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Effect of Coenzyme Q10 alone and it's Combination with Pentoxifylline in Cisplatin- Induced Nephrotoxicity in Rats

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ABSTRACT:

Aim & objective: To study the nephroprotective effect of coenzyme Q10 and pentoxifylline on cisplatin induced nephrotoxicity in animals. The study would be beneficial to understand the effects of coenzyme Q10 and its combination with pentoxifylline on experimentally induced nephrotoxicity in animals and to study the histopathology of kidney.

Material & Method: Nephrotoxicity was experimentally induced by cisplatin. Coenzyme Q10 (10mg/kg, i.p), pentoxifylline (45 mg/kg, i.p) and its combination were evaluated for their nephroprotective effect in cisplatin induced nephrotoxic rats. Serum bio-chemicals parameters like Creatinine, Albumin, Calcium, Magnesium and Uric acid were measured using enzymatic kits commercially available. Further histopathologic studies were carried out.

Results: Coenzyme Q10 and pentoxifylline treated group showed significant decrease in serum creatinine, magnesium, calcium, uric acid and albumin levels. Histopathologic studies showed that rats treated with coenzyme Q10 and pentoxifylline individually retain minimal inflammatory cellular infiltration and retain the tissue to normal structure, while combination of both coenzyme Q10 and Pentoxifylline showed normal kidney tissue architecture.

Conclusion: coenzyme Q10 and pentoxifylline has a nephroprotective effect that was proven by biochemical and histopathological analysis. Coenzyme Q10 and pentoxifylline has been shown nephroprotective activity with greater protective action as compare to alone dose treatment.

KEY WORDS: coenzyme Q10, pentoxifyllin, cisplatin, nephrotoxicity

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1. INTRODUCTION:

Nephrotoxicity (from Greek: nephros, "kidney") is a **poisonous** effect of some substances, both **toxic** chemicals and **medication**, on the **kidney**. There are various forms of toxicity. ^[1] Nephrotoxicity should not be confused with the fact that some medications have a predominantly renal excretion and need their dose adjusted for the decreased **renal function** (e.g. **heparin**).^[2] The nephrotoxic effect of most drugs is more profound in patients who already suffer from renal impairment. Some drugs may affect renal function in more than one way. Drug toxicity-risk for kidney problem may be from-Chemotherapy drugs

such as: Cisplatin, Carboplatin, carmustine, Mitomycin, high-dose Methotrexate.^[3], Biologic therapy such as interleukin-2, or interferon alfa, Antibiotics such as Amphotericin B, Gentamycin and Vancomycin, Angiotensin-converting enzyme (ACE)inhibitors-used in heart failure or after a heart attack, ACE inhibitors are given to diabetics with mild kidney disease, yet you should not stay on them once your creatinine levels are elevated significantly, or a specialists has recommended that you stay on these medication, NSAID's like Ibuprofen, Some diuretic- such as Furosemide-may cause kidney failure; yet it may, in some cases (like CHF with fluid overload), be

used in the treatment of your condition. "Picture" that is seen on CT scan, MRI or x-ray. These dyes, if you are at risk for kidney failure, or when given in combination with certain other medications, may cause further kidney problems.

Coenzyme Q10 (CoQ10) is an endogenous lipid-soluble benzoquinone compound that functions as a diffusible electron carrier in the mitochondrial respiratory chain. CoQ10 also acts as a powerful antioxidant which scavenges free radicals, prevents the initiation and propagation of lipid peroxidation in cellular biomembranes, and helps regeneration of tocopherol^[4]

Also, histopathological renal tissue damage mediated by cisplatin was ameliorated by coenzyme Q10 treatment. Immuno-histochemical analysis revealed that coenzyme Q10 significantly decreased the cisplatin-induced over expression of inducible nitric oxide synthase, nuclear factor-B, caspase-3 and p53 in renal tissue. It was concluded that coenzyme Q10 represents a potential therapeutic option to protect against acute cisplatin nephrotoxicity commonly encountered in clinical practice.

In addition, CoQ10 has anti-inflammatory^[5] properties decreasing the production of pro inflammatory cytokines as tumor necrosis factor. Previous studies demonstrated the protective effects of CoQ10 in various models of oxidative and inflammatory tissue damage. Therefore, CoQ10 has the potential to protect against renal tissue injury and renal dysfunction induced by cisplatin. This was encouraging to conduct the present study in order to evaluate the protective effect of CoQ10 in mice exposed to acute cisplatin nephrotoxicity. Also, the possible mechanisms underlying this effect were investigated.

Cardiovascular^[5] benefits of ubiquinone have been previously demonstrated, and we administered it as a novel therapy in an experimental model of type 2 diabetic nephropathy. db/db and dbH mice were followed for 10 weeks, after randomization to receive either vehicle or ubiquinone (CoQ10; 10 mg/kg/day) orally. db/db mice had elevated urinary albumin excretion rates and albumin:creatinine ratio, not seen in db/db CoQ10-treated mice.

