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ORIGINAL ARTICLE

Zinc Oxide Nanoparticles Absorption Rate in the Heart Tissue of Female Mice

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KEYWORDS

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ABSTRACT: Nanotechnology researchers have identified a wide range of nanoparticle applications that may have an important role in medicine and treatment of diseases. Due to lack of detailed documentation about the toxicology of zinc oxide (ZnO) nanoparticles, this study was aimed to evaluate the absorption of ZnO nanoparticles in hearts of female NMRI mice. Overall, 20 adult NMRI female mice were studied in experimental and control groups. ZnO nanoparticles with concentration of 100 and 300 mg/kg were administered in the drinking water for 28 days and the mice were dissected after 28 days. Then, the heart tissues were isolated and dissolved in acid and the amount of ZnO deposited into the heart tissue was measured by atomic absorption spectrophotometer. ZnO nanoparticles treatment groups were significantly influenced by the nanoparticles compared with the control group. The experimental group 1 and 2 had a significant increase in ZnO NPs absorption in heart tissue compared to the control group (P<0.01). Due to the physiological similarities between mice and humans, the results of this study can be applied in prevention of the cardiac damage during the consumption of ZnO NPs.

INTRODUCTION

Nanoparticles (NPs) are important scientific tools employed in a variety of industrial, biotechnological, medical and pharmacological arenas. Such particles possess two specific properties entailing their large surface area, which dominates the contributions that have been made through small bulk of the material along with their quantum effects [1].

Nanotoxicology is a progressive knowledge, with a few studies published to date. There is no sufficient material in the literature regarding the behavior of NPs to

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determine whether they pose enhanced risks to human health or not [2, 3].

Many questions arise regarding the risks and the impacts of human health exposure to NPs because it has already been proven that inhaled NPs are capable of being rapidly translocated to other organs like liver and kidney [4]. Nanotechnology is developing rapidly and is used in areas including health, cosmetics, toiletries, food, and even toys [5- 7].

Zinc oxide (ZnO) nanoparticles are of great interest for applications in various fields including their use **in** skin creams to prevent sunstroke, biosensor, food additives, pigments, resins and electronic materials production [8]. Furthermore, due to the antibacterial properties of ZnO NPs, they could be applied in preventive drugs against microbes associated with infections and diseases [1].

Zinc, which is an essential element, required in small quantities, yet toxic at higher doses, is able to induce apoptosis or necrosis [9]. Zinc behaves as a contributing factor in more than 300 metaloenzymes participating in the metabolism of proteins, lipids, carbohydrates, DNA transcription and protein synthesis [1]. Since DNA replication is an important part of the development of germ cells, zinc is a vital element for reproduction [10].

Zinc acts as a cleaning agent of the superoxide produced by malformed spermatozoa or leukocytes in vivo. It is capable of cleaning the free radicals induced by a variety of factors, including ionizing radiation and reduced malonyl dialdehyde (MDA) levels. Therefore, it is known as an antioxidant with high protective power [11].

Application of ZnO as the most common combination of zinc is preferred for two reasons [9]: first, it has the highest concentration of zinc [12] and second, the absorption is high in body and better tolerated by the digestive system [13].

Recently, ZnO NPs have been of great interest in medical and biological studies [14]. Nano materials with remarkable biological properties and low toxicity appear to have a great potential in traversing the physiological barriers and having access to specific target tissues [6].

Since heart is a vital organ, the present study was conducted to evaluate the absorption of ZnO nanoparticles in hearts of female mice.

MATERIALS AND METHODS

Samples were female NMRI mice with one-month age and a body weight of 32-40 g. The mice were purchased from Pasteur Institute of Iran. Each mouse was used only once. Animals were kept in the Animal House of Islamic Azad University, Damghan Branch under a 12-hour-light-dark cycle at a temperature of 23 ± 2 °C along with the relative humidity of 60-40. The animals were freely exposed to food and water at standard conditions. Then, the animals were weighted and divided into three groups (n= 10 per group):

1- Control group (recipients of only drinking water).

2- Experimental group 1 (recipients of drinking water + 100 mg/kg of ZnO NPs).

3- Experimental group 2 (recipients of drinking water + 300 mg/kg of ZnO NPs).

Procedures involving animals and their care were conducted in conformity with the Helsinki Declaration and guidelines for the care and use of laboratory animals approved by the Animal Care and Use Committee of Damghan Branch, Islamic Azad University.

