Original Article

Amelioration of Aminoglycoside Induced Nephrotoxicity by α Tocopherol and Selenium; A Morphological Study

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ABSTRACT

Objective: The objectives of the study were to evaluate the morphological changes observed in aminoglycoside (Amikacin) induced nephrotoxicity in rabbits and their attenuation by concomitant administration of Alpha tocopherol and selenium in animal model.

Study Design: Experimental study

Place and Duration of Study: This study was conducted at the Department of Pharmacology, Azra Naveed Medical College, Lahore for the duration of six months.

Materials and Methods: Twenty-four rabbits were divided equally into four groups. Group 1 being control group was given 2ml of isotonic solution while group 2 was induced nephrotoxicity by giving Amikacin 150 mg/kg body weight daily for 20 days intramuscularly twice a day. Group 3 Amikacin was given along with alpha tocopherol (1g/kg body weight) and selenium (2mg/kg body weight) Intramuscularly for the same study period. Group 4 was given only alpha tocopherol and selenium in above doses. At the end of study, histopathology of kidney tissues was evaluated and morphological changes were noted.

Results: Histological evaluation showed that Amikacin produced degenerative changes in proximal tubules causing interstitial infiltration and vascular congestion which were later on histologically seen to be minimized by giving treatment with alpha tocopherol and selenium.

Conclusion: It was concluded that morphological changes induced by Amikacin were attenuated when alpha tocopherol & selenium were co-administered in specific doses.

Key Words: Alpha tocopherol, Selenium, Nephroprotection, Oxidative stress, Tubular necrosis, nephrotoxicity, Aminoglycosides, Reactive oxygen species, Glutathione peroxidase

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INTRODUCTION

Aminoglycosides have still maintained a central role in antimicrobial therapy for more than 70 years. Their story of success and continuing use can be claimed to their various properties which are unique to Aminoglycosides but such an extensive use is limited due to their adverse effects. Renal toxicity is one of the most frequent kidney troubles which might also be enhanced when aminoglycoside antibiotics, non-steroidal anti-inflammatory agents and chemotherapeutic agents are administered.[1] Various chemical reagents including ethylene glycol, CCl4 and heavy metals such as lead, cadmium, mercury and arsenic can also possess definite nephrotoxic potential which also present as an increased serum creatinine and urea levels along with severe proximal renal tubular necrosis; though it is reversible renal damage because of high regenerative capacity of tubular cells[2,4]. They can produce devastating effect on the kidneys resulting in acute renal failure, chronic interstitial nephritis and nephritic syndrome[2,3].

In the pathogenesis of renal injuries, inflammation and oxidative stress due to reactive oxygen species (ROS) are also documented as causative factors[4]. Medic B et al (2019) even described that sometimes a single dose of aminoglycosides may lead to renal damage[5]. As a consequence, drugs with prominent anti-inflammatory, anti-oxidative and nephroprotective properties were

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tested in various research projects to be used as nephroprotectants.

Since nephrotoxicity by aminoglycosides affects 15-20% of patients during treatment, preservation of normal renal function during life-saving treatments is a problem that needs to be resolved. So keeping in mind the nephrotoxic potential of so many substances, scientists are trying to find out nephroprotectants since decades to prevent nephrotoxicity [6].

Being the role of antioxidants and anti-inflammatory substances to shield nephrotoxicity, Alpha tocopherol is a lipophilic natural antioxidant while Selenium possesses essential elements & Co factor glutathione peroxidase protects DNA and other cellular organelles from oxidative stress. It has also some effects in preventing malignant transformation of cells[7]. Literature also reveals a protective effect of selenium and alpha-tocopherol against prostate cancer in humans[8].

In our previous study, we observed biochemical changes in blood and urine in aminoglycoside treated animals and their attenuation by alpha tocopherol and selenium [9]. Presently we investigated the morphological changes caused by aminoglycosides in renal tissue and possible nephroprotective effect of alpha tocopherol and selenium in animal model.

MATERIALS AND METHODS

The study was conducted on twenty-four males, local breed rabbits, weighing 1 to 1.5 Kg and age ranging from 7 to 8 months. They were fed on local diet with water ad libitum. Animals were divided in four groups at random with 6 animals in each group.