Renal cortices from db/db mice had lower total and oxidized CoQ10 content, compared with dbH mice. Mitochondria from db/db mice also contained less oxidized CoQ10 (ubiquinone) compared with dbH mice.

Diabetes-induced increases in total renal collagen but not glomerulosclerosis were significantly decreased with CoQ10 therapy. Mitochondrial superoxide and ATP production via complex II in the renal cortex were increased in db/db mice, with ATP normalized by CoQ10. However, excess renal mitochondrial hydrogen peroxide production and increased mitochondrial membrane potential seen in db/db mice were attenuated with CoQ10.

Pentoxifylline is a methylxanthine that improves perfusion in the impaired microcirculation of peripheral and cerebral vascular beds. This hemorheologic activity mostly involves inhibition of cyclic-3',5'-phosphodiesterase (PDE), leading to raised intracellular cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA). The superfamily of PDE isozymes consists of at least 11 gene families: PDE 1 to PDE 11,2,3. The recent development of selective PDE isozyme inhibitors has advanced the identification of the specific role of PDE isozymes in several patho-biologic processes.^[6]

Pentoxifylline inhibits PDE 1–5 with IC50 values ranging from 50–200 M, thereby classifying it as a non-selective PDE inhibitor.^{4,5} Notably, pentoxifylline is a safe drug that is usually well tolerated when administered as the conventional controlled-release formulation: gastrointestinal symptoms (i.e. nausea and dyspepsia) and dizziness are the most common complaints and affect about 3% of patients.^[7]

Besides its hemorheologic activity, growing evidence has demonstrated that pentoxifylline has broad-spectrum effects to slow the progression of chronic kidney disease (CKD).^[8-20] Although accumulation of the active metabolite of pentoxifylline has been documented in moderate and severe renal dysfunction during multidose pharmacokinetic studies, the clinical significance of this is unclear.^[21]

Dosage reductions to 400 mg twice daily in patients with moderate renal dysfunction, and to 400 mg once daily in patients with severe renal dysfunction, are recommended. This article reviews the rationale and evidence for the renoprotective effect of pentoxifylline, and raises some unanswered questions.^[22]

Pentoxifylline (PTX), a methylxanthine derivative and phosphodiesterase inhibitor with hemorrheologic properties, affects arachidonic acid metabolism and inhibits pro-inflammatory mediators such as tumor

necrosis factor α (TNF- α). The TNF- α has a role in the activation of macrophages and increasing the pro-inflammatory secretion of neutrophils, resulting in the stimulation of apoptosis.^{[23],[24],[25]} These effects trigger cell death, resulting in necrosis of target organs. The PTX is known as an antioxidant and a free radical scavenger that decreases free oxygen radicals and nitric oxide synthase^{[26],[27],[28]}

It was previously stated that Cisplatin is an effective chemotherapeutic agent that is widely used for treatment of malignant tumors including head and neck, ovarian, testicular, lung and breast cancers. Despite the antineoplastic efficacy, the optimal clinical usefulness of cisplatin is usually limited due to its dose-related nephrotoxicity.

While acute renal injury can occur after an initial dose of cisplatin with about 20% of patients experiencing various degrees of renal dysfunction. Cisplatin exerts its nephrotoxic^[29] effect mainly in the proximal tubular cells where it is preferentially accumulate. The precise mechanisms underlying this toxicity are not fully elucidated.

It was previously reported that Cisplatin induced nephrotoxicity is associated with oxidative stress, redox state unbalance, impairment of energetic metabolism and apoptosis in rat kidney mitochondria which affects the various parameters of the normal cells function and other activities which had been carried out during the experiment conducting and while check the reports of the activities.^[30]

It was previously showed that the studies were to examine the role of cytokines in the pathogenesis of cisplatin nephrotoxicity. Injection to mice with cisplatin (20 mg/kg) led to severe renal failure. The expression of cytokines, chemokines, and ICAM-1 in kidney was measured by ribonuclease protection assays and RT-PCR. We found significant upregulation of TNF- α , TGF- β , RANTES, MIP-2, MCP-1, TCA3, IL-1 β , and ICAM-1 in kidneys from cisplatin-treated animals. In addition, serum, kidney, and urine levels of TNF- α measured by ELISA were increased by cisplatin. Inhibitors of TNF- α production (GM6001, pentoxifylline) and TNF- α ^[31]Ab's reduced serum and kidney TNF- α protein levels and also blunted the cisplatin-induced increases in TNF- α , TGF- β , RANTES, MIP-2, MCP-1, and IL-1 β , but not ICAM-1, mRNA. In addition, the TNF- α inhibitors also ameliorated cisplatin-

induced renal dysfunction and reduced cisplatin-induced structural damage. Likewise, TNF- α -deficient mice were resistant to cisplatin nephrotoxicity. These results indicate cisplatin nephrotoxicity is characterized by activation of pro inflammatory cytokines and chemokines. TNF- α and Pentoxifylline appears to play a central role in the activation of this cytokine response and also in the pathogenesis of cisplatin renal injury.

