±4.55 µmol/mL) (P<0.001). Urine osmolality in the concomitant treatment group with vitamin C (1681±60.9 mOsm/kgH2O) was significantly reduced, compared to the deferasirox group (612.5±18 mOsm/kgH2O) (P<0.001).

The level of tissue MDA in the concomitant treatment group with vitamin C (1.94±0.355 µmol/gkw) was significantly reduced, compared to the deferasirox group (4.31±0.5 µmol/gkw, P<0.001) (Figure 2).

Renal tissue FRAP level was significantly increased in the concomitant treatment with vitamin C (1.07±0.25 µmol/gkw,) compared with the deferasirox group (001.75±0.61 µmol/gkw, P<0.0) (Figure 3).

In the concomitant treatment group with vitamin C, the amount of tubular cell necrosis, the formation of protein molds in the lumen of the tubule, the vacuolation of tubular cells, and the increase in the space of the Bowman capsule were significantly different, compared to the deferasirox group (P<0.001).

4. Discussion

The current study results indicated that vitamin C decreased renal toxicity due to deferasirox by reducing plasma urea and creatinine, the relative and absolute excretion of sodium and potassium and MDA, as well as increasing creatinine clearance and FRAP. The concomitant use of vitamin C plus deferasirox protects kidneys by reducing oxidative stress. Previous studies reported that vitamin C reduces oxidative stress during gentamicin nephrotoxicity [2].

An effective factor in causing deferasirox-induced kidney damage is oxidative stress, which increased MDA and decreased FRAP.

As in previous studies, mice treated with vitamin C had lower levels of MDA than the deferasirox group. Furthermore, the extent of FRAP in the tissue of all explored rats treated with vitamin C was much higher than that in the deferasirox group [9].

In the vitamin C concomitant treatment group, compared with the deferasirox group, a lower rate of relative excretion of sodium and potassium ions was observed; thus, such data indicated the prevention of kidney damage. The effect of vitamin C on the renal toxicity of deferasirox with decreasing creatinine and blood urea, and tissue MDA with decreasing

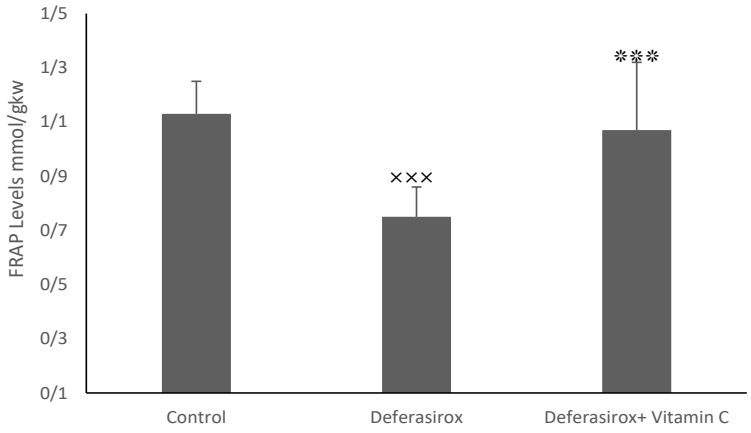

Figure 3. Comparing renal tissue FRAP levels between the research groups

×××P<0.001 compared with the control group; ***P<0.001 compared with the deferasirox group. One-way ANOVA and Tukey's test (Mean±SEM) (n=10). Compared with the controls, the amount of FRAP was significantly lower in the deferasirox group (P<0.001). There was no significant difference between the vitamin C treatment groups and the deferasirox group (P<0.001).

oxidative stress is similar to the effect of vitamin C on the renal toxicity of gentamicin [9]. Vitamin C reduces the renal toxicity induced by deferasirox administration by decreasing oxygen species. In this study, in line with the previous studies, administrating vitamin C significantly maintained creatinine clearance and significantly increased plasma creatinine concentration, compared to the deferasirox group [9, 17, 25].

Oxidative stress is a major factor in the development of the renal toxicity of deferasirox with the destruction of epithelial cells; increased necrosis and fibrosis of renal tissue; as well as tubular and glomerular atrophy on renal function [4, 22]. The kidney toxicity of deferasirox is believed to be due to the production of oxygen free radicals; the increased production of cytokines; as well as the induction of apoptosis and necrosis [23]. Apoptosis plays a crucial role in cell death and may be involved in the removal of damaged cells [16].

5. Conclusion

The concomitant administration of vitamin C in treatment with deferasirox presented a significant efficacy in maintaining renal function. The protective effect of vitamin C is due to its antioxidant properties and the trapping of free radicals. It prevented hemodynamic changes in the kidneys, impaired salt excretion, and tissue changes caused by deferasirox.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Arak University of Medical Sciences (code: IR.ARAKMU.REC.1396.309). All ethical codes approved by the Ministry of Health and Medical Education and Arak University of Medical Sciences were observed regarding maintenance and testing in this investigation.

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Authors' contributions

Methodology, validation, data analysis, and writing: Dr. Saeed Haji Hashemi; Conducting research experiments, resources, and drafts: Dr. Taha Fereydoni and Dr. Ali Rahbari; Conceptualization: Dr. Parsa Yousefi Chaijan.

Conflicts of interest

The authors declared no conflicts of interest.

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