After 28 days, the mice were anesthetized by ether and then, dissected. Then, their hearts were separated from the body, and their wet weight was measured**.** Next, the hearts were placed in an oven for 2 hours at 60 °C for drying. After that**,** samples were placed in test tubes, 3 ml of nitric acid was added to the tubes, and the samples remained in nitric acid for 3 days. After 3 days, they were heated in water bath at 90 °C for 45 minute. Finally yet importantly, 2 ml of hydrogen peroxide were added to them and then were filtered by filter paper. Finally, the atomic absorption of ZnO NPs deposition rate was measured by a spectrophotometer.

RESULTS

The results of the current study on the deposition rate of ZnO NPs in the heart tissues of female mice show that the experimental group 2 (dose of 300 mg/kg) revealed significantly different results compared to those of the experimental 1 and control group (Figures 1, 2 and 3).

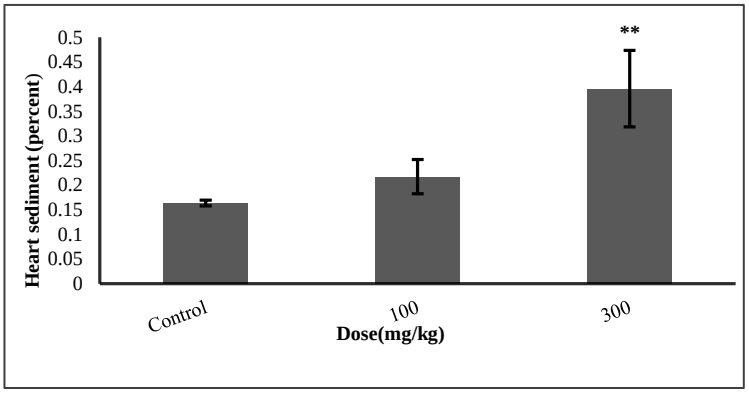

Figure1. Mean ± Standard deviation of ZnO NPs in the heart tissue. **: Significant difference in the level of $P<0.01$. Results indicate that the experimental group 2 had a significant increase in ZnO NPs absorption in heart tissue compared to the control group ($P<0.01$)

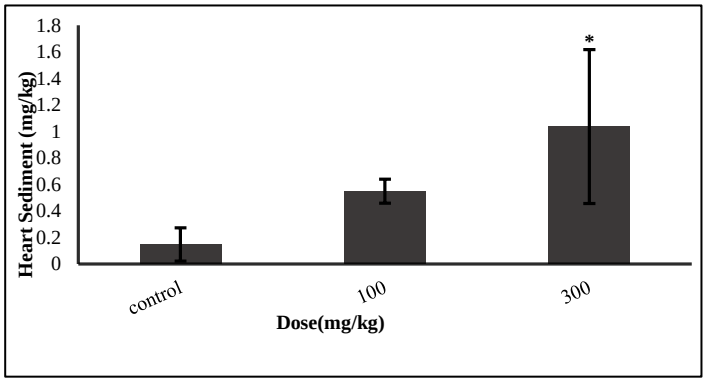

Figure 2. Mean ± Standard deviation of ZnO NPs in 1 gram of heart tissue. *: Significant difference in the level of $P<0.05$. Results indicate that the experimental group 2 (dose of 300 mg/kg) had a significant increase in ZnO NPs absorption in heart tissue compared to the control group ($P<0.05$)

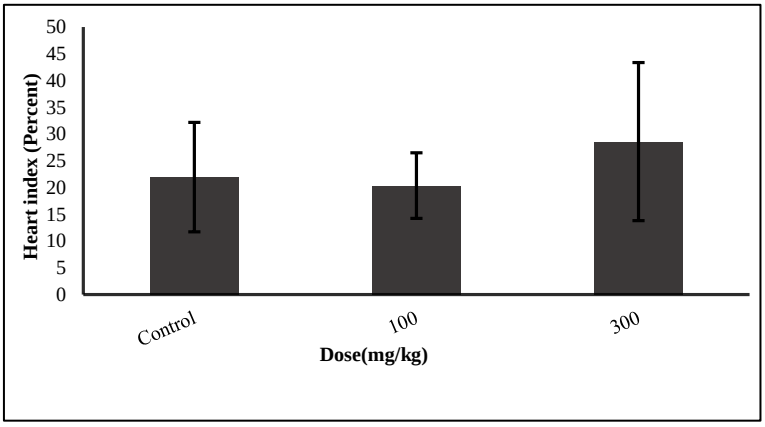

Figure 3. Mean ±Standard deviation of heart index. Results indicate that the experimental groups 1 and 2 show no significant difference with control group ($P<0.01$)