It was previously reported many patients being treated for cancer use dietary supplements, particularly antioxidants, in the hope of reducing the toxicity of chemotherapy and radiotherapy. Some researchers have claimed, furthermore, that antioxidants also increase the effectiveness of cytotoxic therapy and have explicitly recommended their use. However, mechanistic considerations suggest that antioxidants might reduce the effects of conventional cytotoxic therapies. Preclinical data are currently in conclusive and a limited number of clinical studies have not found any benefit. Clinicians should advise their patients against the use of antioxidant dietary supplements during chemotherapy or radiotherapy. Such caution should be seen as the standard approach for any unproven agent that may be harmful.

2. MATERIALS AND METHODS:-

2.1 Drugs and Chemicals

Pentoxifylline & Co-enzyme Q10 were procured from commercial source. All biochemical kits were purchase from Span Diagnostic Ltd. All other chemicals and reagents used in the study were of analytical grade.

2.2 Animals

All experiments and protocols (SVU/DP/IAEC/03/23) described in present study were approved by the Institutional Animal Ethics Committee (IAEC) of SBKS & MIRC, Sumandeep Vidyapeeth, Baroda and CPCSEA. Healthy adult Wistar rats weighing 200-250gm were used. Rats were housed in polypropylene cages, maintained under standardized condition (12-h light/dark cycle, temp 24°C, 35 to 60% humidity) and provided free access to pelleted CHAKKAN diet (Nav Maharashtra Oil Mills Pvt. Ltd., Pune) and purified drinking water *ad libitum*.

2.3 Method for preparation of Coenzyme Q10 & Pentoxifylline

Coenzyme Q10 & Pentoxifylline suspension were prepared in 0.9% of normal saline and administered i.p.

2.4 Experimental design:

All the animals were divided in the following groups (n=5) and treated accordingly.

Group I: Normal control (1 ml/kg of 0.9% normal saline, i.p)

Group II: cisp Control (5 mg/kg, i.p.)

Group III: cisp + coenzyme Q10 (10 mg/kg, i.p.)

Group IV: cisp+ pento (45 mg/kg, i.p.)

Group V: cisp + coenzyme Q10 + pento

At the end of the experiments, blood samples were collected from the retro orbital plexus of rats. Blood was allowed to clot for 15 minutes and it was then centrifuged at 5000 rpm for 20 minutes. The separated serum was stored at -20°C until further biochemical estimation. Body weights of all animals were recorded daily.

2.5 Bio-chemical studies

Serum bio-chemicals parameters like Creatinine (mg /dl, Alkaline Picrate Method), Albumin (gm /dl, Pyrogallol Red Method), Calcium (mg /dl, OCPC Method), Magnesium (mEq / L, Calmagite Method) and Uric acid (mg /dl, Uricase / PAP Method) were measured using enzymatic kits commercially available (Span Diagnostic India Limited)

2.6 Histopathological study

Kidney was collected after the rats were sacrificed and blotted free of blood and tissue fluids and kept in 5% formalin. After 24 hours the tissues were washed thoroughly with 70% alcohol and then dehydrated in ascending grades of alcohol (70-100%). Dehydration in absolute alcohol was followed by treatment of tissues with toluene: xylene (50:50) followed by paraffin wax in toluene and finally in 100% wax (paraffin wax, 60-62°C) followed by embedding of tissue in wax. 5-15µm thick section was serially cut on a leitz microtome in horizontal plane and mounted on glass slide with the help of egg albumin in glycerin solution (50% v/v). They were then stained with 10% hematoxylin for 3-5 minutes and the staining was intensified by placing in running water. The hematoxylin stained sections were stained with 10% eosin for 2 minutes and were then quickly passed through ascending grades of alcohol and finally treated with xylene followed by mounting.

The sections were observed and desired areas were photographed in an Olympus photomicroscope. The

sections were viewed under 40X and 100 X magnifications.

2.7 Statistical analysis

All the values are expressed as mean ± S.E.M. Statistical significance between more than two groups was tested using one-way ANOVA followed by the Turkey's multiple comparisons test appropriate using computer based fitting program (Prism, Graph pad 3.). Differences were considered to be statistically significant when $p < 0.05$.

