EFFECT OF L-CARNITINE ON CISPLATIN INDUCED NEUROPATHY AND NEPHROPATHY IN MALE ALBINO RATS

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Abstract. Cisplatin, as an antineoplastic drug belonging to the platinum family, has severely nephrotoxic and neurotoxic side effects. L-carnitine (LC) is an antioxidant-rich natural substance. The notion that LC may play a protective function in Cisplatin-induced nephropathy and neuropathy was investigated in this study. Nephropathy was created by a single intraperitoneal injection of Cisplatin at 20 mg/kg body weight, while neuropathy was induced by daily intraperitoneal injections of Cisplatin at 2.3 mg/kg body weight over two rounds of five days, with five days break in between. The rats were subsequently given LC at a dose of 250 mg/kg body weight, followed by estimation of serum urea and creatinine with histological examination of renal tissue for the nephropathy group and evaluation of nerve conduction velocity for the neuropathy group. In comparison to the nephropathy group, blood urea and creatinine levels were significantly lower after treatment with LC. Furthermore, LC therapy improved the physiological characteristics of the sciatic nerve significantly. In conclusion, the significant impairment of renal function and the decrease in sciatic nerve conduction velocity induced by Cisplatin may be avoided if L-carnitine is administered as a preventative medication.

Keywords: Cisplatin, L-carnitine, neuropathy, nephropathy.

List of Abbreviations

DNA – Deoxyribonucleic acid
GFR – glomerular filtration rate
CIPN – Cisplatin-induced peripheral neuropathy
AKI – acute kidney injury
N – number
LC – L-carnitine
NCV – nerve conduction velocity
E.M. – electron microscopy
IGF-I – insulin growth factor - I
TGF – tumor growth factor

Introduction

Malignant tumors are a major health problem that affects socioeconomic development. Its prevalence is increasing as a result of ageing and bad lifestyle habits (Kurt & Can, 2018; Abalo *et al.*, 2017).

Chemotherapeutic drugs are one of the treatment options for cancer (Wang *et al.*, 2016). For some solid tumors, The Platinum-containing drug Cisplatin is used as first-line therapy (Jin et al., 2020; Yang *et al.*, 2020). Its anticancer activity is exerted via the generation of apoptosis through many signal transduction pathways such as cellar DNA damage pathway, mitochondrial DNA damage pathway, endoplasmic reticulum stress pathway, and death receptor pathway (Ghosh, 2019; Florea & Büsselberg, 2011; Al-Bahlani & Al-Jaaidi, 2018).

Apoptosis is a programmed cell death and is generally characterized by morphological changes in the cell, such as cell shrinkage, chromatin condensation, plasma membrane budding, exposure of phosphatidylserine at the cell surface, and caspase activation (Achkar *et al.*, 2018).

Besides its therapeutic effect, Cisplatin has some serious side effects that are dependent on numerous parameters, such as cumulative dose, age of the patient, and glomerular filtration rate (GFR) during chemotherapy (Kim *et al.*, 2015; Brouwers *et al.*, 2008).

This medication has a larger tissue concentration and takes longer to excrete at higher doses (Astolfi *et al.*, 2013). Neurotoxicity, ototoxicity, vomiting, and nephrotoxicity are the major limiting factors in the use of Cisplatin (Jin *et al.*, 2020).

Patients treated with this drug frequently suffer progressive, often irreversible nerve damage, termed as Cisplatin-induced peripheral neuropathy (CIPN) (Carozzi *et al.*, 2015) and this side effect is due to the accumulation of Cisplatin in Dorsal Root Ganglion of the sensory neurons (DRG) (Radwan & Fattah, 2017).

The kidney is the chief target for Cisplatin toxicity as it accumulates in the proximal renal tubules (Yang *et al.*, 2018). Cisplatin Treatment causes acute kidney injury (AKI) with a sudden decline in renal function. Patients with AKI have a high mortality rate; those who survive AKI are more likely to develop chronic kidney disease in the months to years after their diagnosis (Hauschild *et al.*, 2019).

L-carnitine as a natural substance has a major role in lipid metabolism, mitochondrial defense, and maintains many physiological activities (Wang *et al.*, 2019).

