

Erythropoietin Attenuation Of Early Upregulation Of Kidney Injury Parameters Levels In Cisplatin-Treated Rats

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Abstract

Background: cisplatin chemotherapy can cause acute kidney injury (AKI) in about 30% of patients that act as a major dose-limiting problem complicating chemotherapy by cisplatin that still commonly indicated as first line treatment of cancer management without relatively less toxic and equally effective substitutes. Cisplatin induced-DNA damage and oxidative- inflammatory hyper-reactivity with apoptosis are the bases for cisplatin-induced AKI. Erythropoietin has approved antioxidant, anti-inflammatory and to some extent antiapoptotic effects that may have ameliorative effect on early cisplatin-induced AKI. Kidney injury molecules-1 (KIM-1) and interleukin-18 (IL-18) were assumed to be more sensitive for detecting AKI than the traditional kidney function tests (serum creatinine and urea).

Objective: assess the effect of erythropoietin on early upregulation of kidney injury parameters after cisplatin treatment.

Methods: 27 adult male rats were randomized into three groups containing nine rats for each as follow: *Sham group*: rats received daily intraperitoneal injection of placebo for 4 days. *Cisplatin group*: rats received single intraperitoneal injection of 6 mg/ kg cisplatin. *Cisplatin+Erythropoietin group*: rats received single intraperitoneal injection of 6 mg/ kg cisplatin and daily intraperitoneal injection of 100 IU/kg erythropoietin for 4 days. After scarification, blood samples are collected for serum creatinine measurement, kidneys are processed for measurement of renal MDA, KIM-1 and IL-18 and histopathological evaluation.

Results: cisplatin produced significant ($P<0.05$) change in serum creatinine level, kidney MDA, KIM-1, IL-18 and score of histopathological damage severity when compared to that of other groups. In Cisplatin + Erythropoietin group, Serum creatinine, and kidney MDA, KIM-1, IL-18 and total severity score were significantly ($P<0.05$) less than that in cisplatin group.

Conclusion: erythropoietin ameliorated early cisplatin-induced AKI evidenced by improving early injury parameters that give rise for early involvement of erythropoietin as early preventive measure for protection from nephrotoxicity.

Keywords: cisplatin, acute kidney injury, erythropoietin, KIM-1, IL-18

Introduction

Cisplatin (cis-diamminedichloroplatinum (II)) is an antitumor agent that commonly used in the management of various solid-organ tumors. Toxicities due to cisplatin can occur as nephrotoxicity, myelosuppression, gastrotoxicity, neurotoxicity, and allergic reactions (1,2). Nephrotoxicity act as a major dose-limiting problem complicating chemotherapy by cisplatin that still commonly indicated as first line treatment of cancer management without relatively less toxic and equally effective substitutes. Cisplatin chemotherapy can cause nephrotoxicity as AKI in about 30% of patient despite use of powerful hydration as a protective measure (3-5).

Cisplatin induced-DNA damage and oxidative- inflammatory hyper-reactivity with apoptosis are the bases for cisplatin-induced AKI through a complex mechanism (6). Inflammation associated with apoptosis are suggested by many studies to act as crucial pathophysiological mechanism in cisplatin-induced AKI (7-9). The proinflammatory cytokine, tumor necrosis factor (TNF)-alpha mediate reactive oxygen species overproduction, apoptosis (10,11) and stimulation of the overproduction of cytokines and/or chemokines that leads to again further inflammation (8,9). Thus, interfering with the inflammation, oxidation and /or apoptosis processes due to cisplatin administration may be protective from cisplatin-induced AKI.

Kidney injury molecule-1 (KIM-1) is a 36 kDa (unglycosylated) type I glycoprotein found on the cell membrane that contains a six-cysteine

immunoglobulin-like domain and a mucin domain in its extracellular portion (12). KIM-1 is found to be undetectably expressed in the normal rat kidney but significantly upregulated post-ischemia (12). After proximal tubular injury of varying etiology in vitro, KIM-1 ectodomain was expressed out from cells (13) while in vivo, expressed into the urine in rodents and humans (14-17). In many experimental and clinical studies, KIM-1 was considered as an earlier indicator of AKI than the traditional tubular enzymes and biomarkers (18,19). Acute tubular necrosis (ATN) caused about 12-fold increase in KIM-1 level that normalized by gender, age and delay period between insult and sampling adjustment (18). KIM-1 suggested and considered be a stable, specific and sensitive AKI biological marker in adult clinical studies (20).

Interleukin-18 (IL-18) is previously recognized as interferon- γ -inducing factor. Biologically active form of IL-18 is produced after activation by caspase-1 of a 24 kDa inactive precursor (21-23). IL-18 have various immunomodulatory properties and found to play a essential role in host defense mechanism against various infections (23). IL-18 levels upregulated significantly in patients with AKI after ischemic ATN and transplantation (24). Urinary IL-18 was found to be an early marker of AKI in adult patients with acute respiratory distress syndrome, that upregulated before increasing in serum creatinine

by 1 – 2 days, and was an independent predictor of death (25). In mice, cisplatin induced AKI and increased levels of kidney IL-18 (26).

