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Histological Evaluation of L-Carnitine's Ability to Restore kidney Architecture Following Ceftriaxone Toxicity

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Abstract

Background: Ceftriaxone (Ce) (a third-generation antibiotic) treats severe bacterial infections. it has been reported to induce rare toxic effects on the kidneys, But L-carnitine (Lc) (a naturally occurring antioxidant) is highly effective for renal protection in experimental studies via antioxidant activity.

Objective: The purpose of this study was to assess the nephrotoxic effect of high dose long-term ceftriaxone therapy in a rat model and to determine whether this effect could be prevented by a natural antioxidant, L-carnitine.

Methods: A total of 40 adult male Wistar rats (250-300g body weight) were divided into four groups (n=10) as follows: a Control group that was administered distilled water; a Ceftriaxone (CE) group that received daily injections of ceftriaxone (250 mg/kg body weight/day); a CE+LC group that received daily injections of ceftriaxone (250 mg/kg body weight/day) plus oral L-carnitine (600 mg/kg body weight/day); and an LC group that was administered L-carnitine (600 mg/kg body weight/day). Animals were treated for 30 days. After 30 days of treatment, Renal tissues were collected for histopathological analysis using Hematoxylin and Eosin (H&E) staining, to assess morphological alterations .

Results: Treatment with ceftriaxone (CE group) significantly ($p < 0.05$) increased Cr and BUN levels measured in serum compared with the control group, indicating renal dysfunction. Pathological examination of the kidney tissues in the CE group showed severe tubular necrosis, cast formation and inflammatory cells. Pre-treatment with L-carnitine (CE+LC group) significantly improved the side effects, as demonstrated by significantly reduced Cr and BUN and largely maintained kidney structure. The L-carnitine-treated (LC group) showed normal biochemical parameters and healthy histology similar to a normal control group, suggesting that the dose used is safe.

Conclusion: Prolonged ceftriaxone exposure induces significant nephrotoxicity in rats. L-carnitine supplementation demonstrates a potent protective effect against this injury, suggesting it could be a

promising adjunct to mitigate nephrotoxicity risk during long-term ceftriaxone therapy, warranting further clinical investigation.

Keywords: Ceftriaxone; Nephrotoxicity; L-Carnitine; Renal Function; Oxidative Stress; Acute Kidney Injury; Histopathology; Rat Model.

Introduction

Cephalosporins are β-lactam antibiotics used in the treatment of different infections of gram-positive and gram-negative bacteria. Cephalosporins are classified into 5 generations based on their activity against gram-positive/negative bacteria and year of discovery. (Bui, et al., 2024). The most widely used cephalosporins are from the third generation. They are semisynthetic cephalosporins that have varying substitutions on the C7 acylamido chain. (Arumugham, et al., 2023). Being a third-generation cephalosporin, its unique characteristic is once-a-day administration making it safe for intramuscular and intravenous administration in outpatients and Ceftriaxone is resistant to β-lactamases, so it's commonly used over first generation and second generation cephalosporins (Gelaw et al., 2022).

The common infections diagnosed are; pneumonia, sepsis, for surgical prophylaxis, meningitis, and urinary tract infection, Ceftriaxone is rightly indicated in a median of 39.2% of surgical patients (Bishaw, et al., 2021). Ceftriaxone has been developed for clinical use for over 30 years. (Duncan, et al., 2021). ceftriaxone can lead to life-threatening conditions with serious CNS ADRs and even death. (Lacroix, et al., 2021). Ceftriaxone decreases gallbladder and ileum motility. ceftriaxone leads to biliary sludge and pseudolithiasis, Ceftriaxone significantly increases small intestine transit time, large intestine transit time and total intestinal transit times. (Arpacık, & Yıldız., 2023). When using ceftriaxone for patients that have been irradiated to the brain, we saw some side effects,as ceftriaxone decreased the index of the glial fibrillary acidic protein (GFAP) immunostaining, and decreased the brain levels of malondialdehyde (MDA) and tumor necrosis factor alpha (TNF-α). (Cini, et al., 2025).

The third-generation cephalosporin, ceftriaxone, is used to treat bacterial infections in dialysis patients because of its long half-life, broad spectrum and is not reduced in dose. But renal failure is one of the risk factors of ceftriaxone pseudolithiasis that has been scarcely reported in patients on hemodialysis. (Oyama, et al., 2021).