3. RESULT

a) Effect of coenzyme Q10, pentoxifylline or combination of both on serum creatinine:

Cisplatin injection caused a marked reduction in renal function, as characterized by significant ($P < 0.001$) increase in serum creatinine levels as compared to normal control rats. Thus, these data indicate that a single i.p injection of Cisplatin impairs kidney functions. Treatment with coenzyme Q10 (10 mg/kg), Pento (45 mg/kg) or coenzyme Q10 + Pento showed a significant ($P < 0.001$) reduction in serum creatinine levels as compared to cisplatin control rats, respectively. However, co-administration of coenzyme and pento did not show any significant difference in creatinine levels as compared to monotherapy. [Figure 1]

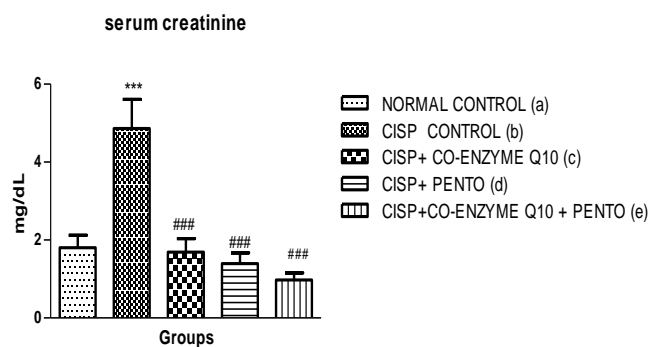


Figure 1: Effect of coenzyme Q10, pentoxifylline or combination of both on creatinine level in serum Values are expressed as mean ± SEM; n=5 a vs. b, *** $P < 0.001$; b vs. c, b vs. d and b vs. e, ### $P < 0.001$

b) Effect of coenzyme Q10, pentoxifylline or combination of both on serum albumin :

There was a significant ($P < 0.001$) increase in the levels of serum albumin in cisplatin control as compared to normal control group. In contrast, the treatment with coenzyme Q10, pento and combination of both showed a significant ($P < 0.05$; $P < 0.01$; $P < 0.001$) decrease in level of serum albumin as compared to cisplatin control rats. However,

co-administration of coenzyme with pento showed a significant ($P < 0.05$) reduction in albumin levels as compared to mono-therapy (coenzyme Q10) [Figure 2].

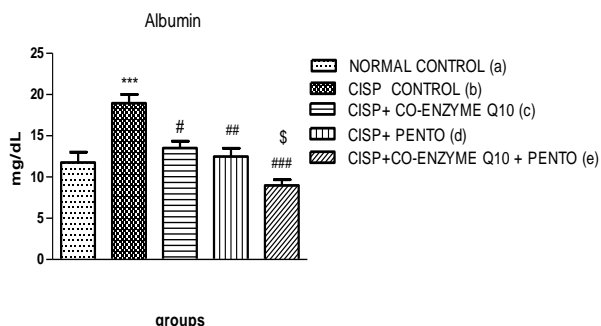


Figure 2: Effect of coenzyme Q10, pentoxifylline or combination of both on albumin level in serum

Values are expressed as mean \pm SEM; n=5

a vs. b, *** $P < 0.001$;
 b vs. c, # $P < 0.05$;
 b vs. d ## $P < 0.01$
 b vs. e, #### $P < 0.0001$
 c vs e, $\text{\$}$ $P < 0.05$

c) Effect of coenzyme Q10, pentoxifylline or combination of both on serum calcium :

There was a significant ($P < 0.001$) increase in the levels of serum calcium in cisplatin control as compared to normal control group. In contrast, the treatment with coenzyme Q10 or pento or coenzyme Q10 + pento showed a significant ($P < 0.001$) decrease in the levels of calcium as compared to cisplatin control rats. However, co-administration of coenzyme Q10 with pento showed a significant ($P < 0.01$; $P < 0.05$) decrease in calcium levels as compared to mono-therapy (coenzyme Q10 or pento) [Figure 3].

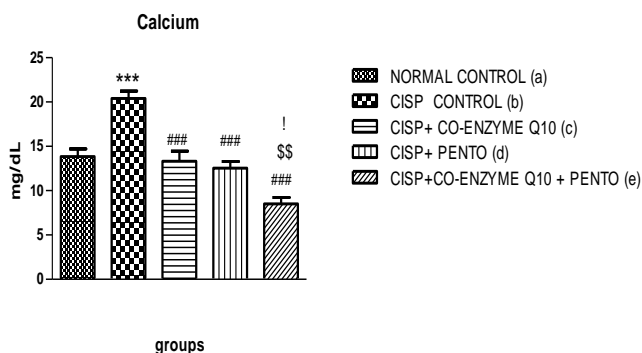


Figure 3: Effect of coenzyme Q10, pentoxifylline or combination of both on calcium level in serum

Values are expressed as mean \pm SEM; n=5
 a vs. b, *** $P < 0.001$;
 b vs. c, b vs. d and b vs. e, #### $P < 0.0001$
 c vs e, $\text{\$}$ $P < 0.01$
 d vs e, $\text{\$}$ $P < 0.05$

d) Effect of coenzyme Q10, pentoxifylline or combination of both on serum magnesium

There was a significant ($P < 0.001$) increase in the levels of serum magnesium in cisplatin control as compared to normal control group. In contrast, the treatment with coenzyme Q10 or pento or coenzyme Q10 + pento showed a significant ($P < 0.001$) decrease in the levels of magnesium as compared to cisplatin control rats. However, co-administration of coenzyme with pento showed a significant ($P < 0.01$; $P < 0.05$) decrease in magnesium levels as compared to mono-therapy (coenzyme Q10 or pento) [Figure 4].