Erythropoietin is a protein with a erythropoietic effect that synthesized in response to hypoxia by peritubular cells in the kidneys and to some extent in the liver (27). Tissue oxygen levels deficiency leads to stimulation of the activity of hypoxia-inducible factor 2a, which stimulate process of transcription by binding to hypoxia-responsive elements of the erythropoietin gene (28,29).

In the bone marrow, in addition to proliferating factors as stem cell factor, insulin like growth factor 1 and granulocyte macrophage colony-stimulating factor, erythropoietin protects erythroid progenitor cells from apoptosis, and activate specialization of erythroid progenitors from the normoblast stage to ultimately erythrocytes in mature stage (30).

Outside of the erythropoietic system, erythropoietin has been revealed to have an important role in tissues. Erythropoietin receptors are found to be expressed widely and a biological response to erythropoietin have been observed in many cell types like cardiac, neural, and endothelial cells (31,32).

Recombinant human erythropoietin (rHuEPO) is used to treat anemia and has been shown to act as a cytoprotectant in different models of AKI, including ischemic and toxic AKI (33,34).

Erythropoietin can produce nitric oxide by stimulation of endothelial cells, which characterized by anti-apoptotic effects (35,36). The study Work on the confirmation role for rHuEPO in localized cisplatin-induced renal injury and proposed that an anti-apoptosis effect produced by the interaction of erythropoietin with its receptor (EPOR) is an important mechanism for renal preservation (37).

Numerous studies have reported the involvement of erythropoietin in the promotion of cell survival signaling cascades such as the JAK/STAT, PKC, and PI3K/Akt signaling pathways, and in the upregulation of anti-apoptotic protein expression in a spectrum of experimental models (37-39). Erythropoietin activates cell survival pathways by inducing the phosphorylation of JAK2/STAT to attenuate ER stress (40).

Methods

A total of 27 adult male of Swiss Albino rats (weighing 90-110g) were supplied by Animal Resource Center, University of Kufa. Animals were accommodated in the animal house of Faculty of Pharmacy/ Kufa University in a room with 24 ± 2 °C temperature. Rats were under 12-hours light exposure and 12- hours without light exposure throughout the experiment and animals were able to reach water and diet freely. The Animal Care and Research Committee of Kufa University approved the experiments and the study followed the guide of National Research Council for the handling of Laboratory Animals. One week after adaptation, the rats were

classified into three groups containing nine rats for each as follow:

- **Sham group:** rats received daily intraperitoneal injection of placebo for 4 days and underwent the same anesthetic and surgical procedures of other groups of the present study.
- **Cisplatin group:** rats received single intraperitoneal injection of 6 mg/ kg cisplatin for nephrotoxicity induction in rats according to previous studies. It was manufactured by cipla, (India) as 50 mg/50mL (Cytoplatin-50 aqueous vial of 50ml).
- **Cisplatin+Erythropoietin group:** rats received single intraperitoneal injection of 6 mg/kg cisplatin and daily intraperitoneal injection of 100 IU/kg erythropoietin for 4 days. It was manufactured by CinnaGen co, (Iran) as 4000IU in syringe.

Measurement of the early kidney injury parameters

At the end of experiment, all the animals were sacrificed on 4th day of cisplatin administration and right kidney is taken and homogenized with 0.1 M potassium phosphate buffer (pH7.4) in a ratio of mixing of 1:10 (w/v) and the homogenization done by a high intensity ultrasonic liquid processor. kidney homogenate was used for determination of renal KIM-1 (using Sigma MaxiSorp; Nunc- EZ-Biotin Quantitation Kit, USA) and IL-18 (using MBL ELISA kit, Japan).

Measurement of kidney function parameter

Immediately after scarification, directly from the heart, blood about

(1.5 ml) was withdrawn. The samples were left for clotting at 37°C then centrifugation at 10000 rpm for 30 min; then the serum from each sample was separated from samples and examined for evaluation of serum creatinine using SPINREACT kit, Spain.

Measurement of oxidative stress parameter

Malondialdehyde (MDA), the lipid peroxidation final yield, was determined in kidney homogenate of sacrificed animals according to the method described by Buege and Aust (1978) which demonstrated that the reaction of MDA with thiobarbituric acid (TBA) produce a red chromophore (colored) MDA-TBA complex, , which can be estimated for quantification of MDA by spectrophotometry (41).

Histopathological Evaluation

The left kidney was fixed in 10% formalin. Light microscope with magnification power of (×400) was used for examining the slide sections of renal tissues for the histological changes assessment at cortico-medullary junction. Degree severity of damages in kidney parenchyma was evaluated and scored by pathologist who was uninformed of the treatment in the study by a semi-quantitative scale designed by McWhinnie et al (1986) for severity of renal damage evaluation (42) by dividing slide section zone into 10 small zones (intersections). 0 to 3 score was assumed for each intersection

according to its tubular profile as follow:

0 = normal (no damage seen) parenchyma.