It protects the function of neurons against oxidative stress and apoptosis in the nervous system (Rump *et al.*, 2010). It also has a significant renoprotective effect by slowing down the decline of renal function (Ahmad *et al.*, 2016).

Materials and Methods

This research protocol was approved by the local ethics committee of the faculty of medicine at Cairo University (the committee's reference number is I – 131017). The animals were treated according to the recommendations in the ARRIVE guidelines. Also, all experiments were performed following the guidelines for the care and use of laboratory animals (8th edition, National Academic Press) (Albus, 2012).

Animals

Adult male albino rats (180–200g) (n = 48) were included [female rats were excluded due to hormonal changes]. All animals were obtained from the animal care facility and housed in cages (70× 70 ×70 cm, 4/cage) at the animal house. They were provided with ordinary rat chow and water with a 12- hour light-dark cycle. Animals were kept for 10 days before the start of the study to allow proper acclimatization.

The animals were randomly divided into 6 groups, each with eight rats:

- *The control group* received intra-peritoneal injection of 0.9% physiological saline solution (Kim *et al.*, 2015).
- *The LC group* received L-carnitine (250 mg/kg body weight by daily intra-peritoneal injections for 14 days) diluted in 0.9% physiological saline solution (Ahmad *et al.*, 2016).
- *The nephropathy group* received single injection of Cisplatin (20 mg/kg body weight intra-peritoneal) diluted in 0.9% physiological saline solution (Nojiri et al., 2016).
- *The neuropathy group* received daily intra – peritoneal injections of 2.3 mg /kg body weight Cisplatin within two rounds of 5 days with 5 days break in between (Hu *et al.*, 2018).
- *LC treated nephropathy group* – L carnitine was injected IP for 14 days after a single injection of Cisplatin.
- *LC treated neuropathy group* – L carnitine was injected IP for 14 days after the second round of 5 days.

On the last day of the experiment, serum levels of urea and Creatinine were measured in each rat in the following groups (control group, LC group, nephropathy group, and LC treated nephropathy group). The rats were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) (Dehghani *et al.*, 2020) to be sacrificed by cerebral concussion, and their kidneys were excised, processed, and then examined by the electron microscope for structural assessment. In addition, the right sciatic nerve of the following groups (control group, LC group, neuropathy group, and LC treated neuropathy group) was dissected and placed in moist chamber to be stimulated by power lab device for assessment of nerve conduction velocity.

Assessment of renal function

Retro-orbital Blood samples were withdrawn and serum was separated (Yang et al., 2020). Serum urea was estimated by QuantiChromTM Urea Assay kit (DIUR-500) (Jung *et al.*, 1975), and Serum creatinine was estimated by QuantiChromTM Creatinine Assay Kit (Bergman & Ohman, 1980).

Preparation of the renal tissue for scanning by electron microscopy

After weighting of excised kidneys via laboratory scale, they were cut into small parts, fixed with a solution containing 3% glutaraldehyde, and then sent to Cairo University for electron microscopic analysis (Bozzola & Russell, 1999).

Assessment of nerve conduction velocity

After the sacrifice of the rat, the rat was placed in the right lateral position. The skin incision was performed in the line between the greater trochanter and the knee (Stolarczyk *et al.*, 2000). After skin incision and dissection of the muscles, the sciatic nerve was identified, sectioned, and removed (Ganga *et al.*, 2012).

There were no muscular remains left after the nerve was dissected free. After that, the sciatic nerve was placed in a nerve chamber that was designed to record action potentials. It is made out of stainless steel wires. The nerve was placed over these wires. A stimulating electrode was used to stimulate the nerve's proximal portion. The recording electrode was placed 0.5 cm apart from the stimulating one. The experiment was performed at room temperature. (35–38 c). Measurements

