J Renal Inj Prev. 2021; 10(x): x-x.

http://journalrip.com doi: 10.34172/jrip.2021.xx

Journal of Renal Injury Prevention

Protective effect of vitamin E on nickel sulfate-induced renal dysfunction in rats

Raziyeh Boroun[1], Behzad Fouladi Dehagi[1], Massumeh Ahmadizadeh[1,2*]

[1]Department of Occupational Health Engineering, School of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Physiology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

ARTICLE INFO

Article Type:
Original

Article History:
Received: 15 July 2020
Accepted: 9 November 2020
ePublished: 29 Deember 2020

Keywords:
Vitamin E
Nickel sulfate
Kidney
Oxidative stress

ABSTRACT

Introduction: The kidney is a major organ for nickel induced toxicity.
Objectives: The purpose of this investigation was to determine the protective impact of vitamin E on nickel sulfate ($NiSO_4$) caused kidney dysfunction in rats using biochemical and histopathological approaches.
Materials and Methods: Adult male Wistar rats were selected as animal models and randomly divided into four groups (five rats in each group) as follows; group 1. The animals received orally (gavage) 250 mg/kg vitamin E (dissolved in corn oil) 30 minutes before inhalation exposure to1mg $NiSO_4/m^3$. This experiment was performed for 6 hours daily for 10 consecutive days. Group 2; the rats received by gavage corn oil (vehicle) 30 minutes before inhalation exposure to1mg $NiSO_4/m^3$. This experiment was performed for 6 hours daily for 10 consecutive days. Group 3; animals of this group were given by gavage 250 mg/kg vitamin E only (without exposure to $NiSO_4$) for 10 consecutive days. Group fourth were received by gavage an equal volume of vehicle (corn oil) for 10 consecutive days. All animals were killed 24 hours after the last treatments with sodium pentobarbital. Kidney tissues were removed. One part of the tissues were used for glutathione (GSH) and malondialdehyde (MDA) determination, other parts were fixed and processed for light microscopy.
Results: The levels of MDA significantly increased and GSH decreased in rats exposed to $NiSO_4$ in comparison to those in non-exposed rats. Histopathological observations also indicated that $NiSO_4$ induced damage in the kidney. Additionally, administration of vitamin E prior to exposure to $NiSO_4$ markedly decreased renal damage-induced by $NiSO_4$.
Conclusion: The study showed that respiratory inhalation of $NiSO_4$ induced oxidative stress and caused cell damage in rats' kidney. Vitamin E effectively alleviated Ni-induced nephrotoxicity in rats. These observations suggest that vitamin E may have a protective effect against Ni-induced oxidative stress in the rats' kidney.

Implication for health policy/practice/research/medical education:
In an experimental investigation, we showed that vitamin E protects the kidney against nickel sulfate ($NiSO_4$) produced renal dysfunction. The protective mechanism is due to the improvement of oxidative stress generated by $NiSO_4$.
Please cite this paper as: Boroun R, Fouladi Dehagi B, Ahmadizadeh M. Protective effect of vitamin E on nickel sulfate-induced renal dysfunction in rats. J Renal Inj Prev. 2021; 10(x): x-x. doi: 10.34172/jrip.2021.xx.

Introduction

Nickel is one of the most commonly used metals in modern industry and is assumed as the main environmental pollutant. Important uses of nickel include producing stainless steels, special alloys (silver and nickel alloys for home appliances), chrome plating and mulching. Additionally, nickel salts have chemical uses and are used in some batteries. Human exposure to nickel primarily occurs through inhalation (1,2). Nickel is absorbed through the blood and distributed in various vital organs and excreted mainly through urine. The kidney is the major organ where is cumulate as well as responsible for nickel excretion. Thus kidney is known as a target organ for nickel. Exposure to nickel produced physiological and biochemical disturbances in human and animals' body (1-3). Several studies showed that nickel is mainly bio-accumulate in the rat's kidney. Nickel also showed to produce significant kidney damage and also depleted

***Corresponding author**: Prof. Massumeh Ahmadizadeh, Ph.D, Email: Ahmadizadeh_m@ajums.ac.ir

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antioxidant levels (1,3,4).