1 = when not more than 1/3 of tubular profile is damaged. (vacuolation, interstitial edema, atrophy of tubule, severe tubular necrosis, and interstitial inflammation)

2 = when greater than 1/3 and less than 2/3 of the tubular profile is damaged.

3 = when greater than 2/3 of the tubular profile is damaged.

The summation of the all ten intersections scores (with a maximum score of 30) for each kidney (slide section) was referred as total severity score, according to which the severity of kidney injury was categorized as follow: when total severity score is

zero the slide was considered normal, when the score is (1-10) the kidney injury considered mild, when (11-20) considered moderate and when (21-30) considered severe kidney injury.

Statistical Analysis

SPSS 16.0 for windows Inc. was utilized for statistical analysis of data of all the study results. Normally distributed data of quantitative variables were expressed as mean \pm SEM. Multiple comparisons among all study groups were accomplished by Analysis of Variance (ANOVA) then LSD methods used for post-hoc tests. The total severity score statistical significance were examined by the Mann-Whitney U test (non-normally distributed variable). In all analyses, level of statistical significance was 0.05 ($P < 0.05$).

Results

Effects on kidney injury parameters (KIM-1 and IL-18)

Cisplatin administration (6mg/kg) lead to significant increment ($p < 0.05$) in KIM-1 and IL-18 levels when compared with sham group levels of same parameters as shown in figure (1). In Cisplatin + erythropoietin (100 IU/kg) treated group, KIM-1 and IL-18 were characterized by significant ($p < 0.05$) elevation in their level based on sham group level comparisons and significant ($p < 0.05$) lowering based on cisplatin group level comparisons as shown in figure (1) below.

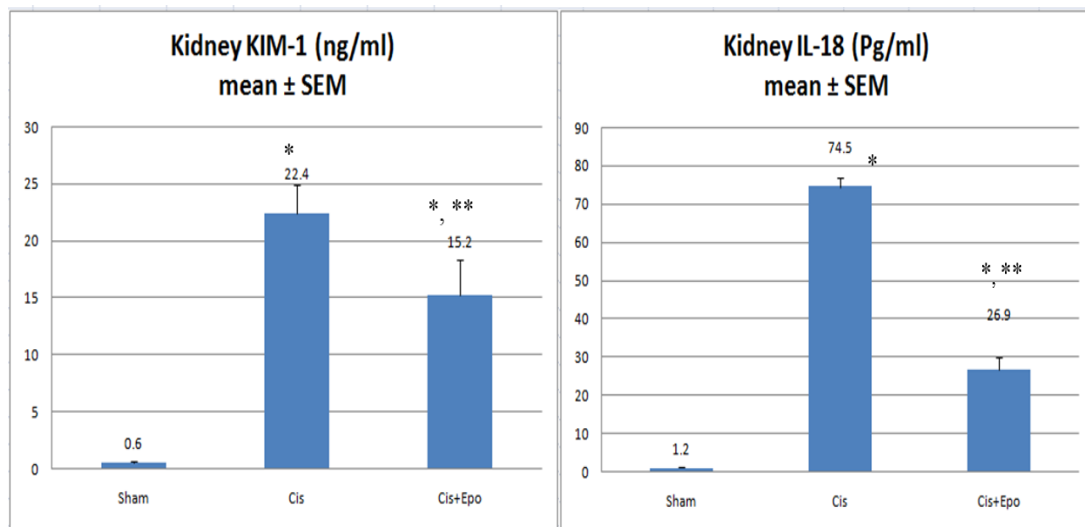


Figure (1): chart shows mean \pm SEM differences in KIM-1 (pg/ml) and IL-18 (ng/ml) levels of the three study groups after the end of experiment. (N=9 for each, * Significant change in comparison to sham group, ** Significant change in comparison to cisplatin group).

Effects on kidney function parameters

Cisplatin administration (6mg/kg) lead to significant increment ($p < 0.05$) in serum creatinin level when compared with sham group level as shown in figure (2). In Cisplatin + erythropoitein (100 IU/kg) treated group, serum creatinin was characterized by significant ($p < 0.05$) elevation in its level based on sham group level comparisons and significant ($p < 0.05$) lowering based on cisplatin group level comparisons as shown in figure (2) below.

