



ORIGINAL ARTICLE

Deferoxamine Protective Effect in Preventing Nephrotoxicity in Children Under Treatment with Doxorubicin: A Randomized Clinical Trial

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ABSTRACT

Background: Nephrotoxicity secondary to doxorubicin (DOX) may be associated with high morbidity and mortality rates. We aimed to assess the efficacy of Deferoxamine (DFO) in preventing DOX-induced nephrotoxicity in pediatric malignancy.

Methods: This Parallel-group randomized clinical trial was done on 62 children aged 2-18 years who had new onset malignancy treated with DOX. They were randomly assigned in three groups; group 1 (no intervention, n=21), group II (DFO 10 times DOX dose, n=20), group III (DFO 50mg/kg, n=21). Patients in the intervention groups received DFO concomitant with DOX 8-hour intravenous infusion in each chemotherapy course. Blood urea nitrogen, serum creatinine, electrolytes, calcium, phosphorus, magnesium and albumin levels, urine microalbumin, urine protein/creatinine ratio, and urine N-acetyl- β -D-glucosaminidase (NAG) as well as findings of kidney ultrasonography were compared between the groups after the last course of chemotherapy. The primary outcome was to compare the radiologic and serologic markers of glomerular and tubular damage between the 3 groups.

Results: Sixty patients were analyzed. Patients treated with DFO 10 times the dose of DOX had significantly lower urine NAG level compared to the control group ($P=0.032$). No significant renal damage was reported in their ultrasonography in the 3 groups. DFO was safely tolerated without any adverse effect.

Conclusion: DFO with 10-times the DOX dose may effectively prevent DOX-induced nephrotoxicity at least at the molecular level. Increasing the dose of DFO is not accompanied by better efficacy.

Trial registration: IRCT2016021915666N3

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Introduction

Anthracyclines are a group of chemotherapy agents that are used in the treatment of various human cancers. They include but not limited to doxorubicin (DOX), daunorubicin, idarubicin, and epirubicin. The most common side effects associated with their use are gastrointestinal disturbance, bone marrow suppression, hair loss, and neurologic dysfunction.

However, the major dose-limiting adverse effects are due to cumulative toxicities of various organs including heart, liver and kidneys.¹ The exact mechanism of DOX-induced nephrotoxicity remains unknown, but it is believed that renal toxicity may be part of a multi-organ damage that is usually caused by the formation of free radicals associated with iron or protein oxidation.^{2,3} Some proposed mechanisms are glomerular podocytes

injury leading to severe proteinuria, formation of iron-anthracycline complex which produces free radicals, lipid peroxidation and depletion of natural antioxidants, over activity of the tissue angiotensin-converting enzyme, and production of reactive oxygen species (ROS) leading to mitochondrial dysfunction.^{1,4-6} The most common consequences of DOX treatment are proteinuria, hypoalbuminemia, dyslipidemia, rise in plasma creatinine, hypercoagulability, and nephromegaly.¹

Children with cancer who undergo chemotherapy particularly with agents like methotrexate, cisplatin, carboplatin, and ifosfamide may also show a wide range of renal damage from mild transient tubular or glomerular dysfunction to irreversible progressive end-stage renal failure.^{7,8} Different factors may contribute such as tubular damage, inflammation, crystal nephropathy, rhabdomyolysis and thrombotic microangiopathy.⁹ There are various risk factors that determine the extent of DOX-induced kidney damage including cumulative dose of chemotherapy drugs, age at time of diagnosis (less than 4 years), concomitant treatment with platinum drugs (such as cisplatin and carboplatin), past history of high dose radiotherapy to the kidneys (>15 Gy), and history of unilateral nephrectomy.^{7,10}

Nephrotoxicity of DOX was first described in 1976 and 1977 in the mice species.^{11,12} Many antioxidants were studied in animal models to assess their efficacy in reducing or preventing nephrotoxicity secondary to anthracyclines. They included nicotinamide, dihydropyridine, calcium blockers, garlic derivatives, and zingiber, but none of them showed satisfactory results to convince the scientists to conduct further clinical trials on the human.¹³⁻¹⁷

With the introduction of iron as one of the main contributors to DOX-induced cardiotoxicity, many iron chelating agents were tried for cardioprotection among which dexrazoxane has been clinically approved.¹⁸ Deferiprone and deferasirox, as oral iron chelating agents, failed to show efficacy in animal studies.^{19,20} Deferoxamine (DFO) is a historical iron-chelating agent that is generally used for treatment of transfusion-related iron overload in patients with thalassemia. With the conventional dose of 50mg/kg three to five times a week, it has an acceptable safety profile. Most of side effects are limited to the site of subcutaneous injection such as erythema, pain, and induration. More serious adverse effects including ocular and ototoxicity are usually encountered in higher doses specially when used for a long period.²¹

Most animal studies showed promising results about protective capacity of DFO in DOX-induced toxicity in different organs including kidneys.^{16,17,22} However, there is no randomized clinical trial (RCT) in human models to introduce a safe and effective agent for prevention of nephrotoxicity secondary to DOX. The aim of this study as the first human RCT in this regard is to assess the efficacy of DFO in prevention of nephrotoxicity in children with cancer who were treated with DOX as part of their chemotherapy regimens.

