



Hepato-renal protective effect of vitamin C against toxicity induced by ceftriaxone in rats

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ABSTRACT

The current study was carried out to evaluate the effect of vitamin C on ceftriaxone induced adverse effects in rats. Twenty-four adult male albino rats were randomly divided into 3 equal groups. Group(I) received 1ml saline orally once daily for 14 days. Group(II) received 1ml saline orally once daily for 7 days followed by a 7-once day-treatment with ceftriaxone intra-peritoneally(180 mg/kg b. wt.). Group(III) received vitamin C orally(100 mg/kg b. wt.) once daily for 7 days , followed by a 7-once day-treatment with both oral vitamin C and intraperitoneal ceftriaxone. At the end of the experiment, half of animals were sacrificed under light ether anesthesia on 1st day post-treatment and the other half on 7th day post-treatment. Blood samples were collected for biochemical analysis. Livers and kidneys were collected for histo-pathological examination. Biochemical analysis revealed a significant increase in serum levels of alanine aminotransferase (ALT), aspartate aminotransferase(AST), urea, creatinine and malondialdehyde (MDA). with a significant decrease in catalase(CAT) and superoxide dismutase (SOD) activities in ceftriaxone treated group. Group(III) showed a significant decrease in serum levels of ALT, AST, urea, creatinine and MDA, with a significant increase in CAT and SOD activities. Histopathological examination of liver and kidney of rats in group(II) showed severe hepatocellular necrosis, macrosteatosis, portal fibrosis, portal inflammatory cells infiltrations, necrotic renal tubules and glomerular changes. An improvement of histopathological pictures of liver and kidney was recorded in group(III). This study concluded that vitamin C ameliorates the biochemical and histopathological changes associated with ceftriaxone treatment in rats.

Key words: Biochemical analysis, Ceftriaxone, Histopathology, Rat, Vitamin C

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1. INTRODUCTION

Ceftriaxone is an antibacterial third-generation cephalosporin that has a broad

spectrum of activity against both gram-negative and gram-positive bacteria (El-

sayed et al., 2011a,b). It is effective against *Streptococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus pneumonia*, *Brucella melitensis*, *Haemophilus influenza*, and *Neisseria gonorrhoeae* (Neu et al., 1981). Ceftriaxone acts via inhibition of transpeptidase enzyme which is responsible for the final step in bacterial cell wall synthesis and it resists beta-hydrolysis (Neu,1985).

Ceftriaxone can produce serious adverse effects such as leukopenia, eosinophilia, thrombocytosis, respiratory system disorders, elevations of liver enzymes, elevations of bilirubin and creatinine levels, skin and appendages disorders or in some cases anaphylactic shock and some less common side effects such as nausea, vomiting, diarrhea, itchiness, dizziness, headache and rash (Shalviri et al., 2011). Xenobiotics and drugs were reported to be a cause of reactive oxygen species (ROS) production inside mammalian cells (Abdel-Daim, 2014).

Antioxidants are free radical neutralizing substances (Hwang and Bowen, 2007). A relation was made between coronary artery disease, DNA damage and total antioxidant capacity (TAC). In coronary artery disease, total antioxidant capacity was decreased while the level of DNA damage was increased (Demirbag et al., 2005). Also, Szeto and Benzie (2002), reported that antioxidants protect the body against oxidative stress associated with DNA damage and the pre-treatment with some antioxidants increases DNA resistance to oxidative damage in human lymphocytes.

Vitamin C is a natural antioxidant that can inhibit inflammation and has ameliorative effect on oxidative stress of cells as it can scavenge the produced free radicals and prevent further production of them (Ryan et al., 2010; Monacelli et al., 2017). In a study done by Jacobs et al., (2015), vitamin C was found to reduce the side effects of chemotherapeutic treatment. The increased intake of vitamin C and subsequent elevated serum levels of it, is associated with lower risk of coronary artery disease and cancer (Chung et al., 2001).

Thus, the present study is carried out to investigate the protective role of vitamin C as a powerful anti-oxidant on reducing the side effects of ceftriaxone via biochemical and histological analysis.

2. MATERIALS AND METHODS

Ceftriaxone vials were supplied by Smith Kline Beecham Egypt Pharmaceutical Co., each vial contains one-gram ceftriaxone in the form of ceftriaxone sodium.