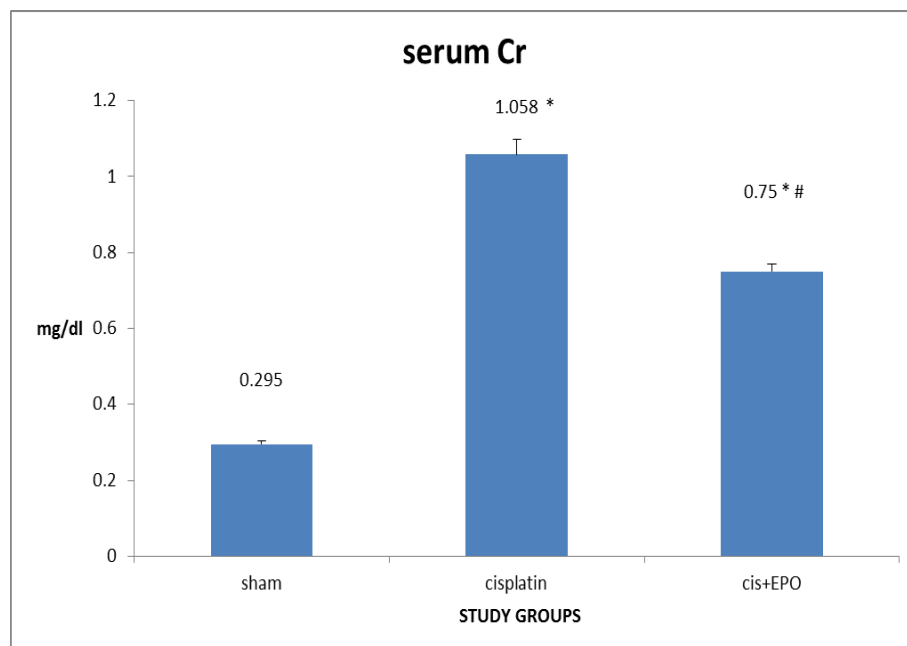


Figure (2): chart shows mean \pm SEM differences in serum creatinin levels (mg/dl) of the three study groups after the end of experiment. (N=9 for each, * Significant in comparison to sham group, *# Significant in comparison to cisplatin group).

Effects on renal oxidative stress (Kidney MDA)

Cisplatin administration (6mg/kg) lead to significant increment ($p < 0.05$) in kidney MDA level when compared with sham group level as shown in figure (3). In Cisplatin + erythropoietin (100 IU/kg) treated group, kidney MDA was characterized by significant ($p < 0.05$) elevation in its level based on sham group level comparisons and significant ($p < 0.05$) lowering based on cisplatin group level comparisons as shown in figure (3) below.

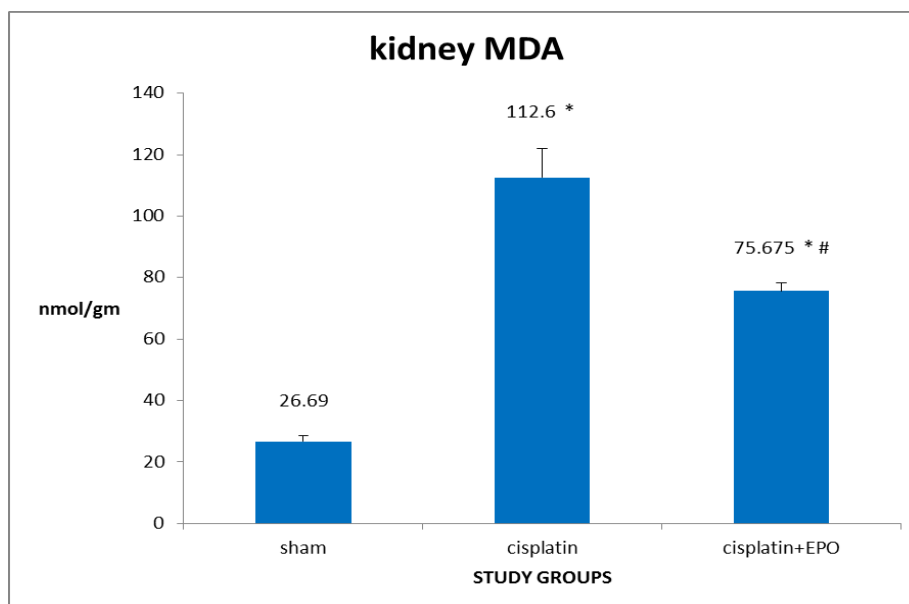


Figure (3): chart shows mean \pm SEM differences in kidney MDA levels (nmol/gm) of the three study groups after the end of experiment. (N=9 for each, * Significant in comparison to sham group, *# Significant in comparison to cisplatin group).

Effects on Kidney Parenchyma

Cisplatin treatment lead to severe kidney injury for 6 rats (66.6 %) in cisplatin group and 3 rats (33.4 %) show moderate severity. These damages are significant when compared with that of sham group where slide sections of kidneys of 7 rats (77.7 %) in this group showed normal parenchyma while 2 rats (22.2%) showed mild damages. In cisplatin group, slide sections of kidneys of showed severe grading while in cisplatin + erythropoietin group, 2 rats (22.2 %) in this group showed severe damages, 3 rats (55.5 %) showed moderate damages and 2 rats (22.2%) showed mild damages.