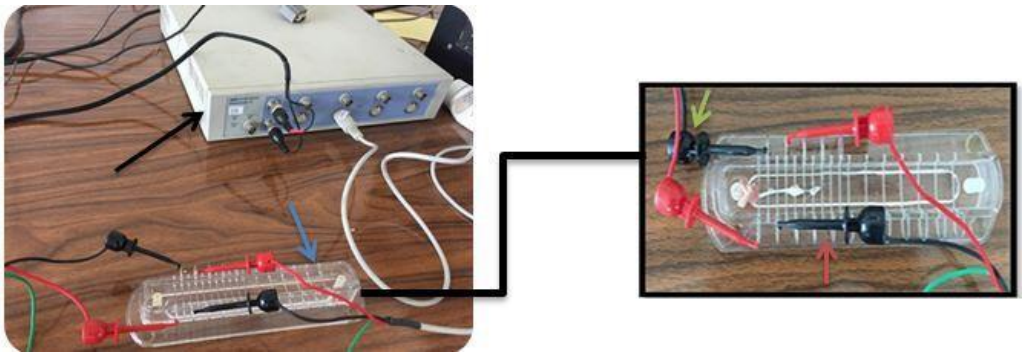

Fig. 1. A power lab device (black arrow) with stimulating and recording electrodes (green and brown arrows, respectively) connected to the wires of the nerve chamber (blue arrow)

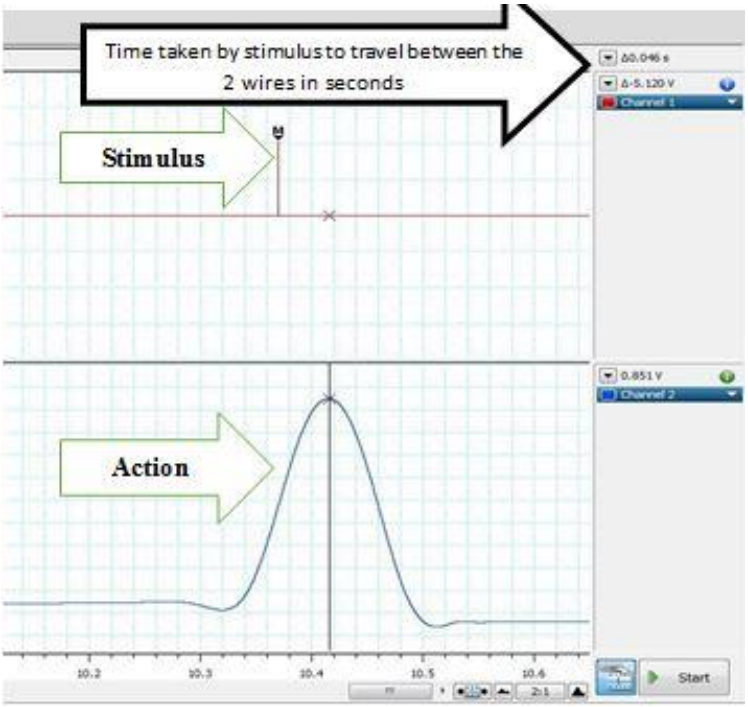

Fig. 2. Zoom window in overlay mode showing the analysis procedure for calculating conduction velocity

Table 1

The mean values and SD of sciatic nerve conduction velocity (meters/second)

	Control group	L-carnitine group	Cisplatin group	LC treatment group
Mean ± SD	0.14 ± 0.05	0.13 ± 0.03	0.09 ± 0.005*	0.1 ± 0.01@
P – value	< 0.001			

* – significant change compared to the control group, p-Value ≤ 0.05
@ – significant change compared to the Cisplatin group, p-Value ≤ 0.05

Table 2

The mean values and SD of serum urea and creatinine (mg)

	Control group	L-carnitine group	Cisplatin group	LC treatment group
Mean ± SD (urea)	38 ± 9	38.2 ± 9.5	97.99 ± 15.1	56.8 ± 11.2
Mean ± SD (creatinine)	0.15 ± 0.053	0.16 ± 0.06	1.17 ± 0.37*	0.48 ± 0.19@
P – value	< 0.001			

* – significant change compared to the control group, p-Value ≤ 0.05
@ – significant change compared to the Cisplatin group, p-Value ≤ 0.05