Ceftriaxone is readily soluble as a salt of sodium. But it can form an insoluble complex with calcium ions to become a ceftriaxone-calcium salt which can precipitate in the urinary tract (also called urolithiasis). Although this kind of urolithiasis is uncommon, ceftriaxone-induced urolithiasis can cause serious adverse effects such as acute kidney injury (AKI). (Yifan et al., 2020).

Carnitine (3-hydroxy-4-N-trimethylaminobutyrate) is an amino acid derivative and a micronutrient with a major role in intermediary metabolism as it is the most important carrier of long-chain fatty acids from the cytosol to the mitochondrial matrix, the site of fatty acid β-oxidation. Carnitine is also known to maintain membrane integrity, maintain a physiologic coenzyme A (CoASH) /-acetyl CoA ratio in mitochondria and decrease lactate levels. (Gnoni et al., 2020). Carnitine is a natural antioxidant that resides in the seminal plasma of all mammals which scavenges the reactive oxygen species (ROS) it suppresses sperm membrane lipid peroxidation, and preserves the membrane itself (Nazari et al., 2021).

demonstrated that LC improves the activity of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase and the total antioxidant capacity. It has been reported that LC improves renal function via amelioration of oxidative damages and the anti-oxidant defensive system, and it was further suggested that L-carnitine supplementation or nutritional therapy may have some benefit in patients suffering from chronic renal failure (Sharma, & Yadav, 2023).

L-carnitine plays a vital role in fatty acid β oxidation and mitochondrial energy production. Kidney and dialysis patients are deficient due to decreased endogenous synthesis, disturbed fatty acid metabolism, decreased intake (dietary restrictions) and also due to non-specific loss through the dialysis process. Free carnitine concentrations are <40 μmol/L in dialysis patients, leading to complications of dialysis including a low level of anemia that is resistant to treatment with erythropoietin, intradialytic hypotension, cardiovascular disease and skeletal muscle dysfunction with muscle weakness and fatigue. L-carnitine deficiency also occurs in acute kidney disease (AKD) due to trauma and/or ischemia, medicines like cisplatin and infections such as covid. L-carnitine deficiency can further renal injury and result in multiple organ dysfunction syndrome (MODS). (Ulinski, et al., 2023).

Existing literature demonstrated the capacity of Ceftriaxone (Ce) to restore kidney function and ameliorate nephrotoxicity caused by cadmium, cyclosporine A, tobramycin and isepamicin according to its anti-lipid peroxidative, anti-inflammatory and anti-oxidative activities. (Hakimizadeh et al., 2020). The research highlights the antioxidant properties of L-carnitine and its ability to safeguard kidneycells from oxidative stress, proposing its use as a supplementary therapeutic or preventive agent during extended or high-dose antibiotic therapy.

Material and methods

2.1. Animal

The present research is shown on fourty adult healthy male rats' weight between 225-250 grams. The rats housed in distinct cages under area temperature (30 ±3°C), and humidity (62 ± 5%) with natural light/dark cycle, and had ad libitum appetizer to standard pellet fare and water throughout the study.

2.2. Design of study

Forty rats are randomly divided into four groups, each group consisting of 10 animals. After that, the animals are. The first group is the control, the second group is treated with ceftriaxone, the third group with ceftriaxone and L-carnitine, and the fourth group is treated with L-carnitine for 30 days. After that, take a sample from the kidney of all rats.

- The control group was given an oral dose of distilled water.
- Group 2: received 250 mg/kg ceftriaxone injections (daily) for 30 days.
- Group 3: injected with ceftriaxone250 mg/kg, and given the Oral dose 600 mg/kg b. w daily (Carnitine) for 30 days.
- Group 4: Orawnal dose 600 mg/kg b. w daily (Carnitine) for 30 days.

2.3 Histological examination

The histopathology work is performed according to the method (Bancroft and Suvarna., 2021), where a sample is removed from the kidney of an animal's tissue and it undergoes a series of steps (fixation,

washing, dehydration, clearing, infiltration, embedding, cutting, staining using hematoxylin -eosin stain) and the slides will be viewed by a light microscope to get an image.

Result

Histological analysis of the normal kidney demonstrates that the organ is enclosed by a delicate connective tissue capsule. Internally, it is organised into two main regions: the cortex and the medulla, with the medulla forming conical structures known as renal pyramids. The functional units, the nephrons, are clearly identified and consist of the renal corpuscles together with their associated tubular components including the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule (Figure 1) (Junquiera, 2021).