Vitamin C was supplied by Kahira pharmaceutical Co., Cairo, Egypt in the form of tablets (each tablet contains 500 mg ascorbic acid). Tablets were prepared for oral administration to rats by being crushed into fine powder then dissolved in distilled water. Rats were obtained from Animal Breeding Unit, Faculty of Veterinary Medicine, Zagazig University, Egypt. The animals were kept under hygienic conditions in metal cages and fed on rodent diet and water was provided ad-libitum throughout the experimental period. Housing and management of the animals and the experimental protocols were conducted as stipulated in the Guide for Care and Use of Laboratory Animals Guidelines of the National Institutes of Health (NIH), and approved by the local authorities of Zagazig University, Zagazig, Egypt.

2.1. Experimental design

A total of 24 adult male albino rats of 10-12 weeks old and 160-180 g b. wt. were used in this study. After two weeks of acclimatization to the laboratory environment, the rats were randomly allocated into 3 equal groups, each of 8 rats. Group I (control group) was orally administered saline 1 ml/kg b. wt. by gastric tube once daily for 14 days. Group II (ceftriaxone treated group) in which rats were administered 1 ml saline orally by gastric tube once daily for the first 7 days then rats were administered intraperitoneal injection of ceftriaxone once daily for the next 7 days in a dose of (180 mg/kg b. wt.), calculated according to El-sayed et al. (2011a,b). Group III (vitamin C + ceftriaxone treated group):

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rats received a single oral dose of vitamin C by gastric tube once daily for the first 7 days in a dose of 100 mg/kg b. wt according to Sheweita et al. (2001) , and in the following 7 days , rats received the same oral single dose of vitamin C by gastric tube once daily and after two hours of taking it, rats were injected with ceftriaxone once daily intraperitoneally in a dose of (180 mg/kg b. wt.), calculated according to (El-sayed et al. 2011a; El-sayed et al. 2011 b).

2.2. Blood samples

Blood samples were collected from retro-orbital plexuses on 1st and 7th day post-treatment. The samples were placed in a slant position at room temperature and allowed to clot then centrifuged at 3000 RPM for 20 minutes to obtain clear serums which were then transferred to dry tubes by a means of micro-pipette then kept frozen at -20°C for biochemical analysis.

2.3. Biochemical analysis

Serum alanine and aspartate aminotransferase (ALT and AST) activities were determined according to the method of Reitman and Frankel (1957). Creatinine and urea levels were estimated according to the methods of Henry et al. (1974), Chaney et al. (1962) respectively. Malondialdehyde (MDA) was measured according to the method of Yagi (1994). Superoxide dismutase (SOD) and catalase (CAT) activities were determined according to the methods of Marklund et al. (1974) and Sinha (1972) respectively.

2.4. Collection of tissue specimens

Liver and kidney samples of rats were collected on 1st and 7th day post-treatment. The livers and kidneys were rapidly collected, cut into small pieces and immersed in 10% neutral formalin and kept for.

2.5. Histopathological studies

The histopathological examination of liver and kidney of rats was done according to the methods of Suvarna et al. (2013).

2.6. Statistical analysis

Data were expressed as the mean \pm standard error (SE). Differences between groups were determined by one-way analysis of variance (ANOVA). Post hoc testing was performed for intergroup comparisons using the Least Significant Difference (LSD) test, and a *P* value <0.05 was considered significant (Tamhane and Dunlop, 2000).

3. RESULTS

3.1. Biochemical findings

There were a significant increase in serum levels of ALT and AST activities in ceftriaxone treated group on both 1st and 7th day post-treatment when compared to the control group, while rats in the group treated with both vitamin C and ceftriaxone showed a significant reduction in serum level of ALT activity with non-significant changes of serum level of AST activity on 1st and 7th day post-treatment when compared to group II (Table 1).

There was a significant increase in serum level of urea in ceftriaxone treated group on 1st and 7th day post-treatment with a significant increase in serum level of creatinine on 1st day post-treatment when compared to the control group, while rats in the group treated with both vitamin C and ceftriaxone showed a significant reduction in serum level of urea on both 1st and 7th day post-treatment with a significant decrease in serum level of creatinine on 1st day post-treatment when compared to the ceftriaxone treated group (Table 2).

Group treated with ceftriaxone showed a significant increase in MDA concentration with a significant reduction in CAT and SOD activities on 1st and 7th day post-treatment when compared to the control group, while in groups treated with both vitamin C and ceftriaxone , there was a significant decrease in MDA conc. on both 1st and 7th day post-treatment with a significant elevation in CAT and SOD activities on 7th day post-treatment when compared to ceftriaxone treated groups (Table 3).

Table (1) Effect of vit. C (100 mg/kg b. wt. orally once daily) on the liver enzymes of ceftriaxone (180 mg/kg b. wt. I.P. once daily) treated male albino rats.