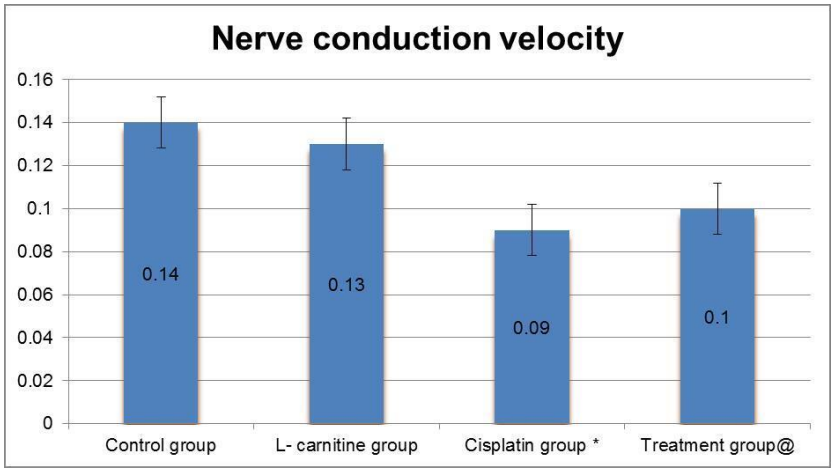

Fig. 3. The effect of Cisplatin and L-carnitine on nerve conduction velocity in comparison to the control group. * – significant change compared to the control group; @ – significant change compared to the Cisplatin group

were performed using an AD instruments Power Lab 4/25 stimulator, followed by computer-assisted data analysis (Fig. 1). The sciatic nerve was stimulated at 10 volts to measure conduction velocities. The distance between the –ve black cathode of stimulating and –ve black cathode of recording electrodes is divided by a latent period, which is the time passed between stimulus applications to the peak of the compound action potential (Alves *et al.*, 2013) (Fig. 2).

Statistical analysis

Quantitative data were summarized as means and standard deviations and compared using one-way ANOVA, followed by a Bonferroni post-hoc test to determine which groups caused the significant difference. P-values < < 0.05 were considered statistically significant. Calculations were made on a social package of statistical science (SPSS) software 16 (Emsley *et al.*, 2010).

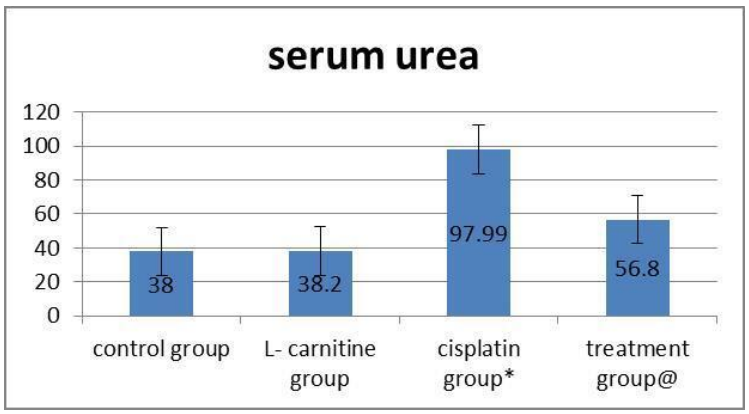

Fig. 4. The effect of Cisplatin and L-carnitine on the serum level of urea in comparison to the control group. * – significant change compared to the control group; @ – significant change compared to the Cisplatin group

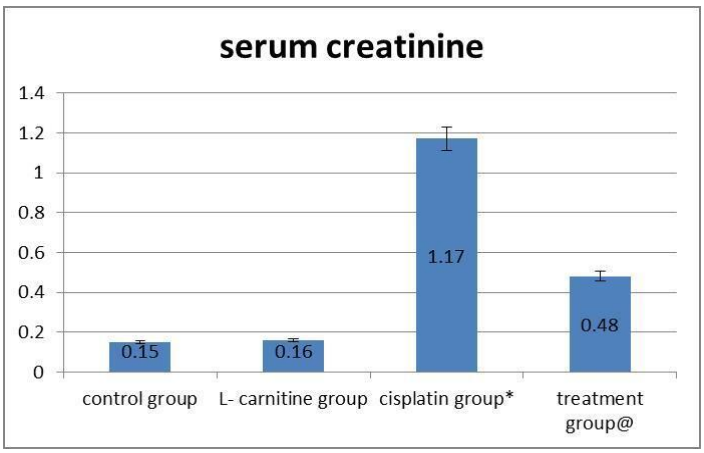

Fig. 5. The effect of Cisplatin and L-carnitine on serum level of creatinine in comparison to the control group. * – significant change compared to the control group; @ – significant change compared to the Cisplatin group

Results

The mean values of NCV of the Cisplatin group showed a significant decline (P-value < < 0.001) in comparison to the control group, while the mean values of the NCV of LC treatment group showed a significant increase (P-value < 0.001) in comparison to the Cisplatin group (Table 1, Fig. 3).