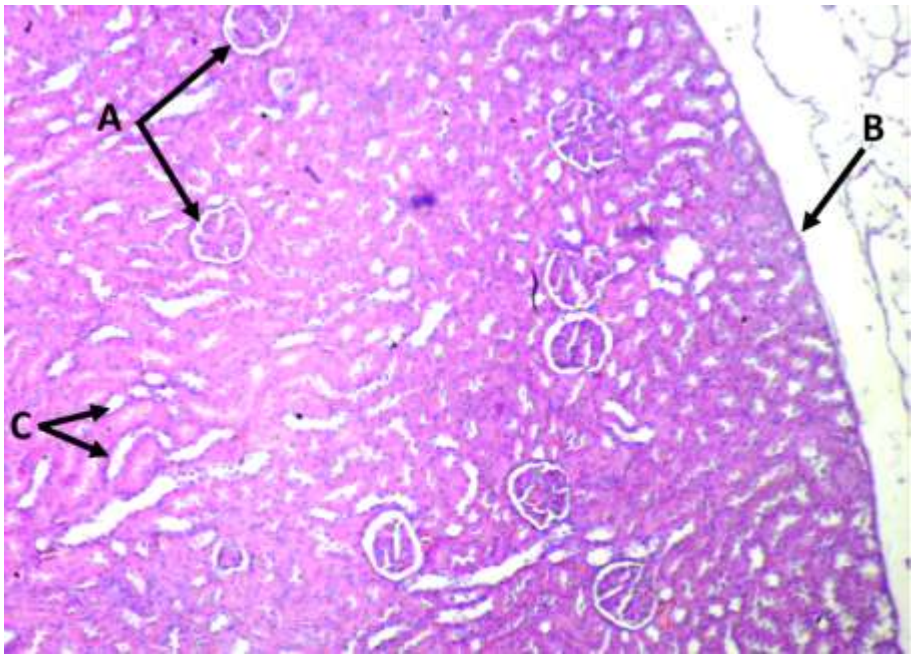

Figure 1: Light micrograph represented the kidney of control group appeared normal renal capsule (A), normal capsule(B) and normal renal tubules (C) 10X H&E

Histological examination of renal tissues exposed to ceftriaxone (250 mg/kg/day for 30 days) revealed evident distortion of the renal cytoarchitecture. There was an apparent hypercellularity in the glomeruli due to cellular proliferation of endothelial cells, accompanied by infiltration of inflammatory cells. Several of these cells appeared degenerated or necrotic, and cellular debris was observed within the lumina of renal tubules. The glomeruli demonstrated shrinkage and signs of glomerular cell necrosis. Tubular cells exhibited degenerative changes Degenerated tubules showed detachment of epithelial cells from the basement membrane, the tubular lumina were partially or filled with cellular exudates, and there was an accumulation of amyloid in tubules. The cytoplasmic vacuolations were obvious, and many nuclei of tubular epithelial cell showed karyolysis, pyknosis, or fragmentation that resulted due to the late phase of necrosis. These features were accompanied by a reduced density of parenchymal cells and marked cytoplasmic and nuclear changes, suggesting severe toxic changes in the kidney by ceftriaxone (Figure 2, 3, and 4).