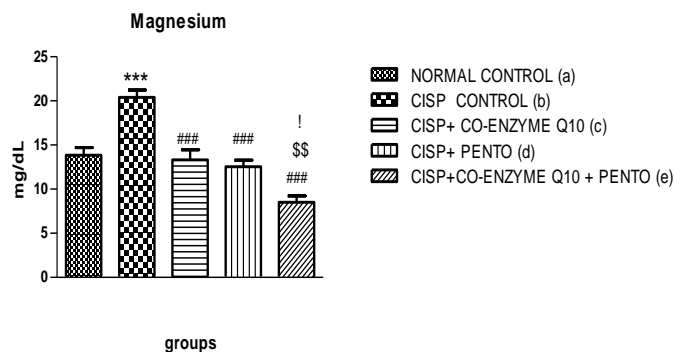


Figure 4: Effect of coenzyme Q10, pentoxifylline or combination of both on magnesium level in serum

Values are expressed as mean \pm SEM; n=5
 a vs. b, *** $P < 0.001$;
 b vs. c, b vs. d and b vs. e, #### $P < 0.0001$
 c vs e, $\text{\$}$ $P < 0.01$
 d vs e, $\text{\$}$ $P < 0.05$

e) Effect of coenzyme Q10, pentoxifylline or combination of both on serum uric acid :

There was a significant ($P < 0.001$) increase in the levels of serum uric acid in cisplatin control as compared to normal control group. In contrast, the treatment with coenzyme Q10, pento or coenzyme Q10 + pento showed significant ($P < 0.001$; $P < 0.01$; $P < 0.001$) decrease in the level of uric acid as compared to cisplatin control rats. However, co-administration of coenzyme Q10 with pento showed a significant ($P < 0.05$) decrease in uric acid levels as compared to mono-therapy (pento) [Figure 5].

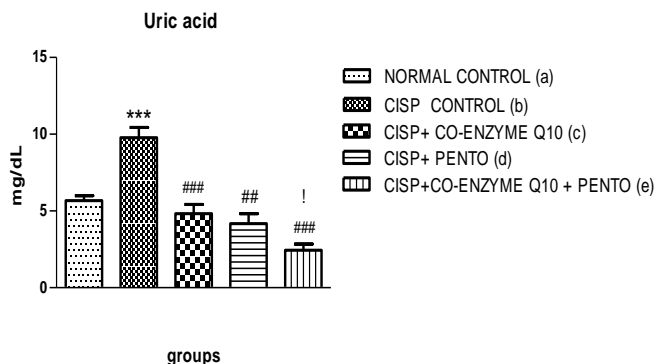


Figure 5: Effect of coenzyme Q10, pentoxifylline or combination of both on uric acid level in serum

Values are expressed as mean ± SEM; n=5

- a vs. b, ***P<0.001;
- b vs. c, and b vs. e, ###P<0.001
- b vs. d, ###P<0.01
- d vs e, ¹P<0.05

f) Effect of coenzyme Q10, pentoxifylline or combination of both on MDA:

There was a significant (P<0.001) increase in the levels of MDA level in renal tissue of cisplatin control as compared to normal control group. In contrast, the treatment with coenzyme Q10 or pento or coenzyme Q10 + pento showed a significant (P<0.001) decrease in the levels of MDA as compared to cisplatin control rats.. However, co-administration of coenzyme Q10 with pento showed a significant (P<0.05) decrease in MDA levels as compared to mono-therapy (pento) [Figure 6].

