

Comparative effects of tocopherol and ubiquinol on arsenic induced nephrotoxicity in sprague dawley rats

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Abstract: Millions of the people worldwide are drinking arsenic polluted water. The need of time is to find out the mitigation strategies to cope with this issue. To evaluate the effects of tocopherol and ubiquinol individually and collectively on arsenic induced nephrotoxicity in Sprague Dawley rats. 150 Sprague Dawley rats were divided into 5 groups randomly. Animals of group I were provided with distilled water and sterile diet pellets. All other groups were given arsenic contaminated water (5mg/L) *ad libitum*. Moreover, ubiquinol and tocopherol (250mg/kg each) were given to group III and IV rats respectively. Whereas, both tocopherol and ubiquinol (125 mg/kg each) was given to rats of group V. After 2 weeks of intervention period, serum RFTs were evaluated on micro lab. After exposure to arsenic, animals of group II showed a significant ($p < 0.01$) elevation of serum RFTs. Treatment with ubiquinol in group III animals and tocopherol in group IV animals reduced the levels ($p < 0.01$) of serum RFTs in these groups. Whereas, the combined effects of both these antioxidants reversed these changes to normal values ($p > 0.05$). Both tocopherol and ubiquinol (synergistically) are more efficient in minimizing the nephrotoxicity induced by arsenic.

Keywords: Arsenic, nephrotoxicity, tocopherol, ubiquinol.

INTRODUCTION

Arsenic is a well-known toxic metalloid which is ubiquitously present in the ground water. Naturally, it has 2 main forms e.g., organic and inorganic form (more lethal). Sodium arsenite is a highly reactive and toxic inorganic form of arsenic (Kuivenhoven *et al.*, 2020). According to WHO, the permissible concentration of arsenic in the drinking water is less than 0.01 mg/L (Organization, 2019). Approximately, 200 million people globally are drinking arsenic contaminated water and most of them are Asians (Shaji *et al.*, 2020). Among various South Asian countries, Pakistan, India, Nepal and Bangladesh are found to be the hotspots of arsenic toxicity (Uppal *et al.*, 2019, Ahmad *et al.*, 2020). The concentration of arsenic in potable water of sub-continent has alarmingly increased up to 37-47 mg/L (Chatterjee *et al.*, 2010). A meta-analysis performed in Pakistan in the year 2018 has indicated that more than 45 million Pakistanis are at a potential risk of arsenic toxicity (Shahid *et al.*, 2018). The province Sindh and Punjab of Pakistan are the epicenters of arsenic polluted water where the concentration of arsenic in drinking water is higher than 0.001 mg/dl and 0.005 mg/dl respectively (Sanjrani *et al.*, 2017). The use of arsenic in different industries is one of the major contributory factors leading to water contamination. Arsenic is used in agriculture as herbicide and pesticide, as wood preservative, in glass manufacturing, cosmetics industries and as a conductor in car batteries (Tessema *et al.*, 2020). Due to lack of water purification systems, the non-biodegradable waste materials from these sources get freely incorporated into drinking water thus harming the health of both animals

and humans (Ullah *et al.*, 2019). Hazardous effects of arsenic have been observed on multiple organs of the human body. The most lethal effects of arsenic on human body are teratogenic, mutagenic and carcinogenic (Minatel *et al.*, 2018). Chronic exposure to arsenic causes black foot disease, diabetes mellitus, endocrinopathies and cancers of skin, lungs and urinary bladder. Kidneys and liver are the main sites of metabolism and excretion hence, particularly are more compromised by arsenic exposure (Bjørklund *et al.*, 2018).

The most common mechanism by which arsenic induces toxicity is production of oxidative stress at cellular levels. Arsenic produces free radicals, induces lipid peroxidation, damages the natural structure and hence the performance of important anti-oxidant enzymes of human body e.g. glutathione reductase thus, induces cell death (Hu *et al.*, 2020).