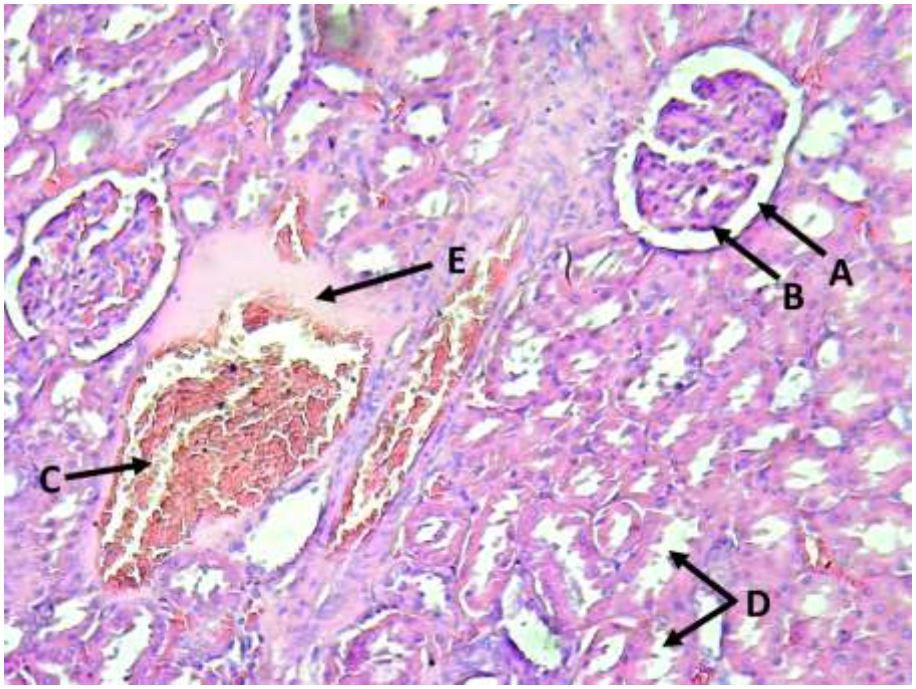

Figure 2: Light micrograph represented the kidney of rat exposed to 250 mg/kg of ceftriaxone daily for 30 days, appeared distention of the capsular spaces of Bowman's capsule (A) glomerulus atrophies (B), higher congestion of blood vessels(C)and convoluted-tubule degeneration (D), accumulation of amyloid (D) (20X).

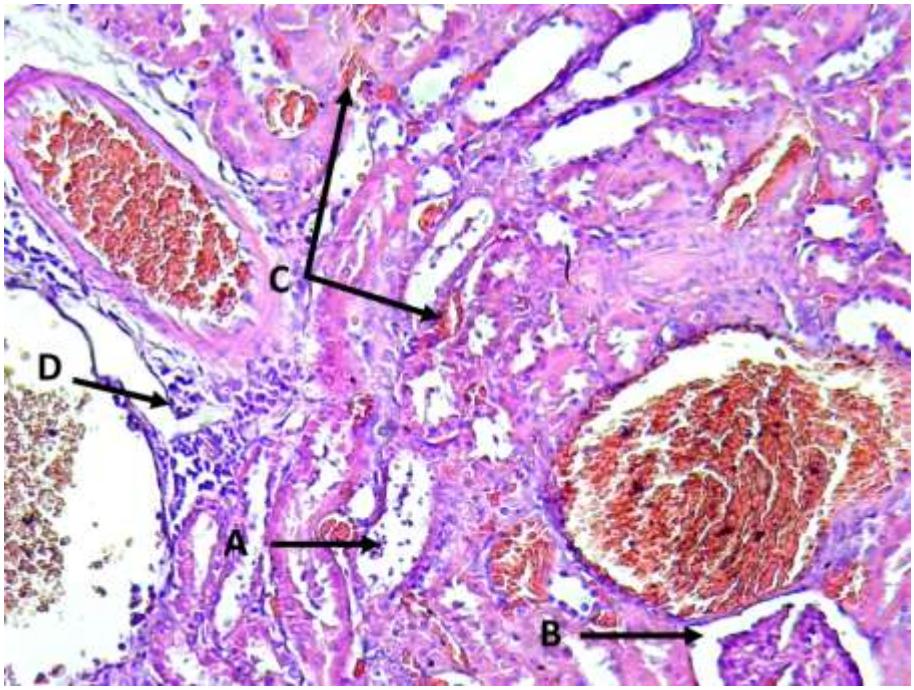

Figure 3: Light micrograph represented the kidney of rat exposed to 250 mg/kg of ceftriaxone daily for 30 days appeared distortion of the renal cytoarchitecture, degeneration cellular exudation filled the luminal

tubules (A) distention of the capsular spaces of Bowman's capsule (B), and hemorrhages between renal-tubular (C), higher percentage of inflammatory cells (D) (20X)