Groups	Liver Enzymes			
	1 st day post-treatment		7 th day post-treatment	
	ALT (U/L)	AST (U/L)	ALT (U/L)	AST (U/L)
Control	26.07 ^c ± 1.79	41.03 ^b ± 0.67	21.00 ^b ± 0.89	32.78 ^a ± 2.08
Ceftriaxone	53.27 ^a ± 1.18	49.43 ^a ± 3.96	28.83 ^a ± 2.61	35.23 ^a ± 3.14
Vit. C + Ceftriaxone	43.77 ^b ± 1.69	47.30 ^a ± 3.22	21.58 ^b ± 1.29	31.40 ^a ± 0.95

Means within the same column in each category carrying different superscriptions are significantly different at (p 0.05).

Table (2) Effect of vit. C (100 mg/kg b. wt. orally once daily) on the kidney function of ceftriaxone (180 mg/kg b. wt. I.P. once daily) treated male albino rats

Groups	Kidney function			
	1 st day post-treatment		7 th day post-treatment	
	Urea (mg/dl)	Creatinine (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)
Control	31.13 ^b ± 3.09	0.63 ^b ± 0.02	28.78 ^b ± 1.22	0.73 ^a ± 0.03
Ceftriaxone	70.53 ^a ± 2.51	0.98 ^a ± 0.06	38.88 ^a ± 3.20	0.81 ^a ± 0.04
Vit. C + Ceftriaxone	52.17 ^b ± 2.50	0.73 ^b ± 0.06	30.13 ^b ± 1.87	0.74 ^a ± 0.05

Means within the same column in each category carrying different superscriptions are significantly different at (p 0.05).

Table (3) Effect of vit. C (100 mg/kg b. wt. orally once daily) on the oxidative/ antioxidant status of ceftriaxone (180 mg/kg b. wt. I.P. once daily) treated male albino rats.

Groups	Oxidative / Antioxidant status					
	1 st day post-treatment			7 th day post-treatment		
	MDA (nmol/ml)	CAT (U/L)	SOD (U/ml)	MDA (nmol/ml)	CAT (U/L)	SOD (U/ml)
Control	4.90 ^c ± 0.40	139.50 ^a ± 3.52	30.27 ^a ± 2.65	6.35 ^b ± 0.38	129.38 ^a ± 1.50	36.93 ^a ± 0.58
Ceftriaxone	16.93 ^a ± 1.44	102.20 ^d ± 3.07	13.33 ^c ± 0.66	10.08 ^a ± 0.60	117.90 ^b ± 3.94	26.45 ^b ± 1.48
Vit. C + Ceftriaxone	10.03 ^b ± 0.78	119.00 ^{cd} ± 4.82	16.13 ^c ± 1.32	7.13 ^b ± 0.15	128.53 ^a ± 1.70	32.00 ^a ± 0.39

Means within the same column in each category carrying different superscriptions are significantly different at (p 0.05).

3.2. Histopathological observations

3.2.1. on 1st day post-treatment:

3.2.1.1. In control group: Kidney and liver sections of rats showed normal histomorphological structures (Fig.1&2).

3.2.1.2. In ceftriaxone treated group: Kidney sections revealed perivascular edema, degenerative changes mainly cloudy swelling and hydropic degeneration beside necrotic changes in some tubular epithelium. Mild cystic dilatation of some renal tubules

especially in the cortex was seen. Some glomeruli showed shrinkage with widening of the glomerular space. The renal pelvis and renal papillae appeared normal. Liver sections showed focal hepatic necrosis, hemorrhage and aggregation of neutrophils. An inflammatory zone separate the necrotic tissue from the healthy one ,moderate congestion of portal blood vessels, biliary hyperplasia and mild portal fibrosis were also seen (Fig.3&4).

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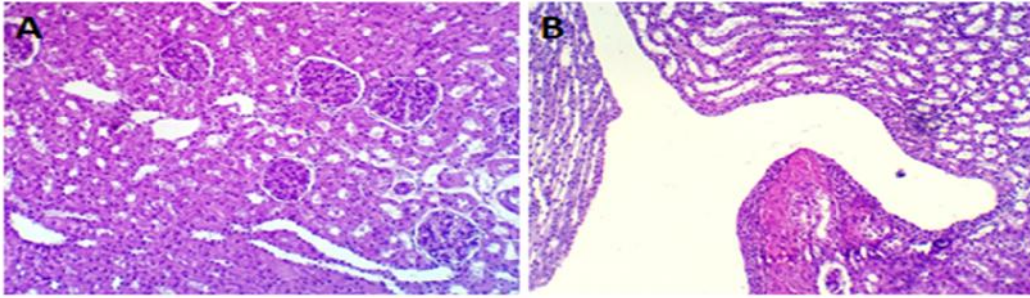