DISCUSSION

Development of nanotechnology has increased its use in cosmetic and medical supplies. Hence, precautions are required when using appliances containing nanoparticles. In a study on the chronic effects of zinc on liver, kidney and spleen of rats, a dose of 10 mg/kg of zinc was injected to rats for a period of thirty days and results revealed that most of the changes resulting from zinc on the liver, kidneys and spleen were reversible [15].

Nanoparticles uptake is conducted by macrophages through an intermediary protein called opsonin. By adsorption of proteins on the surface of NPs, the immune system identified them as aliens and therefore, macrophages attracted them. Opsonization is a dynamic and complex process that involves a wide variety of proteins including immunoglobulins and complement system components (ie, C3 and C5) that play an important role in immune system. Firstly, proteins are absorbed on the surface of NPs reversibly, and 50 to 60% of the molecules are randomly stuck to the surface and then, the molecules are slowly ordered and the possibility of their removal from the surface would decrease. Then, the protein is denatured and its chains spread over the surface with more adhesion to the surface and therefore, the possibility of dislodge from their surface is less compared to the extent that macrophages identify them. In some cases, the hydrophobic forces are the dominant force in protein binding to the surface of foreign bodies. Further proteins expose more of their internal hydrophobic surfaces through spreading of unfolding side chains and therefore, have more reactions with the surface [16].

Most of nanoparticles are not easily absorbed in body. For example, bipolarity of molecules causes their difficult pass through cell membranes. The capacity to absorb is often described as oral bioavailability. The ration of maximum concentration of admixture, fed to the dose concentration when directly injected into blood stream, defines oral bioavailability. Furthermore, less blood velocity in a tissue can enhance absorption. All nanoparticles of chemicals such as PACA, PLGA, PLA albumin and polyester lack good function and hence, possess a short half-life in the body. For instance, to achieve a successful target drug delivery and release, the particles are naturally collected in the MPS system. It has been recognized that the quantity and quality of surface opsonization depends on physicochemical properties, particle size, surface charge and surface hydrophobicity [17].

The absorption of opsonin on hydrophobic surfaces is more than hydrophilic surfaces. The particles, which are more hydrophobic, have been identified more by the MPS system and are excreted faster. The particle surface charge plays an important role in the capture and filtration from circulation by the MPS system. In most vascular areas of the body, blood flow greatly depends on tissue metabolism [18].

At least three factors have strong effects on metabolic control of blood flow: 1- concentration of CO_2, 2- concentration of hydrogen ion, and 3- concentration of oxygen ions. Rising concentrations of carbon dioxide (CO_2) in arterial blood flow of the heart tissues greatly increase the circulation. Moreover, carbon dioxide can increase the acidity and thus, the hydrogen ion concentration and hydrogen ions dilate blood vessels. Nanoparticles move freely in the blood vessels due to their small size and enter into the heart tissues. The amount of capillaries in tissues with higher metabolic activity is more. The heart has many capillaries that absorb the nanoparticles in it due to their high metabolic activity. Since the area of the capillaries is 800 times of the aorta, they have an important role in circulation. On the other hand, the lower rate of blood flow in

capillaries compared to aorta can affect the absorption rate [17]. Nano-sized ZnO particles stimulate neural stem cell apoptosis [19].

The results of the studies conducted on microorganisms about the toxic effects of ZnO NPs indicate that ZnO NPs inhibit the growth of intestinal bacteria, *E. coli* and protect cells against the damage caused by it.

The increased concentration of ZnO nanoparticles in the heart tissue shows that this organ has the ability to absorb these NPs and therefore, it is a vulnerable organ in exposure of NPs materials.

CONCLUSIONS

There was a considerable absorption of NPs in the hearts of female mice. The drinking consumption of ZnO NPs (dose of 300 mg/kg) is capable of affecting the heart tissues in a period of 28 days with no change in heart weight. Moreover, due to the physiological similarities between mice and humans, the results of this study can be applied in prevention of the cardiac damage during the consumption of ZnO NPs.

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