The mean values of both serum urea and creatinine of the Cisplatin group showed a significant increase (P-value < 0.001) in comparison to the control group, while the mean values of both serum urea and creatinine of the LC treatment group showed a significant decline (P-value < 0.001) in comparison to the Cisplatin group (Table 2, Fig. 4, 5).

The mean values of kidney size of the L carnitine and Cisplatin groups showed a significant increase (P-value = 0.004) in comparison to the control group, while the mean values of kidney size of LC treatment group showed a significant decrease (P-value = = 0.004) in comparison to the Cisplatin group (Table 3, Fig. 6).

Histological examination

In the current study, Fig. 7 depicts the typical histological structure of the kidney. Except for slightly increased renal congestion, the L-carnitine group's renal tissues showed no significant differences from the control group (Fig. 8). After Cisplatin injection, the renal tissues of a

Table 3

The mean values and SD of right kidney size (gram)

No.	Control group	L-carnitine group	Cisplatin group	LC treatment group
Mean ± SD	0.555 ± 0.048	0.737 ± 0.031$	0.713 ± 0.16*	0.558 ± 0.12@
P – value	0.004			

$, * – significant change compared to the control group, p-Value ≤ 0.05
@ – significant change compared to the Cisplatin group, p-Value ≤ 0.05

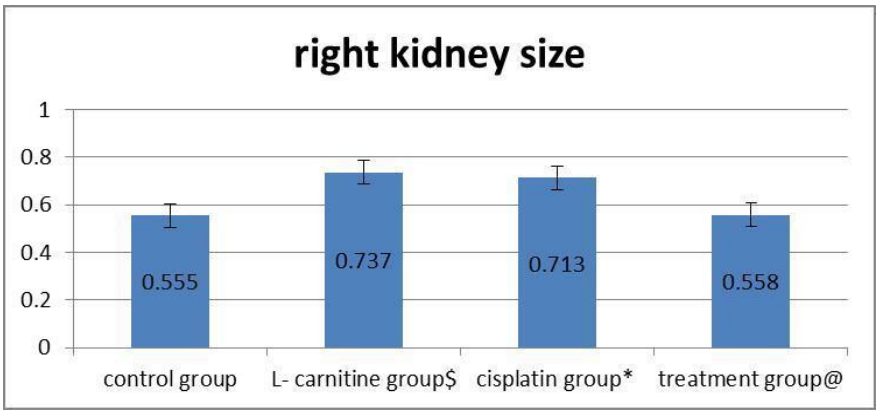

Fig. 6. The effect of Cisplatin and L-carnitine on the size of the right kidney in comparison to the control group. $, * – significant change compared to the control group; @ – significant change compared to the Cisplatin group

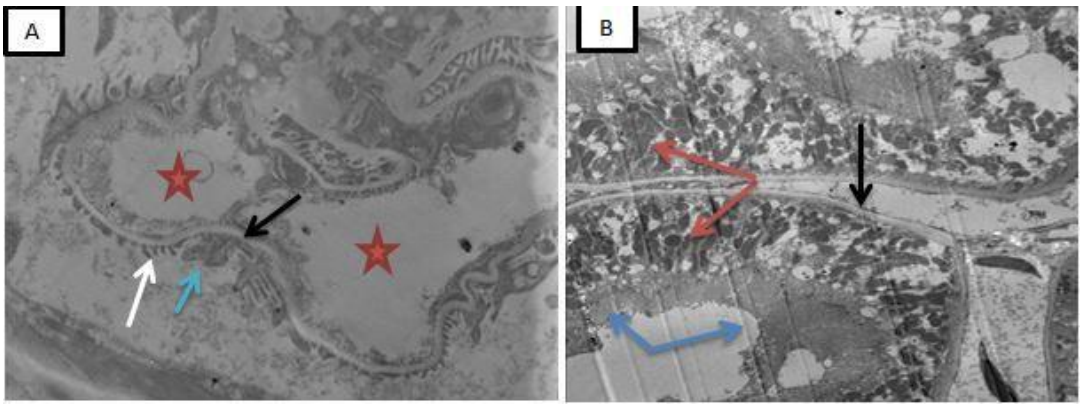

Fig. 7. E.M. pictures of the renal tissue of a control rat. A – showing glomerular capillaries (star), the renal basement membrane (black arrow), and the cell body of podocyte (blue arrow) with its foot processes (white arrow). B – showing the lining cells of the proximal convoluted tubule lying on a definite basement membrane (black arrow). They have numerous mitochondria (brown arrow) and apical long microvilli (blue arrow)