To combat cellular damage, several protection mechanisms can be adopted. One of the best possible strategies is to add natural anti-oxidants in our diet that are strong enough to protect the normal functioning of living cells (Rahaman *et al.*, 2021). Tocopherol and ubiquinone both possess strong anti-oxidant properties and they are recently being used against arsenic induced cellular toxicity (Rasheed *et al.*, 2019).

Ubiquinol / CoQ10 is a naturally occurring vitamin-like anti-oxidant that is present in the inner mitochondrial membrane. It is named as ubiquinol because it is ubiquitously found in nature and it contains quinone in its structure. High concentration of ubiquinol is naturally found in kidneys, liver and heart (Arenas- Jal *et al.*,

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2020). It is also a component of our food and can be obtained by consumption of beef, chicken, fish, broccoli, soybeans, avocado and oranges. De-novo synthesis of ubiquinol from amino acid tyrosine is found in human body (Pravst *et al.*, 2010). Ubiquinol performs several functions in the living body e.g. ATP synthesis, protection of vessels and endometrium and most importantly ROS (reactive oxygen species) scavenging (Gutierrez-Mariscal *et al.*, 2020). It is used as a drug to treat cardiomyopathy, angina and end-stage cardiac failure. Moreover, being neuroprotective, it is used in the treatment of migraine, Parkinson's disease, hypertension, lactic acidosis and stroke-like episodes (Arenas- Jal *et al.*, 2020). Its dietary supplementation has also shown the protective effects on the kidneys against oxidative stress (Adikwu *et al.*, 2021).

Tocopherol belongs to the group of fat-soluble compounds that is collectively called as vitamin E. It includes four tocopherols and four tocotrienols. Four homologs of tocopherol and tocotrienols are α , β , γ and δ respectively. They are different from each other on the basis of number and position of methyl groups on the chromanol ring (Lee *et al.*, 2018). α -tocopherol is strongest anti-oxidant among other members of this group and widely distributed in our diet. It performs different functions in our body and one of them is combating against ROS (Caddeo *et al.*, 2018). It is a chain breaking anti-oxidant that donates its free hydrogen atom to neutralize free radicals thus, halts the propagation of oxidative stress (Holifa *et al.*, 2017). Higher concentration of tocopherol is found in central nervous system and in the cell membrane of red blood cells and lysosomes where it scavenges harmful ROS and thus maintains membrane integrity. Tocopherol also boosts up the immune system by modulating the functions of immune mediated cells (Galli *et al.*, 2017). Dietary intake of α tocopherol has been proven to be nephroprotective against oxidative stress (Abdel-Daim *et al.*, 2019). Besides acting as a potent anti-oxidant, α -tocopherol has a pivotal role in cell signaling, cell division and gene modulation (Gugliandolo *et al.*, 2017).

The significance of rising amount of arsenic in potable water of Pakistan and its hazardous health effects, prompted the designing of present study to probe the protective effects of both ubiquinone and tocopherol dietary supplementation against nephrotoxicity caused by sodium arsenite.

MATERIALS AND METHODS

It was a randomized controlled trial held in Collage of Physicians and Surgeons regional center Islamabad in collaboration with National Institute of Health, Islamabad and Multi-disciplinary Laboratory Army Medical College Rawalpindi. 150 Sprague Dawley rats were taken by non-probability sampling technique from the animal house of