Although the mechanism of nickel-induced cytotoxicity is not fully understood; however, it is accepted that the production of free radicals may lead to lipid peroxidation, and depletion of antioxidant concentration is responsible for cell apoptosis and renal impairment. Chen et al reported exposure to nickel induced oxidative stress and caused injury in kidney cells of rats. These authors concluded that oxidative stress may play a major role in nickel induced nephrotoxicity (5).

Recently vitamin supplements have been generated considerable interest due to mainly their antioxidant capacity. Reddy et al demonstrated that L-ascorbic acid (vitamin C) protected rats against $NiSO_4$-induced cardiovascular disease (6).

Vitamin E is one of the important and essential substances. Vitamin E is a fat-soluble vitamin, also known as a potent antioxidant. Antioxidants protect the body's cells against the damaging effects of free radicals and can reduce the risk of various hazardous diseases such as cancer, heart disease or even Alzheimer's disease (7).

Jargar et al found that vitamin E protected rat's testis against nickel sulfate ($NiSO_4$)-induced toxicity (8). Similarly, Das et al reported that vitamin E protected rat's brain against $NiSO_4$ produced oxidative stress (9).

Objectives

To our knowledge, the protective effects of vitamin E on nickel-induced renal dysfunction in rats have not been documented. Therefore, the purpose of this study was to assess the protective role of vitamin E on nickel induced kidney dysfunction in rats.

Materials and Methods

Chemicals

The substance, 1, 1, 3, 3-tetraethoxypropane (TEP) was prepared from Merck Chemical Co. Other products included $NiSO_4$, 5, 5-dithiobis, 2-nitrobinzoicacid (DTNB), trichloroacetic acid (TCA), thiobarbituric acid (TBA), reduced glutathione (GSH) and sodium pentobarbital were supplied from Sigma Chemical Co.

Animals

Adult male Wistar rats (180-220 g) were obtained from the center of laboratory animal husbandry of Jundishapur University of Ahvaz, Iran. Rats were housed in groups of three in clear propylene cages in a light cycle (12 hours light and 12 hours dark) and temperature-controlled room kept in experimental laboratory for one week before the start of the experiment as an adaptation period. Rats were fed ad libitum with a regular rodent diet.

Experimental design

In this study, 20 adult male Wistar rats were randomly divided into four groups (five rats in each group). Group one received 250 mg/kg vitamin E dissolved in corn oil prior to inhalation exposure to 1mg $NiSO_4/m^3$ for six hours daily for 10 consecutive days. Group two received corn oil (vehicle), then 30 minutes later exposed to 1mg $NiSO_4/m^3$ for six hours daily for 10 consecutive days. Animals in group 3 received vitamin E (250 mg/kg orally), without exposure to $NiSO_4$ for 10 consecutive days while group 4 (control) was given by gavage an equal volume of vehicle (corn oil) for 10 consecutive days (10,11). Twenty-four hours after last treatments, animals were killed with sodium pentobarbital.

Then, the kidney tissues were removed. One part of the tissues were used for GSH and malondialdehyde (MDA) measurement and another piece was fixed in 10 % formalin and processed for light microscopy, by hematoxylin and eosin (H&E) staining. The criteria for cell injury included nuclear dilation, loss of staining capacity and obvious cellular swelling (12,13).

Biochemical assays

The tissue samples were homogenized in 10 mL of ice-cold TCA and centrifuged at 10 000 g for 15 minutes at 4°C and then supernatant was removed. Reduced GSH was determined by spectrophotometric method which was a modification of Ellman procedure (14). Lipid peroxidation was estimated by MDA production in kidney tissues and tested by the method prescribed by Balasubramanian et al (15).

Ethical issues

This experimental protocol was performed according to the regulations of the research ethics committee of Iranian ethical guidelines for the use of animals in research. All animal experiments were in accordance with protocols approved by the United States national institutes of health (NIH, 1978). This study was also approved by ethics committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.ABHC.REC.1397.045). Additionally, this study was extracted from MSc thesis of Raziyeh Boroun at this university (Grant # APRC-9706).