Patients and Methods

This single-center, parallel group, open-label,

randomized clinical trial was conducted in a tertiary-center teaching oncology hospital, affiliated to Shiraz University of Medical Sciences in Southern Iran. Patients were consecutively selected among newly diagnosed, treatment-naïve pediatric cancer patients with the age range of 2-18 years, who were going to be treated with DOX as part of their chemotherapy protocol. Patients with primary or metastatic renal tumors, unilateral nephrectomy, glomerular or tubular dysfunction, history of abdominal or flank radiation or previous chemotherapy were excluded from the study. The benefit and harms of the intervention were clearly explained to the lawful guardians of participants and informed written consents were obtained from volunteers. The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences with the code number IR.SUMS.REC.1394.165, and was registered in the Iranian Registry of Clinical Trials with the registry number IRCT2016021915666N3. The trial was supported financially by the local university with the grant No. 93-01-01-8700.

(The CONSORT flow diagram for RCTs must be filled and sent with the manuscript as a figure. Also cite it as figure q in the appropriate place in the article.)

As it was the first RCT on true patients in this subject and no previous study could be used for sample size calculation, we decided to enter all eligible patients who were admitted in our center during 2014-2015. Totally, 85 patients were admitted during the study period and 78 met the inclusion and exclusion criteria. Eventually, 62 patients were recruited and were randomly allocated to 3 groups using computer-generated block randomization sequence which was done by a statistician who was blind to the study protocol. The radiologist who reported ultrasonographies was also blind to randomization. Group 1 (n=21) consisted of patients who served as control group, and no intervention was done. Patients allocated to group 2 (n=20) and group 3 (n=21) were pre-treated with DFO (Desferal®, Novartis, Switzerland) 10 times the DOX dose and 50 mg/kg respectively. Intravenous infusion of DFO was started 2 hours prior to starting chemotherapy, continued during DOX infusion (at least 4 hours), and for another 2 hours after termination of the infusion, making up a total of 8 hours. This regimen was repeated in each chemotherapy course together with the infusion of DOX.

Kidney and urinary bladder (KUB) ultrasonography was conducted in all participants by an expert radiologist before entering the study and repeated after the last course of chemotherapy. In addition, urine analysis, blood urea nitrogen (BUN), serum creatinine, electrolytes, calcium, phosphorus, magnesium, and albumin were checked in the patients before entering the study and upon completion of the trial. Moreover, protein, creatinine, micro albumin, and N-Acetyl-Beta-D-Glucosaminidase (NAG) were measured in the early morning spot urine samples of the patients when the study ended. NAG was measured by a specific ELISA-kit (E0828Hu, Bioassay, China).

Data were analyzed by SPSS software version 22. Descriptive data were presented as mean, standard deviation, frequency, and percentage. Chi-Square test was

used to study the homogeneity of groups for qualitative variables. Normal distribution of quantitative variables was confirmed by one-sample Kolmogorov-Smirnov Test. To study quantitative variables between the three groups, one-way ANOVA Test was used. P values less than 0.05 was considered statistically significant.

Results

During the study, we lost one patient in the control group who died of cancer after the 2nd course of chemotherapy. Another patient in group 3 withdrew his consent and was excluded from the study. Therefore, the trial ended with 60 patients (n=20 in each group) (Figure 1). The demographic characteristics of the study population is demonstrated in Table 1. The 3 groups were age-sex matched and homogenous in terms of malignancy type, and cumulative dose of DOX. Among the measured laboratory parameters before entering the study, only serum total protein and serum albumin were significantly lower in groups 2 and 3 compared to the control group (P values 0.009, 0.02 respectively) (Table 2).

At the end of the study, all measured parameters including BUN, serum creatinine, albumin, calcium, phosphorus, sodium, potassium, magnesium, urine micro-albumin and urine protein to creatinine ratio did

not show any significant difference between the groups except total serum protein which remained significantly different between the groups (P=0.001). Although urine micro-albumin was lower in groups 2 and 3 in comparison to group 1, the difference did not reach statistical significance (P=0.42). However, mean of urinary NAG was lower in DFO treated groups compared to the control group (P=0.04) (Table2).

In further analysis by Tukey HSD test, mean urinary NAG difference was only significant between the first and second groups (P=0.032), but not between groups 1 and 3 or groups 2 and 3 (P=0.635, P=0.21 respectively). The ranges of urine NAG is illustrated in Figure 1.