NIH (National Institute of Health) Islamabad. Animals selected for this study were healthy male rats with 220-250g body weight and at 10-12 weeks of age. All the rats were placed at the animal house of CPSP (Collage of Physicians and Surgeons) regional center Islamabad and randomly divided into 5 groups (each = 30 rats). (Khan *et al.*, 2019). In the first week, no intervention was applied for the habituation of animals with the optimum environment where 23-27°C was room temperature, 50-70% was humidity level and 12h day and night cycle was maintained. During habituation period, animals were fed on standard rat diet and distilled water *ad-libitum*. After the habituation period, interventions were applied for 2 weeks. Ethical approval for all the interventions were taken by the "Ethical Research Committee of Army Medical College" (number of approval letter=ERC/ID/117) that were in accordance with the guidelines of "National Institute of Health Guide for Care and Use of Laboratory Animals" (publication # 85-23, revised at 1985). Animals of group I were taken as healthy control group and were provided with standard pelleted diet along with distilled water *ad libitum*. Group II was taken as diseased control group and was given standard pelleted diet along with arsenic contaminated water (5mg/L) *ad libitum*. Animals of group III were given ubiquinol (250 mg per kg mixed in rat diet) along with arsenic contaminated water (5mg/L) *ad libitum*. Group IV animals were given tocopherol (250 mg per kg mixed in rat diet) along with arsenic contaminated water (5mg/L) *ad libitum*. Whereas, group V was given mix diet (tocopherol + ubiquinol 125 mg per kg each) along with arsenic contaminated water (5mg/L) *ad libitum*. After intervention period, the animals were euthanized to take the blood samples via single cardiac puncture.

Sample of the blood of animals was collected into gel vacutainers that were placed with ice packs in thermocol boxes. After blood clotting in the vacutainers, serum was extracted by centrifugation at a speed of ~ 2500-3000 rpm for 9-10 minutes. Serum was stored at 4-8°C temperature in sterile eppendorf tubes in the CREAM lab (Center for Research in Experimental and Applied Medicine) of the Department of Biochemistry and Molecular Biology at Army Medical College. Serum estimation of RFTs were done by micro lab.

Serum urea was measured using urea BIOMED diagnostics colorimetric assay kit (LOT 101020). Creatinine was measured by Jaffe's method using CENTRONIC GmbH/ Germany colorimetric assay kit (REF CF11000050-2). Whereas, BUN was measured by standard calculation formula (BUN = Urea/2.1428).

STATISTICAL ANALYSIS

Data was analyzed by 23rd version of SPSS software. We calculated the mean along with standard deviation of the

values of serum urea, creatinine and BUN. Significant statistical difference among all the groups was measured by one way ANOVA test. Significant *p* value was ≤ 0.05 . Whereas, we applied Post hoc Tukey's (HSD) test for inter group comparison.

RESULTS

The comparative results of the means of urea, creatinine and BUN among all the groups are expressed in table 1. In comparison with group I results (healthy control group) after the intervention period (2 weeks), significantly high concentration of urea, creatinine and BUN were observed in the serum of group II rats (diseased control group). These results clearly demonstrate that arsenic has induced nephrotoxicity in these animals ($p < 0.005$). Values of these parameters in the serum of group III animals (treated with ubiquinol) were not only remarkably low but also more towards normal values ($p < 0.005$). Moreover, a significant reduction of these values were observed in the serum RFTs values of tocopherol treated group IV ($p < 0.005$). Whereas, noteworthy and an out-standing improvement in these parameters was observed in group V rats that were supplemented with both ubiquinol and tocopherol (mix diet).

Table 2 represents the comparison in between all the groups evaluated by post hoc Tukey's test. No statistical difference can be appreciated between group I and group V serum RFTs values ($p > 0.005$). Complimentary observations can be appreciated in the group III and IV results comparison ($p > 0.005$).

DISCUSSION

Millions of Pakistanis are exposed to chronically high concentrations of arsenic due to polluted potable water. Although, arsenic imparts toxic effects on almost all the organs of the body but liver and kidneys are its main target. Arsenic is metabolized in the liver by arsenic methyl transferase enzyme and is excreted through kidneys. Hence, its prolonged exposure particularly harms these two organs (Galli *et al.*, 2017).