rat showed significant degeneration of the glomerular basement membrane and podocyte's foot processes. Furthermore, the apical microvilli of the proximal convoluted tubules were lost along with vacuolated cytoplasm and a low mitochondrial density (Fig. 9).

The glomerular basement membrane of L-carnitine-treated rat was more or less normal, and the proximal convoluted tubule displayed apical microvilli, scattered mitochondria, and minimal vacuolated cytoplasm (Fig. 10).

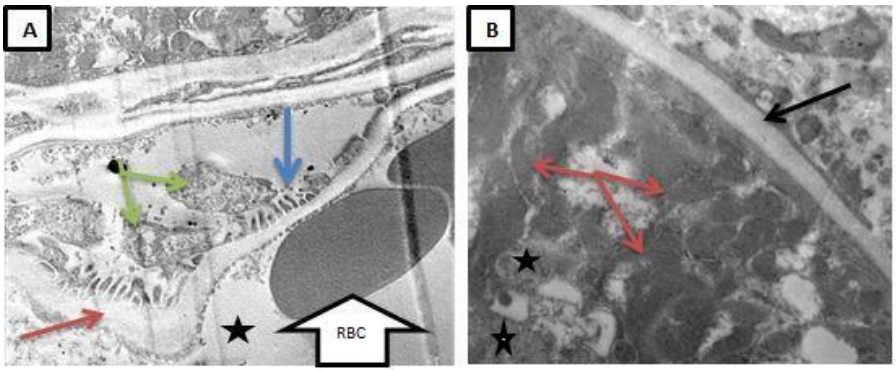

Fig. 8. E.M. pictures of the renal tissue of a rat that received L-carnitine. A – showing the glomerular capillaries (star) filled with RBCs, the renal basement membrane (brown arrow), and the cell body of podocyte (green arrow) with an irregular nucleus and sending foot processes (blue arrow). B – showing the lining cells of proximal convoluted tubule lying on a definite basement membrane (black arrow). They have numerous mitochondria (brown arrow) and apical microvilli (star)

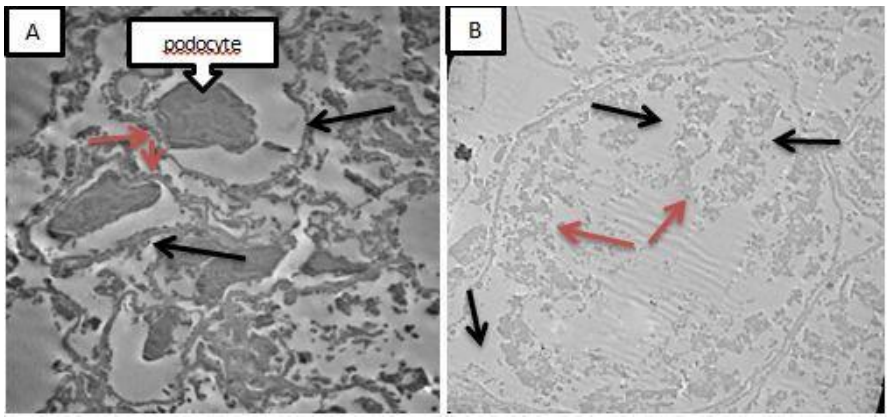

Fig. 9. E.M. pictures of the renal tissue of a rat after Cisplatin injection. A – showing degeneration and irregularity of the glomerular basement membrane (black arrow) with degeneration of foot process of podocyte (brown arrow). B – The cells of proximal convoluted tubules have vacuolated cytoplasm (black arrow) and the apex has remnants of apical microvilli (brown arrow) with marked low mitochondrial density