Fig.1: Photomicrograph from rats' kidney from the control group on 1st day post-treatment (A&B) showing normal histomorphological structures. (H&E) X 100

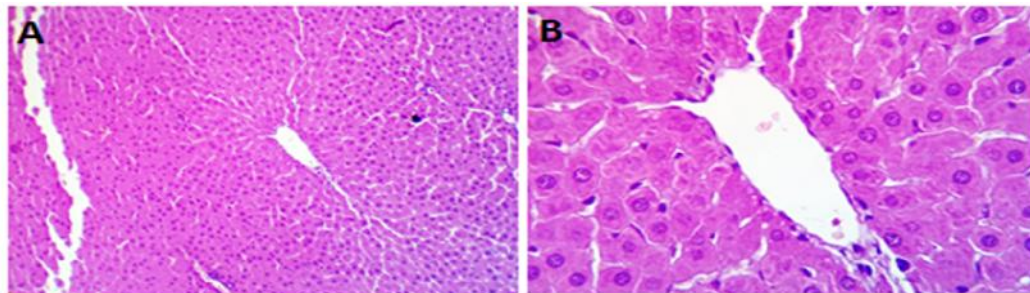


Fig. 2: Photomicrograph from rats' liver from the control group on 1st day post-treatment showing normal histomorphological structure. (H&E) X 100 (A) , 400 (B).

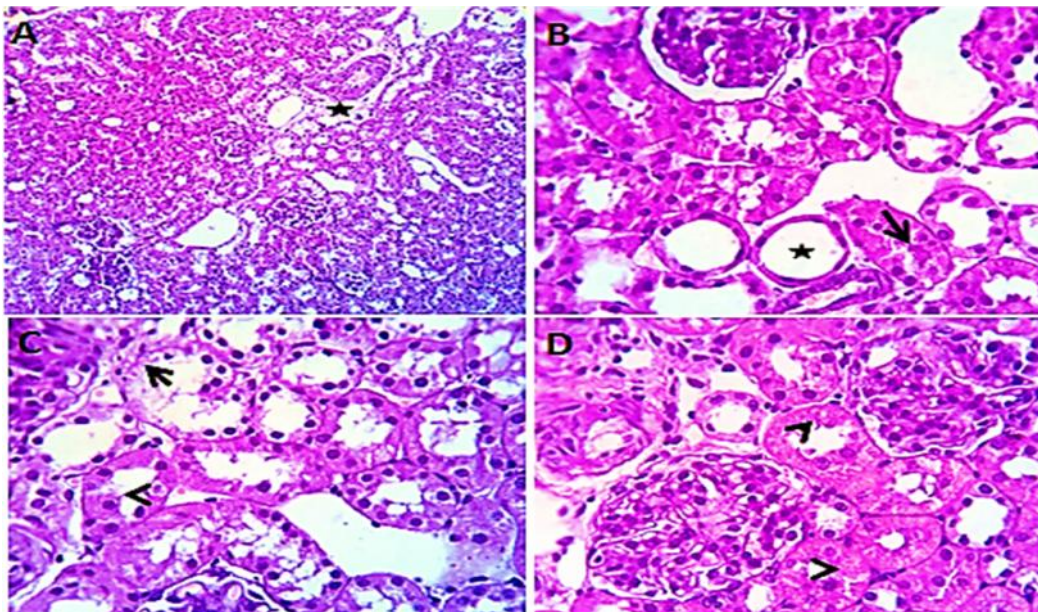


Fig.3: Photomicrograph from rats' kidney of group treated with ceftriaxone on 1st day post-treatment showing (A) perivascular edema (star), (B) mild cystic dilatation of some renal tubules (star) with Hyaline casts (open arrow). (C&D) Degenerative changes mainly cloudy swelling and hydropic degeneration (arrow heads) besides necrotic changes (open arrow) in some renal tubular epithelium. (H&E) X 100(A) , 400 (B,C,D).