The results of our study showed that arsenic exposure prompts nephrotoxicity which is manifested by toxic levels of urea, creatinine and BUN in the serum of group II animals. These findings are similar with the study of Jacques which has proven that prolonged exposure of arsenic also leads to rapid development of kidneys dysfunction in human beings (Saint-Jacques *et al.*, 2018). The biochemical mechanisms by which arsenic induces these toxicogenic effects include generation of free radicals e.g. superoxides ($O_2^{\cdot-}$), hydroxyl ions ($\cdot OH$), peroxy radicals ($ROO\cdot$) and peroxide radicals (H_2O_2). Arsenic un-couples the electron transport chain of mitochondria by inhibiting succinic dehydrogenase

enzyme (SDH). It depletes the concentration of NADPH by inducing NADPH oxidase (No) enzyme. Moreover, arsenic binds with the sulfhydryl group (-SH) of glutathione peroxidase (GSH), superoxide dismutase (SOD) and catalase (CAT) and interferes with their ability to combat against the free radicals and enhances oxidative stress at cellular levels. All of these effects lead to cell damage/autophagy (Souza *et al.*, 2018). So, from our findings, we may conclude that the nephrotoxicity seen in this study is because of the oxidative stress induced by arsenic.

Ubiquinol-a powerful anti-oxidant that is ubiquitously found in nature. Previous studies have proven that it is beneficial against heavy metals induced cellular damage. Fouad in 2011 concluded that intake of ubiquinol (10 mg/kg body weight) at regular basis can protect against arsenic induced testicular damage (Fouad *et al.*, 2011). Our study has shown that ubiquinol is protective against arsenic induced nephrotoxicity. Similar results were observed in the study of Okaily (Al-Okaily *et al.*, 2018). Possible biochemical mechanisms by which ubiquinol reduces nephrotoxic effects of arsenic in group III animals of this study include its ability to scavenge the free radicals produced by arsenic. Ubiquinol chemically reacts with DHLA (dihydrolipoic acid) and keeps itself in active and reduced form. Thus, it maximizes its own anti-oxidant abilities. To halt the oxidative stress, ubiquinol inhibits lipid peroxidation and increases the activity of reduced form of glutathione and glutathione peroxidase (Khalifa *et al.*, 2020). It stimulates the gene expression of superoxide dismutase and catalase by enhancing the Sirt1 (silent information regulator1) and Nrf2 (nuclear factor E2-related factor 2) mRNA expression (Samimi *et al.*, 2019).

Intake of vitamin E in the diet can prevent from several hazardous effects of reactive oxygen species. It significantly raises total anti-oxidant capacity (TAC) and minimizes the concentration of pre-oxidant molecules (TOS) (Parolini *et al.*, 2017). Khatun in 2020 concluded that vitamin E can improve the hematological parameters, body weight and histology of liver and kidneys which were damaged by exposure to arsenic (Khatun *et al.*, 2020). Results of this study showed significant improvement in serum RFTs of group IV animals after tocopherol dietary supplementation and similar results were seen in the study of Affandi (Affandi *et al.*, 2020). These effects are due to two principal oxidation mechanisms of tocopherol. Firstly, tocopherol reacts with highly reactive singlet oxygen to hydroperoxide compound. Secondly, it reduces the level of reactive oxygen species and also neutralizes them. Tocopherol also upregulates the production of catalase and glutathione peroxidase (Amraoui *et al.*, 2018).

Table 1: Mean ± SD and statistical significance of the values of serum RFTs

| Parameters | Group I (n=30) | Group II (n=30) | Group III (n=30) | Group IV (n=30) | Group V (n=30) | P Value |
|--|----------------|-----------------|------------------|-----------------|----------------|---------|
| Urea (32.144.94mg/dl (Johnson-Delaney <i>et al.</i> , 1996)) | 41.40 ± 6.08 | 167.89 ± 23.57 | 62.44 ± 7.11 | 67.92 ± 9.30 | 44.39 ± 6.85 | <0.001 |
| Creatinine (0.2-0.8 mg/dL (Johnson-Delaney <i>et al.</i> , 1996)) | 0.54 ± 0.27 | 2.99 ± 0.49 | 0.97 ± 0.18 | 1.01 ± 0.19 | 0.57 ± 0.26 | <0.001 |
| BUN (15-21mg/dl (Johnson-Delaney <i>et al.</i> , 1996)) | 19.31 ± 2.84 | 78.35 ± 11.00 | 29.13 ± 3.31 | 31.69 ± 4.34 | 20.71 ± 3.19 | <0.001 |