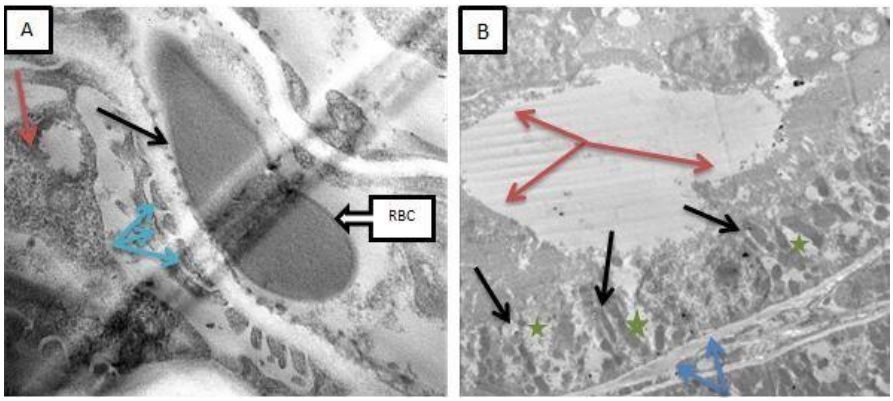

Fig. 10. E.M. pictures of the renal tissue of a rat received L-carnitine after Cisplatin injection. A – showing more or less normal glomerular basement membrane (black arrow). The cell body of the podocyte sends foot processes parallel to the basement membrane (blue arrow). B – the cells of the proximal convoluted tubule rest on the basement membrane (blue arrow) with numerous mitochondria (black arrow). The apical border sends microvilli (brown arrow) into the lumen. Cytoplasm shows minimal vacuolation (star)

Discussion

One of the most significant aspects of using Cisplatin to treat cancer patients is avoiding its negative effects (Alghamdi *et al.*, 2020). In the dorsal root ganglia, its neurotoxic action is linked to decreased neuronal conduction, axonal degeneration, and nuclear DNA damage (DRG). These alterations are caused by mitochondrial malfunction and apoptosis induction (Maj *et al.*, 2017).

According to our findings, treatment of the Cisplatin group with L-carnitine resulted in some improvement in the function of the sciatic nerve. L-carnitine has anti-apoptotic effect (Wang *et al.*, 2019). It prevents the degeneration of nerve fibers and increases IGF-I levels, which enhances the regeneration of sensory nerves, motor nerves, and Schwann cells. In addition, IGF-1 can protect dorsal root ganglion neurons from apoptosis (Mahajan *et al.*, 2017).

In this study, we found that treatment of the Cisplatin group with L-carnitine improved their renal function. In comparison to the Cisplatin group, histological data revealed increased mitochondrial density in the proximal tubules as well as the appearance of podocyte foot processes.

Treatment with L-carnitine restored the number and size of mitochondria and the function of the proximal convoluted tubules (Zheng *et al.*, 2021). It suppresses the progression of tubulo-interstitial inflammation and fibrosis in Cisplatin-induced nephropathy via inhibition of macrophage influx and TGF expression. L-carnitine has also been linked to reduced tissue inflammation and neutrophil infiltration in renal injury (Xiang *et al.*, 2013; Görür *et al.*, 2005).

In addition, L-carnitine has a stabilizing effect on the outer mitochondrial membrane, which can prevent the release of cytochrome C into the cytosol (Moosavi *et al.*, 2016).

The size of a patient's kidneys is a crucial criterion for determining whether or not they have renal disease. When the right kidney sizes of all groups in our study were measured, the L-carnitine and Cisplatin groups had considerably larger kidneys than the control group (P-value = 0.004).

The retention of urine caused by tubular blockage accounts for the rise in kidney weight in the Cisplatin group. Tubular blockage is most commonly caused by a tubular cast (Kpemissi *et al.*, 2019). In addition, Cisplatin-induced renal tubular epithelial cell edema also causes tubular obstruction (Huang *et al.*, 2019).

According to the L-carnitine group, Kidney size is a potential indicator for the number of nephrons, which are the structural and functional units of the kidneys. Most of the glomeruli were more or less restored after the treatment of the nephropathy group with L-carnitine (Ferdous *et al.*, 2018).

Conclusion

Taking L-carnitine as a prophylactic drug may help to avoid the significant impairment of renal function and reduction in sciatic nerve conduction velocity associated with Cisplatin.

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