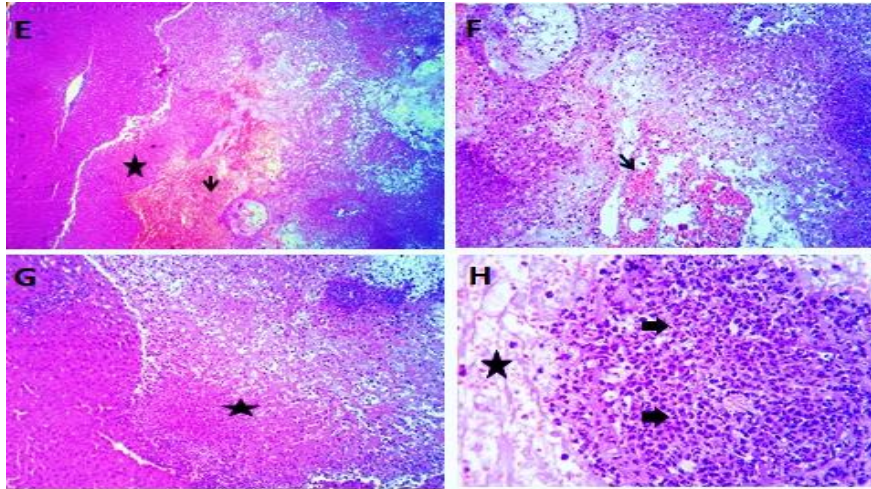


Fig. 4: Photomicrograph from rats' liver of group treated with ceftriaxone on 1st day post-treatment showing focal hepatic necrosis (star), hemorrhage (open arrow) and aggregation of neutrophils (closed arrow).(H&E) X 100 (E,F,G), 400 (H).

3.2.1.3. In vitamin C + ceftriaxone treated group: Kidney sections revealed cystic dilatation in a moderate number of renal tubules especially in the cortex, degenerative changes in some renal tubular epithelium, mild congestion of renal blood vessels together with mesangial cell proliferation in some glomeruli. Liver sections showed that

most of the hepatocytes were apparently normal. The portal blood vessels were moderately congested. The portal triads showed moderate biliary proliferation and round cell infiltration. Such cells were aggregated interstitially (small aggregation) (Fig.5&6).

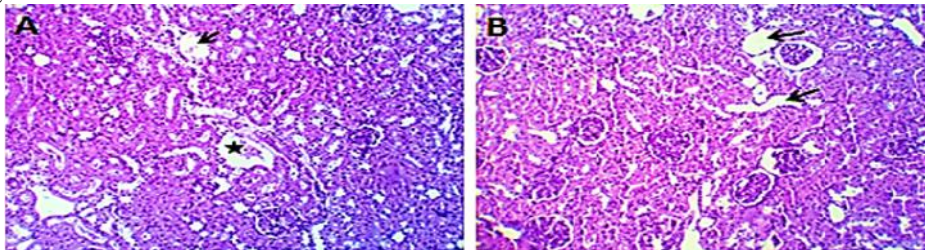


Fig. 5: Photomicrograph from rats' kidney treated with ceftriaxone and vitamin C on 1st day post-treatment showing cystic dilatation in-renal tubules (open arrows)and congestion of renal blood vessels (star). (H&E) X 100.

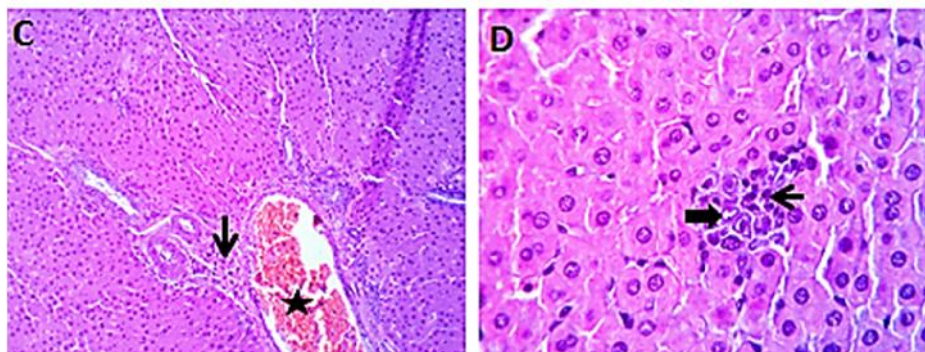


Fig. 6: Photomicrograph from rats' liver treated with ceftriaxone and vitamin C on 1st day post-treatment showing moderately congested portal blood vessels (star), the portal triads showing round cell infiltration (open arrow) (D) Such cells are aggregated interstitially (small aggregation) mainly lymphocytes (open arrow) and macrophages (closed arrow). (H&E) X 100(A), 400(B)

3.2.2. on 7th day post-treatment:

3.2.2.1. In control group:

The examined kidney sections revealed normal glomeruli, renal tubules, papillae and renal pelvis. Liver sections showed normal histomorphological structures (Fig.7&8).

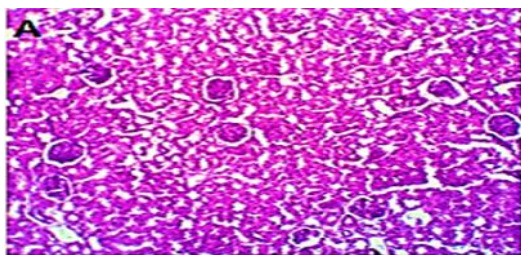


Fig. 7: Photomicrograph from rat's kidney of the control group on 7th day post-treatment showing normal histomorphological structure. (H&E) X 100.