Mean of BUN, serum creatinine, urine micro-albumin, urine protein/creatinine ratio and urinary NAG was not significantly different between the groups regarding the age groups (less than 5 years, 5-10 years and above 10 years), gender, treatment duration (<10, 10-15 and >15 months) and cumulative doses of DOX (<150, 150-300, and >300 mg/m²).

The urinary system of all patients were evaluated by ultrasonography both before and after the study. No significant abnormality was reported in the patients except mild increased renal parenchymal echogenicity (one patient in group 2) and mild pelvocalyceal dilatation

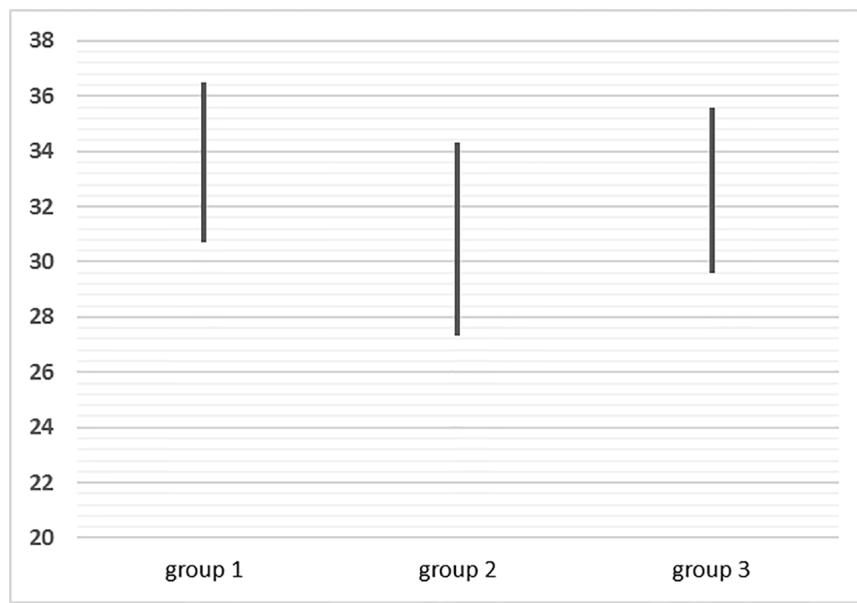


Figure 1: Ranges of urine NAG in the three study groups. Group 1 treated only with doxorubicin (control group); group 2: treated with Deferoxamine 10-times doxorubicin dose; group 3: treated with Deferoxamine 50 mg/kg; NAG: N-Acetyl-Beta-Glucosaminidase

Table 1: Demographic characteristics of the studied population

	Group 1	Group 2	Group 3	P value
Male/female (n)	13/7	14/6	15/5	0.78
Age (month)	87±65	89±58	86±53	0.53
Body Surface Area (m ²)	0.86±0.45	0.89±0.39	0.97±0.35	0.67
Malignancy type				
Lymphoma/ Leukemia	16 (80%)	17 (85%)	17 (85%)	0.87
Solid tumors	4 (20%)	3 (15%)	3 (15%)	
Doxorubicin cumulative dose (mg/m ²)	225.2±132.3	224±115.8	218.3±130	0.83
Treatment duration (month)	13.7±3.6	13.1±2.54	13.5±3.8	0.12

Group 1: treated only with doxorubicin (control group); group 2: treated with Deferoxamine 10-times doxorubicin dose; group 3: treated with Deferoxamine 50mg/kg

Table 2: The measured parameters pre- and post-treatment with Deferoxamine

Pre-treatment values	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	P value
Sodium (mEq/l)	136±2.3	136.3±2.3	136.5±3	0.79
Potassium (mEq/l)	4.1±0.5	4±0.5	3.9±0.4	0.65
Calcium (mg/dl)	9.1±0.6	9±0.6	8.9±0.5	0.07
Phosphorus (mg/dl)	4.8±1	4.5±0.7	4.6±0.8	0.56
Magnesium (mg/dl)	2±0.3	1.9±0.2	2±0.2	0.54
Blood urea nitrogen (mg/dl)	10.3±5.5	10±3.8	10.2±3.3	0.96
Serum creatinine (mg/dl)	0.7±0.1	0.7±0.1	0.8±0.1	0.06
Serum total protein (g/l)	6.7±0.6	6.1±0.7	6.1±0.5	0.009
Serum albumin (g/l)	3.9±0.4	3.5±0.4	3.7±0.4	0.02
Post-treatment values				
Blood urea nitrogen (mg/dl)	8.4±2.7	9.9±3.1	8.5±3	0.28
Serum creatinine (mg/dl)	0.7±0.1	0.6±0.1	0.7±0.2	0.58
Serum total protein (g/l)	6.7±0.5	5.8±0.8	5.9±0.6	0.001
Serum albumin (g/l)	3.7±0.3	3.6±0.5	3.6±0.3	0.8
Urine micro albumin (mcg/mg creatinine)	8.2±5.6	7.2±5.9	5.9±4.3	0.42
Urine protein /creatinine ratio	0.07±0.06	0.07±0.14	0.07±0.05	0.97
Urine NAG (ng/ml)	33.5±2.8	30.7±3.4	32.6±3	0.04