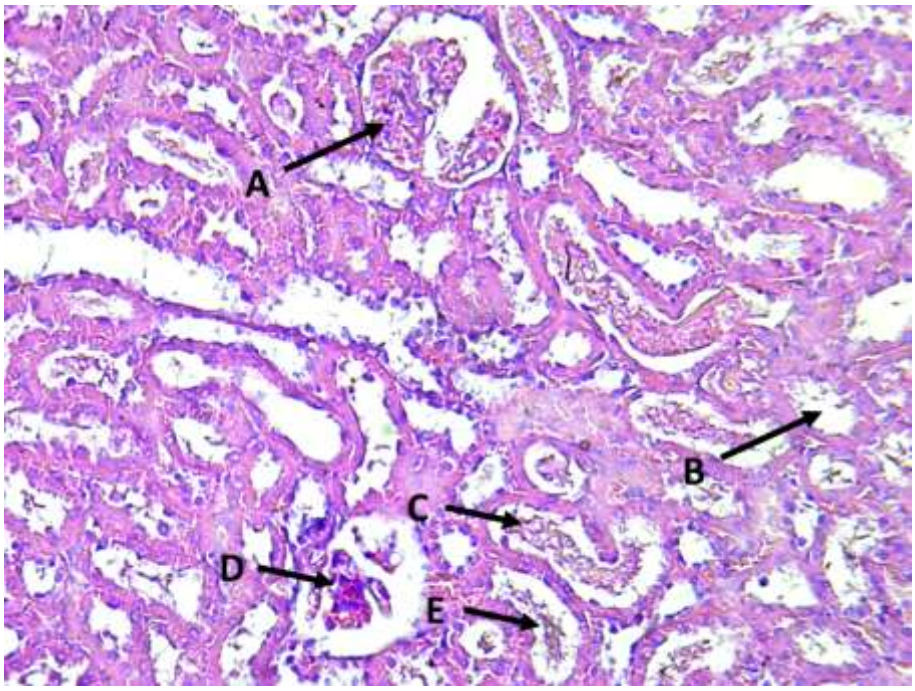

Figure 4: Light micrograph represented the kidney of rat exposed to 250 mg/kg of ceftriaxone daily for 30 days hypercellularity in the glomeruli (A), decreased cellular necrosis, cellular debris within the lumina of renal tubules (B), high glomerulus atrophies (B), detachment of epithelial cells from the basement membrane (C) (20X).

Carnitine 600 mg/kg treatment demonstrated improvement in the renal tissue damage caused by the treatment with ceftriaxone 250 mg/kg of the experiment. This contained fewer glomerulus congestions, mild levels of changes of the parenchymal cell cytoplasm and nuclei, mild degrees of the glomerulus atrophies, and some improvement in the cellular structure, less spaces of Bowman's capsule and reduced cellular necrosis. Moreover, repaired low intensity of glomerulus cellularity and an improvement of the renal congestion were observed. In addition, low intensity of the renal-tubular hemorrhages, and low glomerulus congestions were observed when compared to the (ceftriaxone group) (Figure 5).

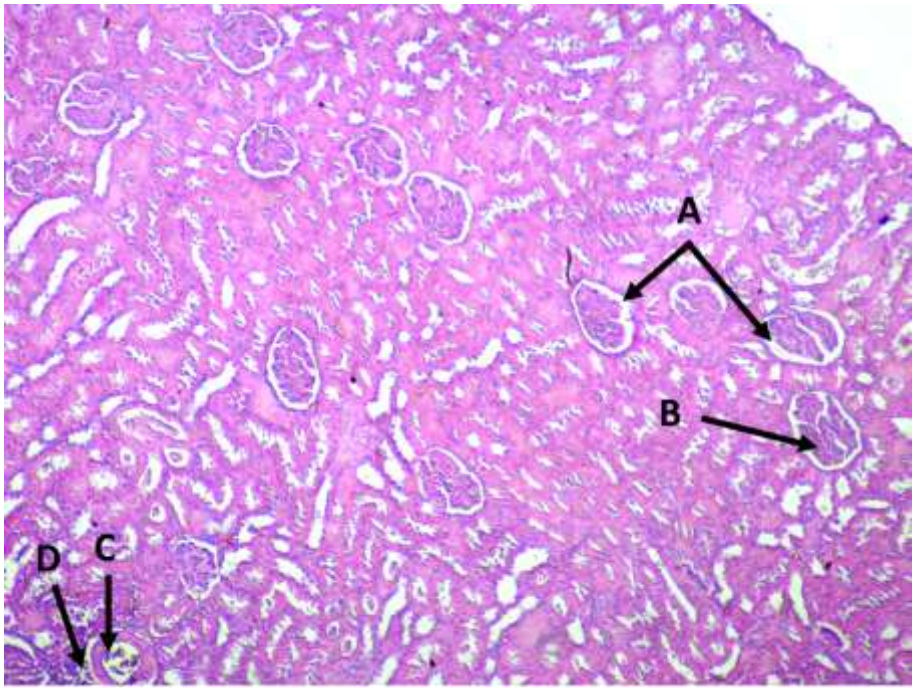

Figure 5: Light micrograph of kidney of rat exposed 250 mg/kg of ceftriaxone daily for 30 days and 600 mg/kg b. w daily and (Carnitine) for 30 days appeared, less distention of the capsular spaces of Bowman's capsule (A) decrease of glomerulus atrophies (B), decrease of congestion of blood vessels(C) and less of inflammatory cells (D) (H&E10 X).