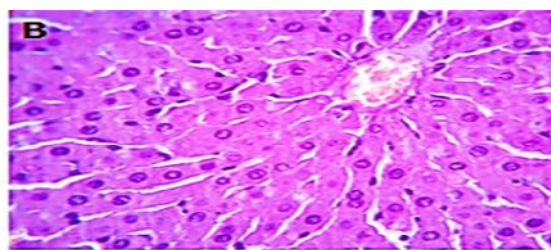


Fig.8: Photomicrograph from rat's liver of the control group on 7th day post-treatment showing normal hepatic morphology. (H&E) X 400.

3.2.2.2. In ceftriaxone treated group: Kidney sections showed moderate cystic dilatation in the collecting tubules of the renal medulla with degenerative changes in some tubular epithelium. Mesangial hypertrophy in some glomeruli, mild perivascular edema and mild interstitial lymphocytic infiltration were detected. The proximal renal tubule suffered from hydropic degeneration and cloudy swelling with cystic dilatation in some of them. Liver sections revealed moderate congestion of hepatic blood vessels and mild biliary hyperplasia and fibrosis. Hydropic degeneration in a few hepatocytes beside fatty change were also noticed. Other hepatocytes appeared normal (Fig. 9&10).

3.2.2.3. In vitamin C + ceftriaxone treated group: Sections from kidneys revealed mild congestion of renal blood vessels, cystic dilatation in a few proximal tubules with

flattened epithelial lining beside degenerative changes (mostly cloudy swelling). Hyaline casts were also detected within some renal tubules. The glomeruli, other renal tubules, papillae and renal pelvis appeared with normal histo-morphological structures. Liver sections showed apoptosis in a few number of hepatocytes besides degenerative changes mainly hydropic degeneration. The portal triads showed normal structure with very little round cell infiltration. The kupffer cells were hypertrophied. Most of the hepatocytes were apparently normal (Fig.11&12).

4. DISCUSSION

Ceftriaxone is a known antibacterial drug which is active against wide variety of gram-positive and gram-negative bacteria (El-sayed et al. 2011a). Ceftriaxone can produce serious adverse effects such as respiratory system disorders, elevations in liver enzymes, elevations of bilirubin and creatinine levels, skin and appendages disorders or sometimes anaphylactic shock and some less common side effects such as diarrhea, , nausea, vomiting, itchiness, dizziness, headache and rash (El-sayed et al. 2011b).

Vitamin C is a very potent antioxidant that can inhibit inflammation and reduce the side effects of chemotherapeutic treatment (Jacobs et al., 2015). The current study is carried out to investigate the effect of vitamin C on adverse effects of ceftriaxone.

The current investigation revealed that administration of ceftriaxone to rats produced a significant increase in ALT and AST activities, and since the elevation of these liver enzyme activities is an indicator to cellular leakage and loss of the functional integrity of the cell membranes in liver, so ceftriaxone can badly affect the liver causing hepatocellular damage (Mansour and Mossa, 2010).

The increase in liver enzymes (ALT and AST) is suggested to be as a result of the recorded histopathological changes of liver tissue.

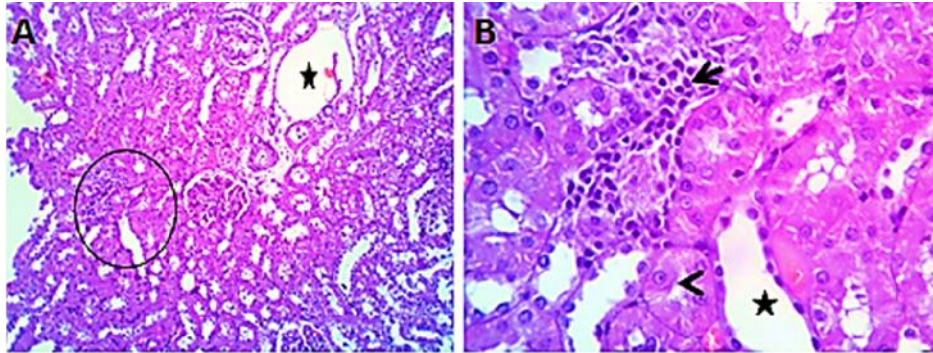


Fig.9: Photomicrograph from rat's kidney of the ceftriaxone treated group on 7th day post-treatment (A&B) showing cystic dilatation of some collecting tubules (star) ,degenerative changes in the renal tubular epithelium mainly cloudy swelling (arrowhead)and mild lymphocytic infiltration (open arrow). (H&E) X 100(A) ,400(B).