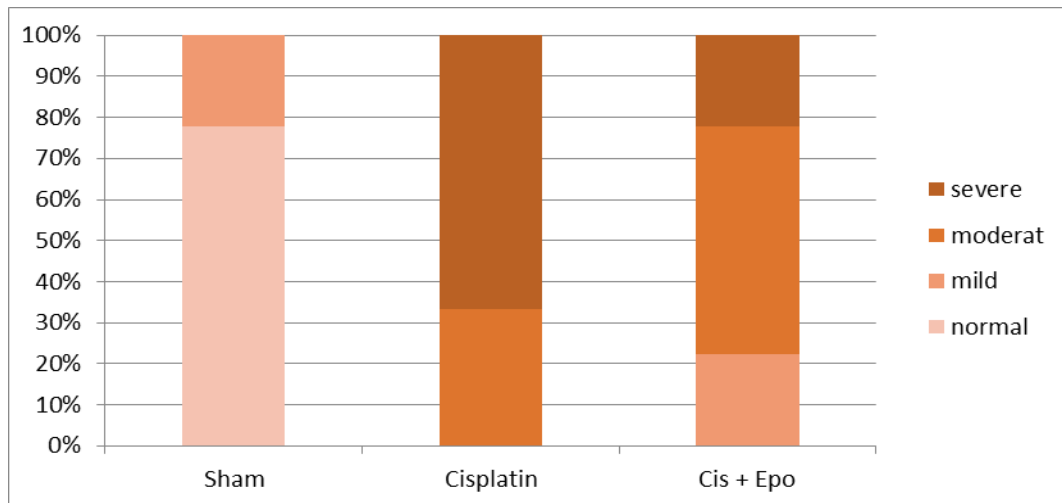
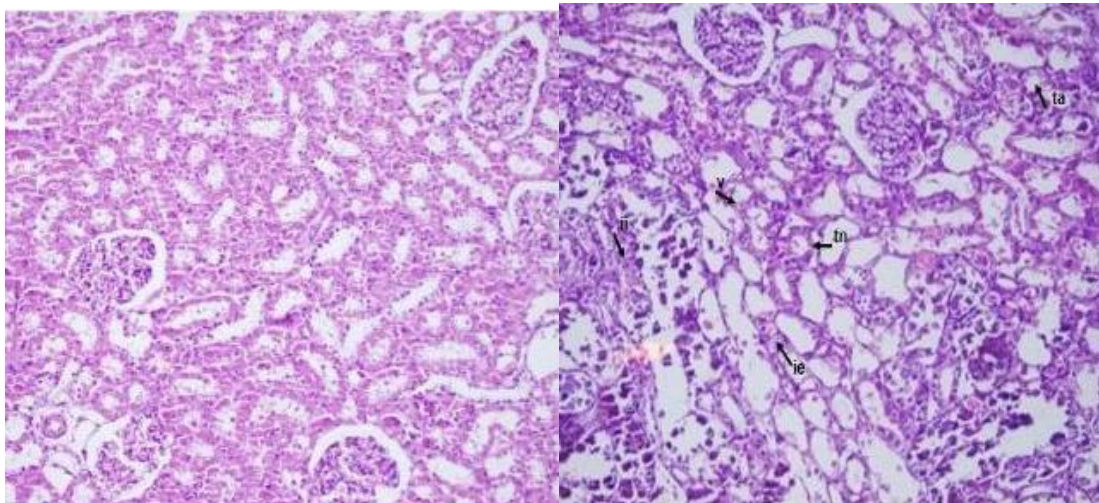


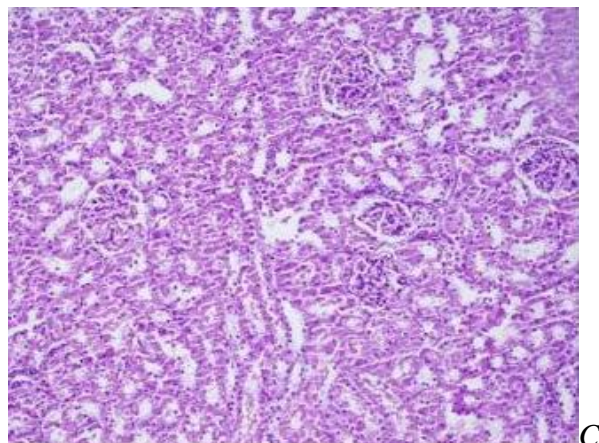
Figure (4): chart shows relative frequency of histopathological damages severity of the three study groups at the end of experiment (N=9 in each).

The below photomicrographs demonstrate the predominant histopathological findings in each group.



A

B



C

Figure (5): Photomicrographs of kidney intersection stained with haematoxylin and Eosin (X 400). A, sham; B, cisplatin treatment alone [left to right (ii) interstitial inflammation, (v) vasculature, (i.e.) interstitial edema, (tn) tubular necrosis, (ta) tubular atrophy]; C, cisplatin + erythropoietin.

Table (1): The injury severity differences among the three study groups at the end of experiment.