Data analysis

Biochemical results were expressed as the mean ± SE and accompanied by a number of observations. The data were analyzed using SPSS 16.0.data analyzed by using one-way analysis of variance (ANOVA), followed by post hoc analysis with LSD (least significant difference) test that probability value of ≤0.05 was determined to be statistically significant.

Results

Oxidative stress of kidney

Inhalation exposure rats to $NiSO_4$ increased MDA and decreased GSH levels in comparison with those in non-exposed (control) rats. Vitamin E had no effect on MDA

and GSH levels; however, pretreatment of rats with vitamin E markedly reduced MDA and increased GSH in animals exposed to $NiSO_4$ (Figures 1 and 2).

Histopathology

Administration of vehicle alone did not produce detectable damage in rats' kidney because the tissue sections presented normal architecture (Figure 3A). However, the $NiSO_4$-exposure animals showed alteration in the architecture of kidney morphology, including formation of vacuoles, tubular epithelial necrosis, dilation and loss of staining capacity (Figure 3B). The most remarkable histopathological modifications were noted in proximal convoluted tubular cells. Light microscopy showed that kidney proximal tubular cells were swollen and had loss of staining capacity, since nuclei appeared to be dilated. Vitamin E had no effect on kidney cells, but the extent of injury markedly decreased in vitamin E pretreatment of rats exposed to $NiSO_4$ (Figure 3C).

Discussion

Nickel is a heavy metal which is hazardous for human and animals. Nickel is found in nature in abundance in water, air and soil. This metal and its various compounds are used in various industries (1-4). Occupational exposure and environmental pollution can cause adverse effects on humans and animals (1,2). Complications of this metal have been reported as neurological, respiratory and liver and kidney failure (2). Kidney because of the high blood supply and ability to concentrate and excrete xenobiotics is susceptible to chemicals-induced renal injury. To our knowledge, limited studies have been reported on the adverse effect of respiratory exposure to nickel. We assessed the nephrotoxicity of nickel in rats following respiratory exposure, using biomarkers of oxidative stress and intensity of renal cell damage. Our histopathological data indicated that nickel produced damage in rat kidney. The extent of injury mainly was observed in proximal convoluted tubular cells. For instance, Elangovan et al showed administration of nickel induced histopathological alterations in rat kidney (16).

Dahdouh et al in an in *vitro* study showed the injury by nickel in rat's kidney proximal tubular cells (17). Similarly, ultrastructural modification of proximal cells of kidney in rats exposed to nickel nanoparticles was observed (18).

The mechanism by which nickel-induced toxicity is not clear. However, several investigators reported that generation of oxidative stress by nickel is responsible for its adverse effects (19,20). We found renal cell impairment is associated with increasing the level of MDA and decreasing the concentration of GSH of the rats' kidney which exposed to nickel. Administration of vitamin E protected the rats' kidney against nickel-induced renal toxicity as evidence by appearance of normal cell histology and enhanced GSH and reduced lipid peroxidation in rats' kidney, exposed to Ni. These data further suggest that

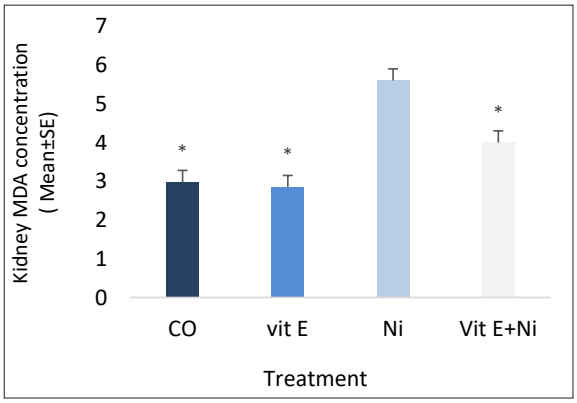

Figure 1. Effect of 250 mg/kg vitamin E on MDA level in rat kidney tissues exposed to 1 mg $NiSO_4/m^3$ (Ni). *Significantly different from rats exposed to Ni ($P \leq 0.05$). Ni, nickel;