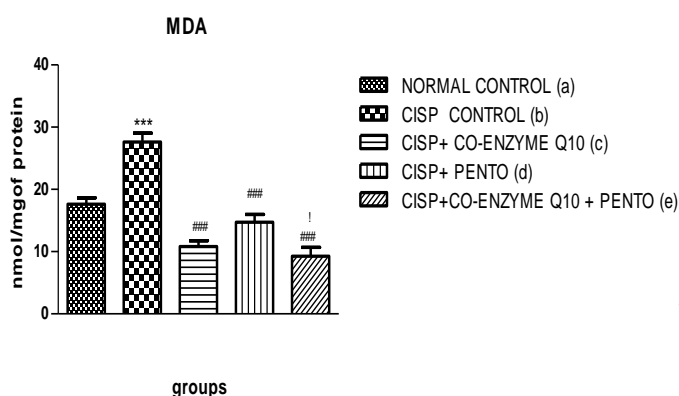


Figure 6: Effect of coenzyme Q10, pentoxifylline or combination of both on MDA level in renal tissue

Values are expressed as mean ± SEM; n=5

- a vs. b, ***P<0.001;
- b vs. c, b vs. d and b vs. e, ###P<0.001
- d vs e, ¹P<0.05

g) Effect of coenzyme Q10, pentoxifylline or combination of both on SOD level:

There was a significant (P<0.001) decrease in the levels of SOD level in renal tissue of cisplatin control as compared to normal control group. In contrast, the treatment with coenzyme Q10 or coenzyme Q10 + pento showed a significant (P< 0.01; P<0.001) increase in the levels of SOD as compared to cisplatin control rats, while the treatment with pento did not show any significant alteration in SOD levels as compared to cisplatin control rats. However, co-administration of coenzyme Q10 with pento showed a significant (P<0.05) increase in SOD levels as compared to mono-therapy (pento) [Figure 7].

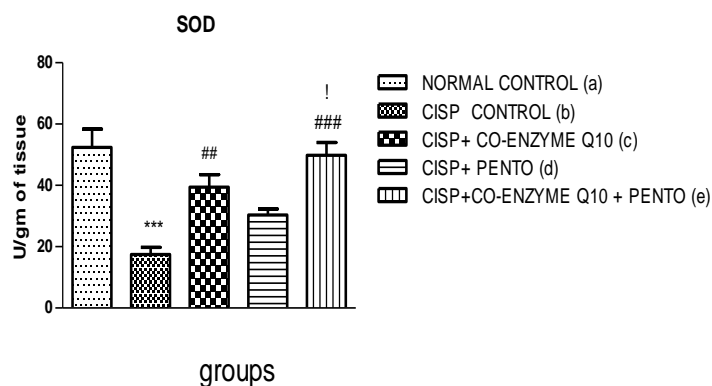


Figure 7: Effect of coenzyme Q10, pentoxifylline or combination of both on SOD level in renal tissue

Values are expressed as mean ± SEM; n=5

- a vs. b, ***P<0.001;
- b vs. c, ###P<0.01
- b vs. e, ###P<0.001
- d vs e, ¹P<0.05

a) Effect of coenzyme Q10, pentoxifylline or combination of both on Catalase level:

There was a significant (P<0.001) decrease in the levels of catalase in renal tissue of cisplatin control rats as compared to normal control group. In contrast, the treatment with coenzyme Q10 or pento or coenzyme Q10 + pento showed a significant (P<0.001) increase in the levels of catalase as compared to cisplatin control rats. However, co-administration of coenzyme and pento showed a significant (P<0.001) increase in catalase levels as compared to mono-therapy(coenzyme Q10 or pento) [Figure 8].

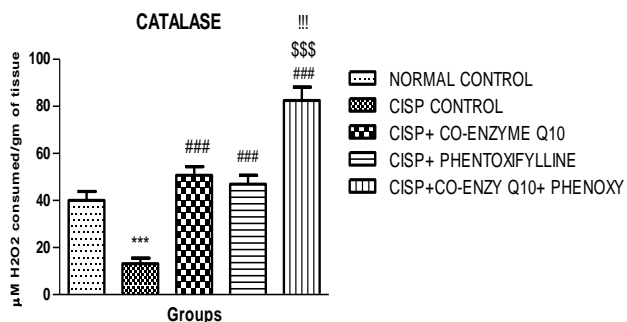


Figure 8: Effect of coenzyme Q10, pentoxifylline or combination of both on Catalase level in renal tissue

Values are expressed as mean ± SEM; n=5

a vs. b, ***P<0.001;

b vs. c, b vs. d and b vs. e, ###P<0.001

c vs e, \$\$\$P<0.001

d vs e, !!!P<0.001

a) Effect of coenzyme Q10, pentoxifylline or combination of both on GSH level:

There was a significant (P< 0.01) decrease in the levels of GSH in renal tissue of cisplatin control group as compared to normal control group. In contrast, the treatment with coenzyme Q10 or pento or coenzyme Q10 + pento showed a significant (P< 0.001) increase in the levels of GSH as compared to cisplatin control rats. However, co-administration of coenzyme and pento showed a significant (P<0.01) increase in GSH levels as compared to mono-therapy (coenzyme Q10 or pento) [Figure 9].