Histopathological injury severity	Study groups					
	Sham		Cisplatin		Cis + Epo	
	N	%	N	%	N	%
Normal	7	77.8	0	0	0	0.0
Mild	2	22.2	0	0	2	22.2
Moderate	0	0	3	33.4	5	55.6
Severe	0	0	6	66.6	2	22.2
Total	9	100	9	100	9	100
Grade of the group	Normal		Severe		Moderate	

As shown in figure (6) below, Cisplatin administration significantly ($p < 0.05$) increased total severity score than that of sham group. Adding erythropoietin to rats in addition to cisplatin therapy led to significant ($p < 0.05$) decrease in total severity score than that in cisplatin treated rats.

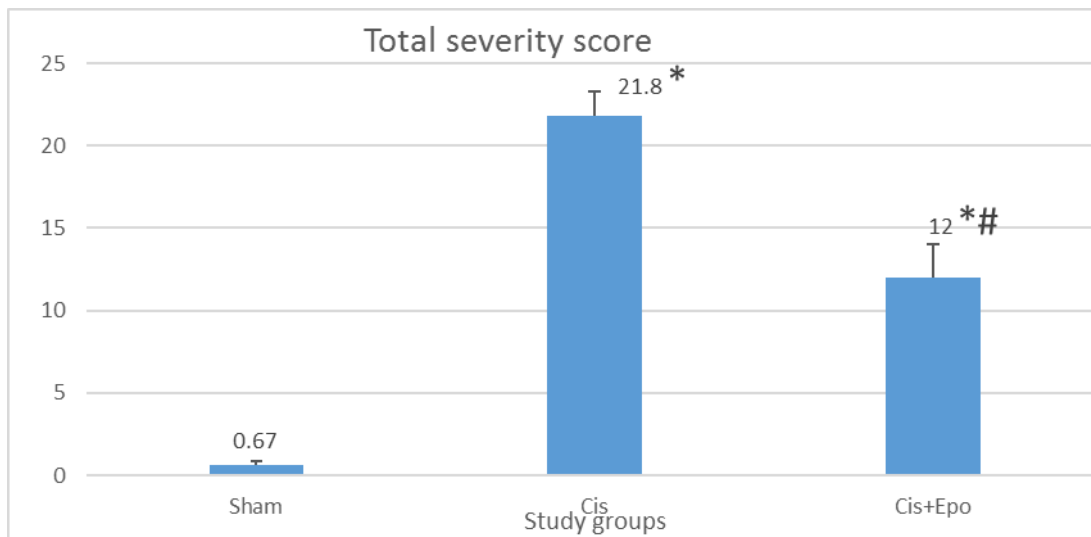


Figure (6): chart shows mean \pm SEM differences in total severity score of the three study groups after the end of experiment. (N=9 for each, * Significant in comparison to sham group, *# Significant in comparison to cisplatin group).

Discussion

Effects of cisplatin on kidney injury parameters (KIM-1 and IL-18)

In the present study, rats of sham group revealed low to undetectable levels of KIM-1. Cisplatin caused dramatical upregulation in levels of KIM-1 in the kidney of rats of Cisplatin group. In several studies, KIM-1 appeared in the urine of experimental rodents and humans after cisplatin-induced injury of proximal tubular (14-17). Furthermore, Kim-1 was considered more sensitive than the conventional BUN, serum creatinine, urinary NAG, glycosuria, or proteinuria for detecting AKI than after cisplatin administration and renal ischemia/reperfusion (I/R) in rat models (19).

IL-18 was significantly elevated in Cisplatin group compared with the normal values in Sham group of the present study. In a study, 0-4 days after operation of transplantation, acute decline in serum creatinine concentrations was predicted by a rapid decline in urinary IL-18 levels (24). An explanation of this was that these inflammatory reactions resulted from TNF-alpha which stimulate the cytokines and/or chemokines generation of such as monocyte chemoattractant protein-1 (MCP-1) and ICAM-1(8,9). IL-18 expression was revealed by immunohistochemical staining of biopsies of the distal tubular epithelium of renal transplant. In the proximal tubules of patients with acute rejection, strong positive

immunoreactivity was demonstrated with strong immunoreactivity of infiltrating leukocytes, and endothelium, that assumed robust upregulation of chemoattractant IL-18 due to immunopathological reactions (43).

Effect of Cisplatin on Kidney Function

This study shows that serum creatinine were elevated significantly ($p < 0.05$) after cisplatin administration in comparison to that of sham group. In many studies, cisplatin nephrotoxic effect was resulted after 10 days of cisplatin treatment and is demonstrated as low GFR and high serum creatinine (4, 6, 44). Several studies have revealed that administration a single dose of cisplatin (7.5 mg/kg BW) can induce renal injury in rat model with prominent elevation in levels of serum creatinine and BUN in cisplatin group compared to that in the group of untreated animals. It is approved that increased creatinine is associated with renal dysfunction or due to nephrotoxic agents (45). Another study showed that 5 mg/kg body weight intraperitoneal injection of cisplatin resulted in significant elevation in the BUN, serum creatinine, urine volume and kidney weight/ the total body weight percentage when compared to that of the cisplatin-untreated rats (46).