Group 1 (C) served as control group and was given isotonic solution 2ml twice a day, intramuscularly for 20 days. Group 2 (A) served as diseased group and was given. Amikacin 150 mg/kg body weight daily for the same study period of time, intramuscularly in two equally divided doses to produce experimental nephrotoxicity while group 3 (ATS) served as treatment group and was administered amikacin in the same dose group alongwith alpha tocopherol (1g/kg dissolved in olive oil) and selenium (2mg/kg in form of sodium selenite) simultaneously. Group 4 (TS) was only administered with alpha tocopherol and selenium in above mentioned doses intramuscularly in two equally divided doses [9].

All animals were sacrificed after 24 hours of the last dose of the drugs. Renal tissues were fixed in 10% formalin. Four sections were taken from each kidney including cortex medulla and pelvis. Renal tissues after processing were embedded in Paraffin blocks and were cut by microtome in 4-5um thickness. Slides were studied in Histopathology section of the department by ordinary light microscope after staining with eosin and hematoxylin [9]. Findings in all four groups of experimental animals were compared with control group for morphological changes.

RESULTS

Group 1 (Control) group showed normal morphology of kidney tissue (Fig. 1) while Group 2 revealed renal injury after administration of amikacin as indicator of nephrotoxicity. The morphological changes were mainly involving the renal tubules which showed patchy necrosis along with hyaline and granular casts in their lumina. Tubular cells were also seen shed in the lumina of renal tubules. There were hydropic changes in epithelial lining with cytoplasmic vacuoles at some areas. Glomeruli also showed congestion and loss of basement membrane. There was also lymphocytic infiltration in renal interstitium Fig. 2.

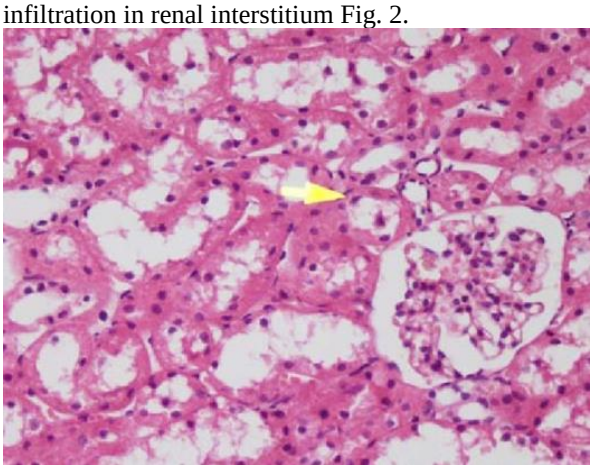

Figure No.1: Group (C)Control group showing normal morphology of renal sections (400 X)

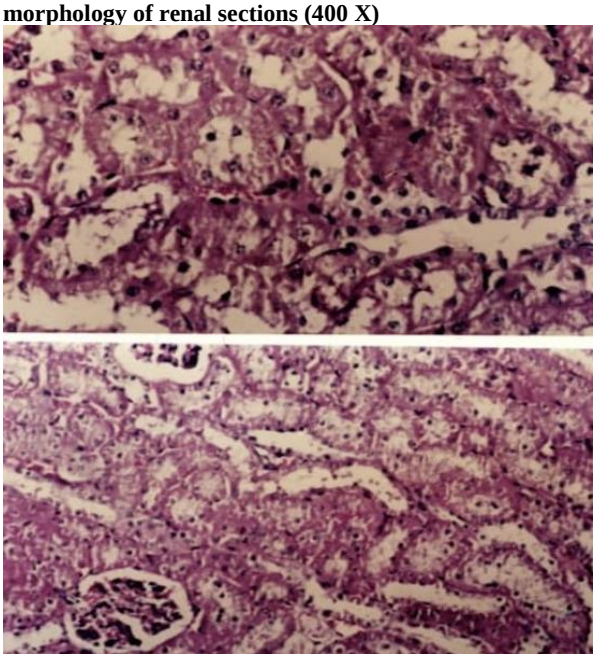

Figure No.2: (Amikacin treated) showing vascular congestion, tubular necrosis and interstitial inflammation, congestion and hypercellularity (400X) (100X)