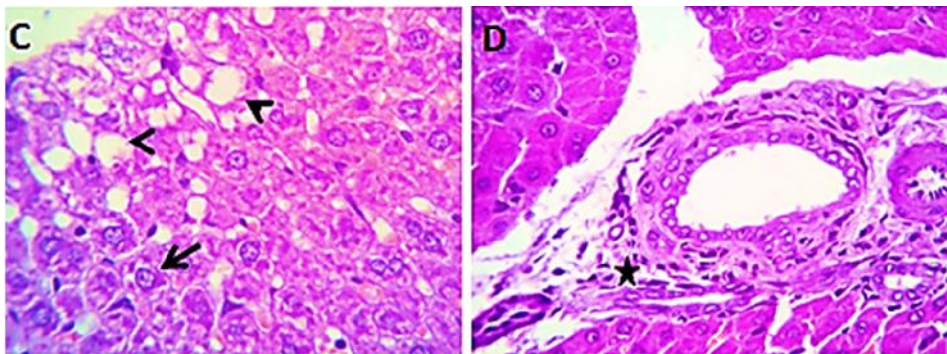


Fig.10: Photomicrograph from rat's liver of the ceftriaxone treated group on 7th day post-treatment (C&D) showing mild biliary hyperplasia and fibrosis (star), hydropic degeneration in a few hepatocytes (open arrow) besides fatty change (arrowhead) (H&E) X 400.

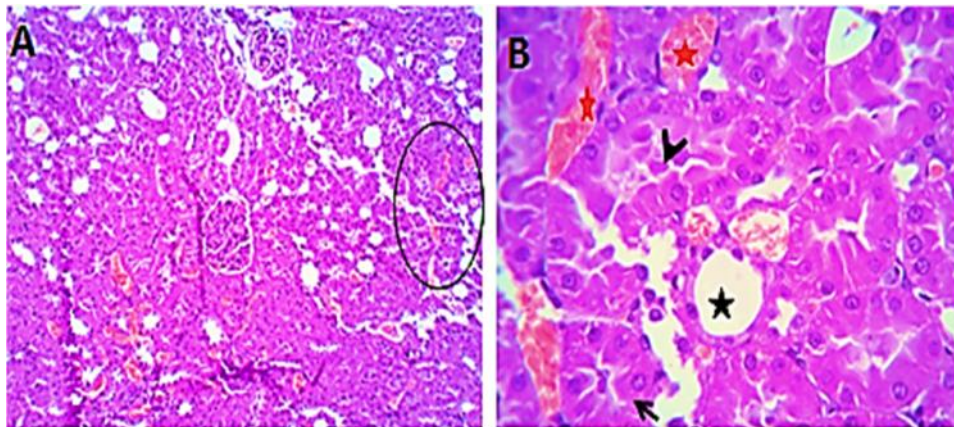


Fig.11: Photomicrograph from rat's kidney of the group treated with ceftriaxone and vitamin C on 7th day post-treatment (A&B) showing mild congestion of renal blood vessels (red stars), cystic dilatation of a few proximal tubules (black star) ,hyaline casts within some renal tubules (arrow head) besides degenerative changes mostly cloudy swelling(open arrow). (H&E) X 100(A), 400(B).

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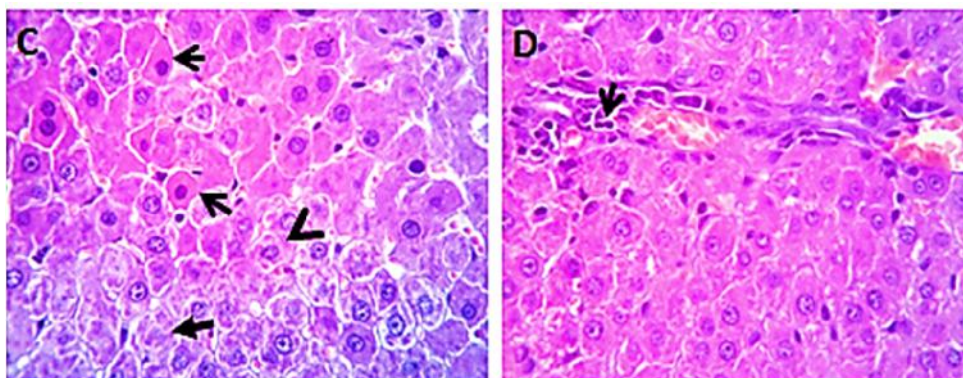


Fig.12: Photomicrograph from rat's liver of the group treated with ceftriaxone and vitamin C on 7th day post-treatment (C&D) showing apoptosis (open arrow) in a few number of hepatocytes, degenerative changes mainly hydropic degeneration (arrowhead) besides a few round cell infiltration (open arrow) in the portal triad. (H&E)X 400.