Table 2: Post hoc Tukey’s results indicating the inter group comparison

| Parameters | Group I | | | | Group II | | | Group III | | Group IV |
|------------|----------|-----------|----------|---------|-----------|----------|---------|-----------|---------|----------|
| | Group II | Group III | Group IV | Group V | Group III | Group IV | Group V | Group IV | Group V | Group V |
| Urea | <0.001 | <0.001 | <0.001 | >0.005 | <0.001 | <0.001 | <0.001 | >0.005 | <0.001 | <0.001 |
| Creatinine | <0.001 | <0.001 | <0.001 | >0.005 | <0.001 | <0.001 | <0.001 | >0.005 | <0.001 | <0.001 |
| BUN | <0.001 | <0.001 | <0.001 | >0.005 | <0.001 | <0.001 | <0.001 | >0.005 | <0.001 | <0.001 |

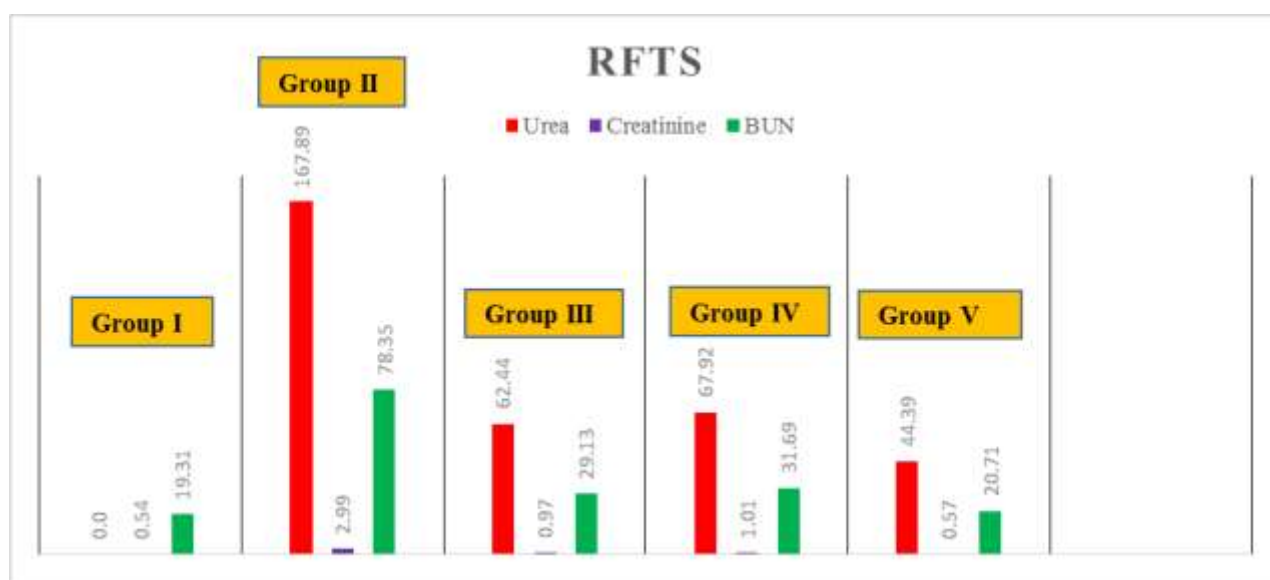


Fig. 1: Bar chart showing the intergroup comparison of the mean RFTs values.