Effects of Cisplatin on Kidney Oxidative Stress Parameter (MDA)

In the current study, kidney MDA levels were significantly ($P < 0.05$) upregulated in cisplatin group as compared to that of sham group, this

result assumed that significant activation in oxidation process leads to higher lipid peroxidation. Our results are in good agreement with that of other studies. Palipoch et al. (2013) showed that MDA level in renal tissues was significantly elevated in animal of cisplatin group as compared with cisplatin-untreated animal in sham group (47). Oxidative stress contributes to cisplatin-induced AKI by severe activation of reactive oxygen species generation and inhibiting of enzymatic antioxidants activities such as superoxide dismutase and catalase (48,49). Cisplatin stimulate reactive oxygen species generation by stimulation of expression of gene of NADPH oxidase causing further stimulation of lipid peroxidation (manifested by increasing the level of end product of lipid peroxidation, the MDA), finally this led to membrane damage and nephrotoxicity (48,49).

Effects of Cisplatin on Kidney Parenchyma

The present study found that the prevalence of kidney injury caused by cisplatin administration was highly severe. The ratio is 77.7% (7 rats), which confirm the effect of cisplatin which induce kidney injury in renal tubules. A study suggested that cisplatin induced sub lethal AKI, with alterations to renal function and histology (50). The mechanisms of cisplatin-induced renal injury are related to several factors, including higher oxidation process, inflammatory process, mitochondrial dysfunction, DNA damage, and apoptosis (6, 51).

The cisplatin uptake by tubular cells led to activation of oxidation and inhibiting antioxidant system that resulted in apoptosis initiation through complex signaling pathways that led to tubular cell injury and ultimately death. Vigorous inflammatory response which activated due to oxidative stress led to additional exacerbation of renal tissue damage (6,44). Cisplatin may initiate ischemic injury of the kidneys by direct injury of renal vasculature and then result in diminished renal blood flow (44). All the stated effects, together, resulted finally in the histological damages to kidney (44).

Effects of Erythropoietin on kidney injury parameters

A significant decrement in KIM-1 and IL-18 levels of rats treated with erythropoietin and cisplatin as comparing with that in cisplatin group noticed in the present study. This believed to be due to the protective effect of erythropoietin in renal tubules. A similar study revealed that erythropoietin can prevent and recover renal injury in rat model administered cisplatin (6 mg/kg) and daily erythropoietin (100 U/kg) for 9 day (52).

In rats, erythropoietin enhanced recovery from cisplatin-induced AKI (52), suggesting that it acts directly on impaired tubular cells and stimulates their regeneration. Studies on renal epithelial cells of tubules demonstrated that caspase and mitochondria play critical role in apoptosis due to cisplatin (53). Mitochondria and the

endoplasmic reticulum (ER) are involved in the intrinsic pathway of apoptosis (54). In addition, the endoplasmic reticulum stimulated apoptosis by making mitochondria more sensitive to many extrinsic and intrinsic stimuli and then inducing apoptotic cell death (55).

Effect of Erythropoietin on kidney Function

In this study, we notice a significant decrement in serum urea and serum creatinine levels of rats treated with erythropoietin and cisplatin as comparing with cisplatin group. This believed to be due to the renoprotective effect of erythropoietin in renal tubules. Several studies have noticed that erythropoietin can inhibit renal damages in rat model administered cisplatin (6 mg/kg) and daily erythropoietin (100 U/kg) for 9 days (52). In another study, significant serum creatinine and BUN concentrations were lowering in rats received erythropoietin after cisplatin injection than in the cisplatin-injected rats (50).

Effect of Erythropoietin on Kidney Oxidative Stress Parameter (MDA)

The animals that received erythropoietin had significant ($P<0.05$) lower level of kidney MDA than that resulted in cisplatin group of the current study. Erythropoietin has approved antioxidant effects (56, 57). Effect of erythropoietin in reduction of apoptosis and oxidative stress (58) may play major ameliorating effects on cisplatin-induced AKI. Erythropoietin stimulate tissue activity of superoxide

dismutase, catalase, and glutathione peroxidase (58). Ates et al (59) reported that increased the level of glutathione (GSH) resulted from erythropoietin treatment after ischemia- reperfusion injury induction in rats. Sakanaka et al (60) have also demonstrated that erythropoietin stimulated the activity of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase in neurons. Activation of antioxidant enzymatic (58,60) and non-enzymatic (59) systems lead to inhibition in lipid peroxidation due to cisplatin exposure and thereby less production of MDA (end product of lipid peroxidation) (48,49).