In the current investigation, it was revealed that vitamin C administration to rats has significantly ameliorated the adverse effect of ceftriaxone on liver, reflected by the reduction in the serum level of liver ALT enzyme activity. Similarly, Abu-Sheir (2016), demonstrated the ameliorative effect of vitamin C on adverse effects of Diazinon on liver tissues causing a significant decrease in the serum ALT and AST levels in adult male albino rats.

Vitamin C is suggested to have the ability to suppress oxidative stress and promote the anti-oxidant capacity of cells inhibiting lipid peroxidation and markers for hepatic damage (e.g. alanine aminotransferase and aspartate aminotransferase).

In the current investigation, the ceftriaxone treated rats exhibited a significant increase in urea and creatinine levels than the control ones. Similar findings were reported by Francioli et al.(1995), who observed an increase in serum level of creatinine in patients treated with ceftriaxone. The increase in serum level of urea and creatinine are supposed to be a significant indicator to kidney dysfunction (Marks and Lieberman, 2009).

In an explanation to the above obtained results, a previous study reported that ceftriaxone has the ability to cause renal damage directly through its toxic effect on the renal tubules as a result of hypersensitivity-induced interstitial nephritis or indirectly through enhancing the effect of

nephrotoxic agents. Also, some cases were reported of impaired renal function following ceftriaxone treatment (Alesbe et al., 1984).

The present data demonstrated that the use of vitamin C has significantly reduced the serum urea and creatinine levels of ceftriaxone treated rats thus enhancing our theory, showing the protective effect of vitamin C on ceftriaxone side effects.

Djeffal et al. (2015), reported that ascorbic acid supplementation to rats has significantly inhibited the renal-induced toxicity markers. Also, Abdel-Daim and El-Ghoneimy (2015), found that the pre-administration of vitamin C to animal models has significantly decreased the serum parameters of kidney injury and also protected the renal tissues from oxidative damage.

The protective effect of vitamin C against ceftriaxone-induced renal injury is suggested to be through inhibition of the induced oxidative stress in renal tissues that may have been either directly via scavenging free radicals or indirectly through potentiation of the enzymatic free radical scavenging system inside the cells.

One of the most important results in this study was revealed in measuring rats' serum oxidative / antioxidant status in which ceftriaxone was proved to cause oxidative stress represented by an increase in MDA concentration (representing oxidative stress damage) with a significant decrease in the activities of the antioxidant enzymes (CAT and SOD). Vitamin C was proved to be an efficient antioxidant reducing oxidative

damage with an obviously reduced MDA concentration and increased activities of CAT and SOD enzymes that participate in modulating oxidative stress.

These results were reinforced by Alhumaidha et al. (2014), who reported an increase in MDA concentration in ceftriaxone treated rats. In addition, Sirmali et al. (2015), recorded an elevation in CAT activity following ascorbic acid treatment in rats with induced renal injury by the ischemia-reperfusion of the hind limbs.

In this current study, ceftriaxone administration to rats caused an obvious hepatic and renal damage represented by necrosis in both hepatocellular tissues and renal tubules, portal fibrosis, inflammation, congested renal blood vessels and glomerular changes.

These results are reinforced by Alhumaidha et al. (2014), who found that, in the ceftriaxone 180 mg/kg b. wt. treated rats, the histopathological examination of liver showed an obvious hepatocyte degeneration of the peripheral zone with shrunken, dark nuclei (pyknosis).

In the present study, supplementation of vitamin C to ceftriaxone treated group has dramatically attenuated the histopathological changes of liver and kidney tissues of rats. In an explanation to these results, vitamin C was previously proven as a potent antioxidant. Thus, it may have acted directly on the hepatic and renal tissues via scavenging free radicals or indirectly via enhancing the natural antioxidant enzyme system of the body.

The current data is in agreement with a very recent study done by Morikawa et al. (2018), who found that vitamin C supplementation to mice reduced the quantitative histopathological measurements caused by oxidative stress. Also, Mazreku et al. (2017), proved the protective action of ascorbic acid on kidney and liver of mice exposed to lead toxicity.

6. CONCLUSIONS

The current study concluded that vitamin C ameliorates the biochemical and

histopathological changes associated with ceftriaxone treatment in rats.

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