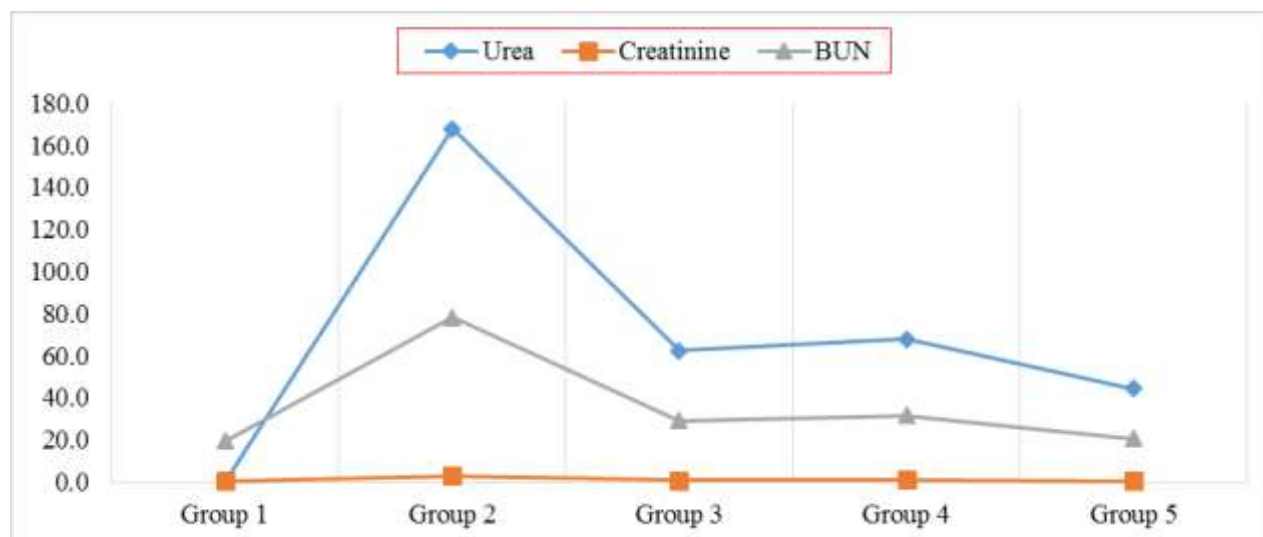


Fig. 2: Graphical presentation of summary of all the results.

Whereas, the combined effects of both of these anti-oxidants are even more protective against arsenic as compared to their individual effects. Sharma, in 2018, evaluated and proved that the combined effects of vitamin E and CoQ10 have positive effects on the nervous system of mice against arsenic (Sharma *et al.*, 2018).

Tocopherol and ubiquinol share many biochemical properties. First of all, both are direct ROS scavengers and strong anti-oxidants. Both amplify the activity of anti-oxidant enzymes and upregulate the gene expression and transcription factors responsible for mitochondrial activity. They are proven to increase the mass of mitochondria and improve its bioenergetics functions. Tocopherol and ubiquinol also work synergistically in many biochemical pathways. For ROS scavenging, vitamin E gives away its proton and stabilizes the free radicals. During this process, vitamin E itself converted into reduced tocopheroxyl radical. It requires another anti-oxidant to get back into original form. One of these anti-oxidants are ubiquinol and this phenomenon is called redox cycle and it is a non-enzymatic spontaneous chain reaction (Wang *et al.*, 1999). That is why, the combined effects of ubiquinol and tocopherol in this study showed more beneficial effects than their individual effects.

CONCLUSION

The results of this study, determine that arsenic induces nephrotoxicity by possibly producing oxidative stress, which is manifested by significantly high levels of serum urea, creatinine and BUN. Whereas, introduction of strong anti-oxidants e.g. tocopherol and ubiquinol can produce near normal levels of serum urea, creatinine and BUN by possibly scavenging the ROS species produced by arsenic and protect against nephrotoxicity.

The combined effects of both these anti-oxidants are even more protective as seen by the results that show no statistical difference between the values of serum RFTs of control group and group V animals (p value >0.005). It is because both these anti-oxidants work simultaneously in the redox cycle to combat ROS species produced by arsenic. For these reasons, we conclude that this combination of ubiquinol and tocopherol is beneficial in reducing arsenic induced nephrotoxicity.

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