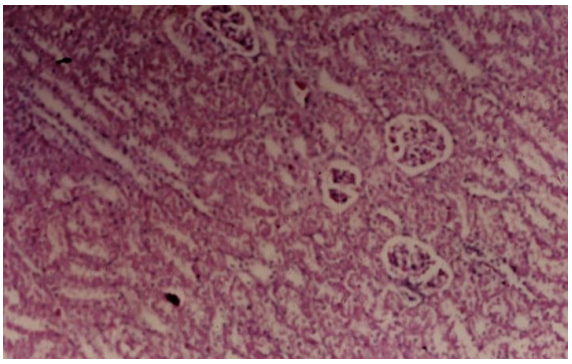

Figure No.3: (ATS; Amikacin , alpha tocopherol and selenium) revealing almost complete prevention of amikacin induced alteration in renal morphology by alpha tocopherol and selenium (100 X)

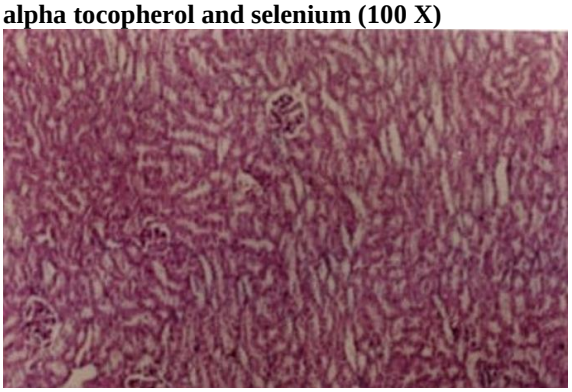

Figure No.4:(TS) Treated with alpha tocopherol and selenium only, showing no change in morphology as compared to control group

Group 3 treated with Amikacin along with alpha tocopherol and selenium showed preservation of tubular epithelial cells with mild changes in glomeruli (Fig. 3). Vascular congestion and interstitial inflammation were also reduced in group 3. Group 4 which was treated with alpha tocopherol and selenium showed normal renal morphology (Fig. 4).

DISCUSSION

Aminoglycoside antibiotics are continuously being used in clinical practice because of their bactericidal efficacy alone or in combination with other antibiotics. They are still indispensable in the treatment of so many life threatening infections because of their highly desirable properties.

Like all other Aminoglycosides, Amikacin induced nephrotoxicity is not only due to accumulation of drug in proximal and distal convoluted tubules but may also result in generation of reactive oxygen species which increase lipid peroxidation and lower the activity of antioxidant enzymes, so it can be blunted out by natural antioxidants like Vitamin E, Vitamin C, Selenium and Zinc [10]. Various studies have been conducted in the past to test this hypothesis and they are found promising in this context. There is always a need to come up with natural nephroprotectants to counteract adverse effects of aminoglycosides [11].

In our study, Group 2 (Amikacin treated) showed patchy tubular necrosis, hyaline and granular casts in tubular lumen, and hydropic changes in epithelial cells and dropped out tubular epithelial cells in the lumina of tubules. At some sites, the tubular epithelial cells also showed hydropic changes with cytoplasmic vacuolization. So our findings are in accordance with many other previous studies including Zahid *et al.*, 2007 [9,11].

In Group 3 (ATS), morphological changes in experimental animals after administrating the high doses of amikacin were evaluated but when coadministered with alpha tocopherol and selenium, showed its protective effect against amikacin induced kidney injury. This is in line with a study conducted by Elgami *et al.*, 2016, in which Alpha tocopherol and selenium confirmed protective effect in lead induced hepatic and renal injury in fish [12]. It is also in accordance with another study conducted by Bulan et al., in 2008 in which antioxidants like Vitamin E and C displayed some nephroprotection on biochemical markers and histopathological findings after cadmium induced renal toxicity in rats[13].

CONCLUSION

It is concluded the present in vitro study demonstrates that coadministration of amikacin with alpha tocopherol & Selenium can give impressive degree of amelioration against AG induced renal damage as assessed by histological criteria. Thus it is recommended to focus on supplementation of these agents to alleviate possible adverse effects of aminoglycosides. However, further studies are required to calculate safe dosage and elucidate exact mechanism of action of these two nephroprotectants.

Author's Contribution:

Concept & Design of Study:	Muhammad Zahid
Drafting:	Asma Inam, Khadija Mastoor
Data Analysis:	Anila Errum, Muhammad Usman Tahir, Faiza Khan
Revisiting Critically:	Muhammad Zahid, Asma Inam
Final Approval of version:	Muhammad Zahid

Conflict of Interest: The study has no conflict of interest to declare by any author.

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