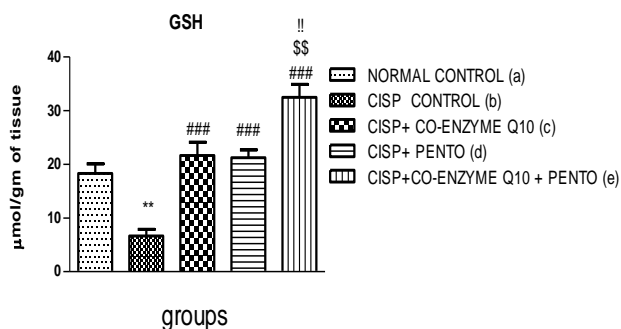


Figure 9: Effect of coenzyme Q10, pentoxifylline or combination of both on GSH level in renal tissue

Values are expressed as mean ± SEM; n=5

a vs. b, **P<0.01;

b vs. c, b vs. d and b vs. e, ###P<0.001

c vs e, \$\$\$P<0.01

d vs e, !!P<0.01

a) Histopathological observation :

The histological profile of the kidney tissue of the normal control animals showed a normal lobular architecture. Normal cells were arranged in single cell cords, while cisplatin treated rats showed disturbed kidney architecture. Cisplatin treated rats treated with coenzyme Q10 and pentoxifylline individually retain minimal inflammatory cellular infiltration and retain the tissue to normal structure, while combination of both coenzyme Q10 and Pentoxifylline showed normal kidney tissue architecture. (Figure 10 A-E)

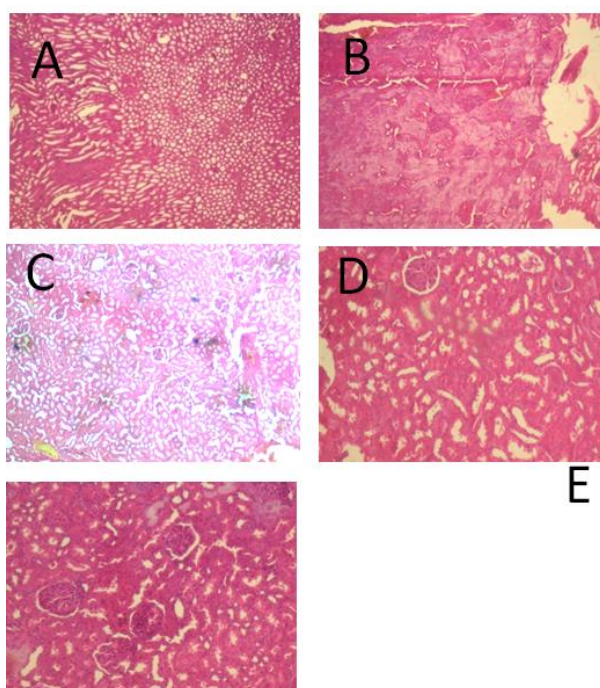


Figure 10: Effect of coenzyme Q10, pentoxifylline or combination of both on histopathological changes in renal tissue:

(A) Normal control ; (B) CISP control; (C) CISP + coenzyme Q10; CISP+ pento ; (E) CISP+ coenzyme Q10 + pento

4. DISCUSSION :

Kidney disease has afflicted humankind since antiquity. Nephrotoxicity continues to be a frequent cause of presentation to hospital. It has been estimated that approximately 122 of every 100,000 hospital admissions can be attributed to Nephrotoxicity [32]. Furthermore, once a patient is diagnosed with acute nephrotoxicity there is an increased likelihood that increase in toxicity will develop. Some studies have shown that 30-40% of patients with a history of acute nephrotoxicity will have another bout of chronic nephrotoxicity within 10 years

[33],[34] Although kidney activity are seldom fatal, they do cause considerable discomfort that results in hospital admissions and time away from work.

Pain is the most common symptom, especially when there is not proper functioning of kidney. The not proper working of kidney affect the facilitating spasms that occur periodically, and thus contributing to the intermittent pain often described by symptomatic patients. As the activity propels distally, the pain migrates in a parallel fashion. [35]

Management of nephrotoxicity depends on rupture and clinical symptoms. Patients with chronic symptoms accompanied with excruciating pain are often taken to the operating room for ureteroscopy, rarely surgery to facilitate relief. [36]

Recent trends towards increased operative management can be attributed to flexible and improved ureteroscopes [37]. Renalcopy, whether it is flexible or rigid, involves cannulation of the renal function. Once the renal orifices are identified, swelling, redness and pain as sign.

In this present study, nephrotoxicity was experimentally induced by the administration of Cisplatin (5mg/kg, i.p). on 5th days.

The present study was carried out to evaluate antioxidant activity of coenzyme Q10 with pentoxifylline on experimentally induced nephrotoxicity in Wistar rats. Antioxidant markers were analyzed from kidney homogenate. Histopathological study was carried out to confirm the biological changes [38]

Nephrotoxicity was experimentally induced in rats by oral administration of cisplatin. Rupture of morphological appearance of kidney was markedly seen in cisplatin control group compared to normal control. Similar results were also reported in previous studies [39-40]. However, treatment with coenzyme Q10 significantly prevented the appearance associated with cisplatin single dose treatment.