For a normal kidney, carnitine intake does not cause pathological changes in the properties of its parts. Instead, the kidney exhibits superior elasticity. Carnitine helps maintain the normal structure and filtration function of the glomeruli, which appear intact and show no signs of hardening, inflammation, or cellular necrosis. Carnitine enhances the kidney's antioxidant defense system and prevents the transformation of tubular cells into fibroblasts. It does not cause any congestion or deposits in the interstitial tissues and collecting tubules (Figure 6).

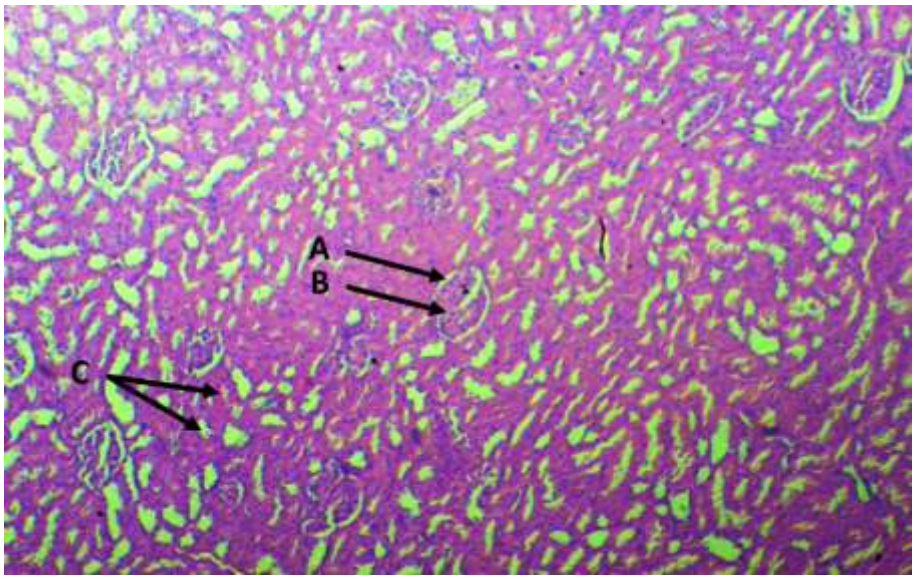

Figure 6: Light micrograph represented the kidney of rat administration with 600 mg/kg b. w daily (Carnitine) for 30 days appeared normal renal capsule (A), normal capsule and normal renal tubules (B) 10X H&E.