Group 1: treated only with doxorubicin (control group); group 2: treated with Deferoxamine 10-times doxorubicin dose; group 3: treated with Deferoxamine 50 mg/kg; NAG: N-Acetyl-Beta-Glucosaminidase

(one patient in group 1) at the end of the study which were not statistically significant ($P>0.05$).

Discussion and Conclusion

This study is the first RCT conducted in children suffering from cancer that investigated the protective role of DFO in DOX-related nephrotoxicity. It was shown that DFO with the dosage of 10-times DOX dose might reduce tubular damage in DOX-treated patients reflected by lower urinary NAG levels.

The urinary activity of the lysosomal enzyme NAG is one of the most sensitive markers of renal tubular dysfunction. It can detect renal parenchymal damage very early when other parameters of kidney function such as serum creatinine and glomerular filtration rate are still within normal range.²³ It was previously shown that NAG might detect subclinical glomerular and tubular damage in survivors of childhood malignancy who were treated with nephrotoxic drugs such as methotrexate and cisplatin.²⁴

The protective role of DFO against DOX-induced renal damage was previously studied in animal models. Saad showed in his study that pretreatment with DFO significantly reduced peroxidative damage in the myocardium, hepatic and renal tissues of rats who had an acute injection of DOX. The maximum effect was obtained with the dosage of 10-fold that of DOX. Higher dosing was not only more protective but exhibited hepatotoxicity.¹⁷ Kajbafzadeh proved in his research that some antiapoptotic medications including DFO and amifostine might have a role in preventing oxidative damage in rats treated with DOX.¹⁶ Bulucu demonstrated the beneficial effects of DFO and N-acetylcysteine in diminishing proteinuria in DOX-treated rats who developed nephrotic syndrome.²⁵ However, when the two drugs were used simultaneously they failed to remain

effective in preventing proteinuria. The authors related this detrimental effect to erythrocyte selenium levels.²⁶

The three groups in our study were comparable in terms of other aspects of renal function including Bun, serum creatinine, and microalbuminuria. It seems that DOX nephrotoxicity at least in short-term could not be detected with routine renal function tests, and more sensitive markers such as NAG is required. Lower serum total protein in the intervention groups can't be attributed to DFO as they had lower serum protein before entering the study.

There was a concern whether iron-chelating agents may interfere with anti-tumor activity of DOX. An in vitro study revealed that DFO might cause cytostasis through iron depletion. It also had the ability to inhibit breast tumor growth, and did not compromise tumoricidal capability of DOX.²⁷ Furthermore, a recent study demonstrated that DFO might induce intracellular calcium that increases their sensitivity to DOX.²⁸

It is not clear what is the most effective dose of DFO in preventing DOX toxicity in different organs. Our study compared 2 different doses of DFO and showed that with the dosing 10-times that of DOX (equivalent to 10-20 mg/kg), it has more beneficial role in reducing nephrotoxicity than the conventional dose (50 mg/kg) used as iron chelator in thalassemia patients. Due to lack of similar human studies, we could not compare our results with them. Further pharmacokinetic studies in a larger scale are required to find the optimum protective dose in the target organs.

While our study is the first one of its own and has opened a new perspective in this field, it faced some limitations. First, our patients were not homogenous in terms of their malignancy type, and they were treated with different chemotherapy protocols some of them contained other nephrotoxic agents such as methotrexate, platinum

drugs and ifosfamide. As randomization was done by a third party who was blind to our study protocol, we could not match the 3 groups from this point of view. Nevertheless, the three groups by chance contained nearly equal number and proportion of patients with hematologic malignancies and solid tumors, which might have reduced this confounding factor. Secondly, the small sample size and short follow up period hindered us to generalize our results. Last but not the least, we didn't measure markers of tubular damage such as NAG and urine micro albumin before starting chemotherapy so we were not able to compare the mean difference of pre-post chemotherapy levels in each treatment arm.

In conclusion, DFO may serve as a promising agent in diminishing DOX-induced nephrotoxicity. Further multicenter trials including patients treated exactly with similar chemotherapy agents are required to elucidate the efficacy as well as the best therapeutic dose of DFO in preventing DOX toxicity in the kidneys and also other susceptible organs.

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Conflict of Interest: None declared.

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