Cisplatin control group significantly increased serum calcium as compared to normal group animals. High calcium concentrations lead to increased saturation of calcium salts and reduced inhibitory activity by way of complexation with negatively charged inhibitors such as citrate [41],[42] Treatment strategies aimed at reducing calcium levels. It was observed that treatment with

coenzyme Q10 and pentoxifylline prevented cisplatin induced nephrotoxicity. Serum calcium level also significantly decreased in treatment groups compared to control group.

Normal urine contains many inorganic and organic inhibitors of crystallization, magnesium is one such well known inhibitors. Cisplatin control treatment significantly increased serum magnesium as compared to normal group animals. The magnesium levels return to normal on treatment with coenzyme Q10 and pentoxifylline while it shows significant decrease in magnesium level as compare to cisplatin control groups.

Serum creatinine was progressively increased in Cisplatin treated group animals. Increased creatinine level has been reported in nephrotoxicity. Treatment with coenzyme Q10 and pentoxifylline lowered the creatinine level and reduced the risk of nephrotoxicity and the level reaches to its normal position in the treatment group as compare to control group.

Serum uric acid level was progressively increased in cisplatin treated group animals. Increased uric acid level has been reported in nephrotoxicity. However, treatment with coenzyme Q10 and pentoxifylline significantly lowered the level of uric acid and the level reaches to its normal position in the treatment group as compare to control group.

Serum albumin level was progressively increased in cisplatin treated group animals. Increased albumin level has been reported in nephrotoxicity. However, treatment with coenzyme Q10 and Pentoxifylline significantly lowered the level of albumin and the level reaches to its normal position in the treatment group as compare to control group.

In nephrotoxicity, the glomerular filtration rate is disturbed due to the obstruction to the flow of urine by destruction in urinary system. Due to this, the waste products, particularly nitrogenous substances such as uric acid, urea, BUN and creatinine get accumulated in blood. However, supplementation with coenzyme Q10 and pentoxifylline significantly lowered the elevated levels of creatinine, uric acid, albumin in serum and take it to the normal level

Several experimental studies have shown that antioxidants can protect against oxidative injury. There was decrease in CAT, GSH, SOD and increase in MDA level

of cisplatin treated animals. Treatment with coenzyme Q10 and Pentoxifylline showed significant increase in CAT, GSH, SOD and decrease in MDA level compare to cisplatin alone treated group.

It was previously reported that the study with coenzyme Q10 and pentoxifylline treated group when compare with cisplatin induced nephrotoxicity various parameters either shows significant increase or significant decrease in the levels while it reaches to significant normal range with coenzyme Q10 and pentoxifylline treatment.

In discussion this study showed that coenzyme Q10 and pentoxifylline has a nephroprotective effect that was proven by biochemical and histopathological analysis.

Coenzyme Q10 and pentoxifylline has been shown nephroprotective activity with greater protective action as compare to alone dose treatment.

Moreover, coenzyme Q10 and pentoxifylline showed very positive and significant antioxidant effect with greater protective action as compare to alone dose treatment.

5. SUMMARY AND CONCLUSION

The nephroprotective effect of coenzymeQ10 and pentoxifylline was confirmed by the following measures:

In case of cisplatin treated groups there were rise in serum marker such as Calcium, Magnesium, Uric acid, Albumin and creatinine were as in case of coenzymeQ10 and pentoxifylline treated groups, there were significant decreased in the levels of serum markers.

In the present study, coenzymeQ10 and pentoxifylline formulations significantly increased the toxicant reduced levels of anti-oxidant parameter such as CAT, SOD, GSH and decreased in the levels of MDA were observed. Hence in the present study the anti-oxidant effects of coenzymeQ10 and pentoxifylline might be playing a major role in nephroprotective effects.

In cisplatin treated animals, there were severe histopathological disturbances in the kidney architecture. In contrast, coenzymeQ10 and pentoxifylline formulation treated group animals exhibited minimal kidney disarrangements and intact kidney architecture was maintained, indicating nephroprotective.

Finally, these results showed that coenzymeQ10 and

pentoxifylline showed a significant protection in dose dependent manner against experimentally induced nephrotoxicity. The possible mechanism behind the nephroprotective effect of coenzymeQ10 and pentoxifylline might be associated with stimulation of antioxidant defense mechanism against the free radicals generated by cisplatin. Therefore, it was concluded that coenzymeQ10 and pentoxifylline has a significant nephroprotective effects. Our present investigation supports the use of coenzymeQ10 and pentoxifylline in the treatment of nephrotoxicity.

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