Discussion

These observations are corroborated by those of Zou et al. (2023), who indicate that ceftriaxone TEM examination of the kidney from the showed typical glomerular changes represented by diffusely unevenly thickened glial basement membrane and foot process fusion or effacement; mild thickening of the gbm and foot process fusion. Similarly, Hakimizadeh et al. (2020), suggest that Ceftriaxone (Ce) is an antioxidant and anti-inflammatory agent in various tissues including brain, kidney and liver. In addition, CTX has free radical scavenging properties, This is in complete agreement with the results of our present study. And in another study by Yifan et al. (2020), H&E staining also revealed kidney morphological changes with severe edema, inflammatory cell infiltration, swelling and even cell necrosis of renal tubular cells. Furthermore, the study conducted by Oyama et al. (2021), confirms that prolonged administration of ceftriaxone may cause a condition known as pseudocalcidia, which is common in patients with kidney failure. In the study he conducted Yifan et al. (2020), Regarding the effect of ceftriaxone crystals on stimulating the inflammatory response, An increase in protein expression in kidney tissue, was observed, along with increased phagocytic cell infiltration into the kidney tissue and inhibition of cell death caused by crystals. The study showed that Scr (Serum Creatinine) and BUN (Blood Urea Nitrogen) levels were significantly elevated and in agreement with the morphological changes and kidney stones. The study conducted by El-Sayed etal. (2011) also confirms what regarding the many indications of the effect of ceftriaxone on kidney tissues and its causing glomerular congestion, Bowman's space enlargement, changes in the proximal tubules, tubular dilation and necrosis, and interstitial edema. In this study by Dayana et al. (2020) we describe the effect of ceftriaxone on plasma, erythrocyte and tissue TBARS (Thiobarbituric Acid Reactive Substances) levels in rats. If ceftriaxone significantly increases the plasma, erythrocyte, and tissue TBARS (Thiobarbituric Acid Reactive Substances) in comparison to control, ceftriaxone is considered to be an inducer of lipid peroxidation. Wang. (2017), His study also confirms that the use of ceftriaxone in some severe cases may lead to acute kidney failure as a result of tubal obstruction by crystals. Histological sections reveal tissue degeneration, inflammatory cell infiltration, tubular epithelial necrosis, and congestion of renal blood vessels. The renal corpuscles lose their normal architecture, with shrinkage or swelling of the glomeruli, while the proximal and distal convoluted tubules display cytoplasmic vacuolization, epithelial desquamation, and, in some cases, tubular lumen obstruction accompanied by interstitial edema. Signs of cellular apoptosis are also evident, including nuclear condensation and increased caspase-3 activity, These changes are in line with Campbell et al. (2023), who describe the antibiotic-induced nephrotoxicity, where renal injury is associated with organelle destruction, lysosomal swelling, and mitochondrial vacuolation, alterations that precede functional disturbances such as proteinuria, elevated serum urea, and increased creatinine levels ultimately leading to acute kidney injury. It seems the main site of ceftriaxone-induced injury is the proximal tubules in the renal cortex where the drug is taken up and retained within the tubular cells, particularly in the lysosomes. Increasing the duration of administration or plasma concetrations of the drug increase the uptake, thus increasing duration of the drug in cells and the severity of nephrotoxic effect.

Our findings are in line with those of Zhang et al. (2020), who described exposure to ceftriaxone (200 mg/kg) in Wistar rats resulted in increased plasma urea and creatinine, decreased hepatic glutathione levels, and increased malondialdehyde level, and extensive tissue damage in kidney and liver. Antibiotics are able to enhance the generation of free radicals, further cause oxidative stress in the tissues, including nephrotoxic in the kidney. In particular ceftriaxone has been shown to elevate reactive oxygen species (ROS), levels and compromise the antioxidant defence system in renal cells especially in vulnerable proximal tubular epithelial cells. Such oxidative damage can impair glomerular basement membrane integrity, disrupt tubular function, and degrade extracellular matrix components.

The remedial effect of L-carnitine on toxic effect renal tissue was described by many authors, Salem et al (2019) noted L-carnitine and its derivatives prevent the formation of reactive oxygen species (ROS) and protect cell against free radical damage lipid peroxidation and oxidative stress. (Akbaribazm et al., 2021) refferes to use of carnitaine as antioxidants is the most important solution to counteract aminoglycoside-induced damages caused by ROS. In addition they have been well tolerated and effective against the nephrotoxic effect of ROS. Dennis and Witting (2017) they found that the antioxidants L-carnitine have the potential to avert or mitigate kidney injury if they are able to target the early events in the process by attacking either the radicals or the oxidant source. Research on kidney cells, kidney tubules and animal models of AKI have shown reno-protective factors that have antioxidant effects that reduce renal oxidative stress.

Kunak et al. (2016) stressed L-Carnitine's protective effects against kidney damage, showing that in rats with contrast-triggered nephropathy, it reduced dysfunction indicators by ramping up antioxidant enzymes and dropping malondialdehyde levels—a clear sign of its antioxidant power. Similarly, Lee et al. (2022) found that L-Carnitine has an anti-oxidative effect in the mitochondria of kidney tubular cells, decreasing the production of reactive oxygen species, improving mitochondrial functions, and inhibiting cell death. This agrees with our finding that L-Carnitine supports the health of kidney cells, and reduces toxin-induced kidney damage.

Conclusions

Here, we showed ceftriaxone caused substantial histophatological changes in rats with L-carnitine providing substantial protection against these phenomena, likely explained by its antioxidant and anti-inflammatory properties. This evidence confirms L-carnitine may be an effective and safe supplement to reduce renal damage incurred during ceftriaxone treatment.

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