Effect of Erythropoietin on Kidney Parenchyma

In the present study, cisplatin + erythropoietin administration caused significant decrement in kidney injury severity in comparison to that of cisplatin treated group. Although no rats in cisplatin + erythropoietin group showed normal kidney parenchyma (same finding of cisplatin group), two rats only (22.2%) have showed severe kidney injury which is good improvement when compared with 6 rats (66.6%) of all cisplatin group rats that revealed severe kidney injury. In another study, almost same result was showed. No glomerular or vascular

lesions were observed, treatment with erythropoietin modified the effects of cisplatin on renal histology, as no or very little necrosis or tubular cast material was detected in the control and erythropoietin treated groups (50). In animals treated with erythropoietin, significant improvement in tubular regeneration, tubular cell proliferation and thereby recovery of the renal function was approved and assumed that this effect may be through growth factor-like effect of erythropoietin in tubular cell (52). In vitro, erythropoietin stimulate (in a dose-dependent manner) proliferation and chemotaxis of endothelial progenitor cells which in turn activates vascular reparative mechanisms and neoangiogenesis (61).

Conclusion: Cisplatin caused nephrotoxicity in rat evidenced by upregulation of kidney injury parameters, deterioration in kidney function, histopathological changes while erythropoietin administration with cisplatin ameliorated early cisplatin-induced acute kidney injury evidenced by improving early injury parameters that give rise for early involvement of erythropoietin as early preventive measure for protection from nephrotoxicity.

Competing interest: none.

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الارثروبويتين يحسن الارتفاع المبكر في مستويات دلائل الاصابة الكلوية في الفئران المعالجة بالسيبلاطين

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الخلاصة

الخلفية: العلاج الكيميائي سيسبلاطين يمكن أن يسبب إصابة الكلى الحادة (أكي) في حوالي ٣٠٪ من المرضى و الذي يشكل مشكلة كبيرة تحد من الجرعة و تعقد العلاج الكيميائي من قبل سيسبلاطين الذي لا يزال يشار إليه عادة كالخط الاول في علاج السرطان دون بدائل أقل سمية نسبيا وفعالة على حد سواء. الضرر الناجم عن سيسبلاطين على الحمض النووي و الجهد التأكسدي وفرط الاحتقان مع موت الخلايا المبرمج هي اساس الضرر الناجم عن سيسبلاطين. التأثير الموثق للإريثروبويتين كمضاد للأكسدة، المضادة للالتهابات وإلى حد ما تأثيرات المضادة للموت المبرمج للخلايا قد يكون لها تأثير محسن على إصابة الكلى الحادة المبكرة التي يسببها سيسبلاطين. من المفروض أن جزيئات إصابة الكلى - ١ (كيم-١) والإنترليوكين ١٨ (إيل-١٨) أكثر حساسية للكشف عن إصابة الكلى الحادة من اختبارات وظائف الكلى التقليدية (مصل الكرياتينين واليوريا).

الهدف: تقييم تأثير إريثروبويتين على الارتفاع الحاد المبكر في معلمات إصابة الكلى الحادة بعد العلاج بالسيبلاطين.

الطريقة: تم عشوائيا تقسيم ٢٧ فئران ذكور بالغين على ثلاث مجموعات تحتوي على تسعة فئران لكل منها على النحو التالي: مجموعة شام: تلقت الفئران الحقن اليومي داخل الصفاق من الدواء الوهمي لمدة ٤ أيام. مجموعة سيسبلاطين: تلقت الفئران حقن واحد داخل الصفاق من ٦ ملغ/ كغ سيسبلاطين. مجموعة سيسبلاطين + إريثروبويتين: تلقت الفئران حقن واحد داخل الصفاق من ٦ ملغ/ كغ سيسبلاطين والحقن اليومي داخل الصفاق من ١٠٠ وحدة دولية/ كغ إريثروبويتين لمدة ٤ أيام. بعد التختبر، يتم جمع عينات الدم لقياس الكرياتينين في الدم، تتم معالجة الكلى لقياس الكلوي للمالونالديهايد، كيم-١ و إيل-١٨ وتقييم الضرر النسيجي.

النتائج: انتجت سيسبلاطين تغيرا معنويا ($P < 0.05$) في مستوى الكرياتينين في الدم، المالونالديهايد الكلوي، كيم-١، إيل-١٨ ومجموع شدة الضرر النسيجي المقارنة مع تلك الموجودة في مجموعات أخرى. في المجموعة سيسبلاطين + إريثروبويتين، المصل الكرياتينين، المالونالديهايد الكلوي، كيم-١، إيل-١٨ ومجموع درجة شدة الضرر كانت معنويا ($P < 0.05$) أقل من ذلك في مجموعة سيسبلاطين.

الخلاصة: الإريثروبويتين حسن في وقت مبكر إصابة الكلى الحادة (أكي) التي يسببها سيسبلاطين الذي يتضح من خلال تحسين معلمات الإصابة في وقت مبكر، التي تؤدي إلى ادخال الإريثروبويتين في وقت مبكر كإجراء وقائي مبكر للحماية من إصابة الكلى الحادة.