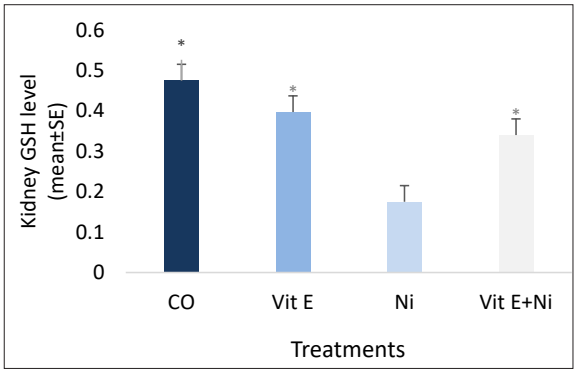

Figure 2. Effect of 250 mg/kg vitamin E on GSH level in rat kidney tissues exposed to 1 mg NiSO4/m^3 (Ni). *Significantly different from rats exposed to Ni ($P \leq 0.05$). Ni, nickel;

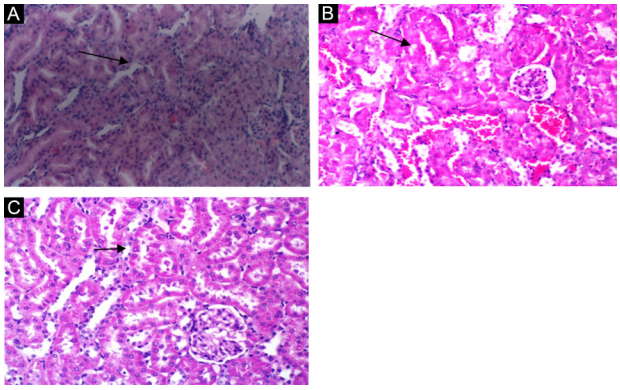

Figure 3. (A) Light micrograph of rat kidney treated with vehicle (control) showing the normal architecture of renal cells (arrow) (H&E ×200). (B) Light micrograph of rat kidney exposed to $NiSO_4$ (1 mg/m^3), showing tubular necrosis, loss of staining capacity and dilation of proximal convoluted tubular cells (arrow) (H&E ×200). (C) Light micrograph of rat kidney pretreated with 250 mg/kg vitamin E, 30 min prior to exposure of $NiSO_4$ (1 mg/m^3), showing no obvious injury in kidney cells. The proximal cells (arrow) (H&E ×200).

generation of oxidative stress is responsible for nickel-produced nephrotoxicity.

Our data showed that nickel elevated MDA as an index for lipid peroxidation and reduced levels of GSH in comparison to unexposed rats. These findings clearly indicated that nickel induced oxidative stress in renal rats' tissue. Likewise, Adedara et al reported that pretreated rats with zinc decreased nickel produced oxidative stress (21). These authors reported that zinc might reduce nickel toxicity through antioxidant activity. Accordingly, Hasanein and Felegari revealed that pretreatment of rats with carnosine, ameliorated nickel-induced nephrotoxicity (22).

Reddy et al showed vitamin C as an antioxidant agent protected cardiac and aortic tissues in rats against nickel toxicity (6). Findings of Rao et al suggests that vitamin E has a protecting role against nickel chloride produced oxidative stress by preventing antioxidant system in mouse ovary (23). Altogether, generation of oxidative stress is responsible for nickel-induced toxicity.

Conclusion

The current study indicated that respiratory exposure rats to $NiSO_4$ caused renal cell impairment and produced oxidative stress when compared to those in unexposed animals. Vitamin E protected the kidney against $NiSO_4$-induced biochemical and histopathological alterations in rats. The renal protective effects of vitamin E include amelioration of lipid peroxidation caused by $NiSO_4$ as well as elevation of GSH level by this vitamin and preserving the normal histological architecture of the renal tissue.

Acknowledgments

The source of data used in this paper was from the master thesis of Raziyeh Boroun, student of occupational health engineering department, school of health, Ahvaz Jundishapur University of Medical Sciences. Our special thanks to Dr. Malaekeh for reviewing histopathological samples.

Authors' contribution

RB provided technical assistance, collection and preparation of the manuscript. BFD acted as a consultant. MA designed, supervised the study and prepared the final draft of the article. All authors read and signed the final paper.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study was supported by physiology research center and the research deputy of Ahvaz Jundishapur University of medical sciences (Grant # APRC-9706).

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