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Original Article

The Acute Inflammatory Response Induced by Fe2nio4 Nanoparticles: In Vivo Evaluation

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Abstract

Introduction: *Despite the ever-increasing beneficial applications of magnetic nanoparticles in biological systems, few studies have been carried out on the combined effects of nanoparticles (Fe and Ni) on human health. In the present study the effects of Fe2NiO4 nanoparticle on inflammatory factors were assessed.*

Methods*: Twenty-four Wistar rats were randomly divided into 3 groups: two groups were treated with Fe2NiO4 nanoparticle; (2,3) and the third group was taken as the control group (1). Group 2 and 3 received 0.5ml of solution containing 100 and 200 ppm Fe2NiO4 for 7 successive days, respectively. Inflammatory cytokines such as IL-6 and Tumor necrosis factorα (TNFα) were measured at various time points (1, 2, 7 and 14 days) by ELISA kits. After 14 days, lung tissue was investigated.*

Results*: On day 7, IL-6 concentration significantly increased in-group2. Also during the 14 days, IL-6 concentration significantly increased in groups1and2 in comparison with control group. The concentration of TNFα on 7th day significantly increased in groups 2 and 3 and on day 14th, TNFα concentration significantly increased in groups 2 and 3compared to control group. There were no pathological changes between the control group and group 2 but in-group3, signals of fibrous and thickening of the air sacs were observed.*

Discussion: *In the present study we found that inflammatory cytokines (IL-6 and TNFα) increased in the groups treated with Fe2NiO4 and high dose of this nanoparticles caused drastic changes in lung tissue.*

Keywords: Fe2NiO4, IL6, TNF, Nanoparticle, Inflammation.
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Introduction

In recent years, nanotechnology has led to great changes in the industry and in this developing technology the role of nano-materials and nano-powders is undeniable. Nanoparticles composed of elements such as cobalt-iron and nickel with magnetic properties are called "Luxuriate or magneticnanoparticles" (1,2).

Magnetic nanoparticles are used for various medical conditions (3,4). Typically, the distribution of magnetic nanoparticles is varied in different types of organs, for example it is 80-90% in the liver, 5-8% in spleen and 1-2% in bone marrow. These particles may be interacting to components of the extracellular matrix such as plasma membrane of different cells including macrophages, endothelial cells, epithelial cells of skin and respiratory system (depending on the application method and particle size).

Iron oxide nanoparticles are widely used as a contrast agent in nuclear magnetic resonance (MRI) and hyperthermia for killing cancer cells. Nickel oxide is also used as catalysts in ceramics and storage batteries (5) and this particle is a compound with very low solubility and high biological resistance in the lungs (6).The physiological and chemical properties of nickel oxide have made it more useful than any other nanoparticles in assessing lung function. Despite the increasing of beneficial applications of magnetic nanoparticles in biological systems, few studies have been carried out on the combined effects of nanoparticles (Fe and Ni) on human health. In the present study, the effects of Fe2NiO4 nanoparticle on inflammatory factors were assessed. We evaluated the effects of intra-peritoneal injection of different doses of (100,200 ppm) Fe2NiO4 nanoparticles on inflammatory cytokines (TNF, IL-6) and lung tissue.

Methods and Material

This experimental study was performed on 24Wistar male rats. These animals were purchased from the Animal Center of the Shahrekord University and housed in stainless steel cages in a ventilated animal room. The room temperature was maintained at 20±2ºC, with relative humidity (60±10%) and 12-hour light/dark cycle.

Distilled water and sterilized food for rats were available ad libitum. They were acclimated to this environment for 7 days prior to dosing. Animals with a mean weight of 234± 43 g were divided into 3 groups: Control (group 1) and treated groups (2,3) received 100 ppm and 200 ppm concentration of Fe2NiO4, respectively. Nanoparticle and saline were injected for 7 consecutive days.

Nanoparticles of Fe2NiO4 and Fe2NiO4 provided by SigmaCo (Germany). In order to make sure of the size nanoparticles, 1 g of them was sent to the department of Materials Engineering of the Islamic Azad University (Najafabad branch), using X-ray tests and confirmed the validity of the nanoparticles size (figure 1).

Concentration of 100 ppm (stock solution 1): 50 mg of nanoparticles was required in 1 mL of distilled water (100 mg/1ml), to achieve 100 ppm concentration of the nanoparticle.

Concentration of 200 ppm (stock solution 2): 100 mg of nanoparticles was required in 2 mL of distilled water (200mg/1ml) to achieve 200 ppm concentration of the nanoparticle.

Detection of according to the manufacturer's instructions (Sigma Co.) at 2nd, 7th and 14th days after treatment inflammatory cytokines (IL-6 and TNF-α) were detected in the sera using enzyme-linked immunosorbent assay (ELISA) kits. All animals (at 14th day) were anesthetized by ether and sacrificed for histological assessment. The lung tissue was collected for histological evaluation.

All animal handling and manipulation procedures were performed according to the guideline of the Animal Welfare Act and Office of Research Ethics Committee of The experimental protocol involving animals was approved by the Committee of University of Shahrekord

Histological evaluation was performed according to the standard laboratory procedures. A small piece of lung fixed in formalin 10% (v/v) was embedded in a paraffin block, sliced into 5 µm thicknesses and then placed onto glass slides. The section was stained with hematoxylin-eosin (HE) and examined by light microscopy.

Tukey's test was used to evaluate differences between groups. P values of less than 0.05 were considered statistically significant.

Results

Biochemical assessment showed an increased in serum levelofIL-6 and TNF-α of mice receiving high dose of Fe2NiO4 (200ppm) after 7th and 14th days.

The level of IL-6 significantly increased in group 3 in comparison with group 2 (P= 0.016) and control group (1) (P= 0.030). In the 14th day, IL-6 significantly increased in groups 2 (P= 0.002) and group 3 (P= 0.007) compared to control group (Figure 2).

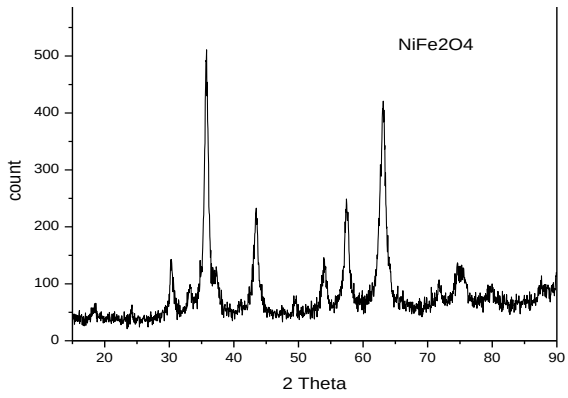

Figure 1. X-ray of Fe2NiO4 nanoparticle

At baseline and the second day, the levels of TNFα were similar in three groups (P>0.05). But on day 7th of the study, the level of TNFα increased in group 2 and 3 compared to group 1. on day 14th of study, the level of TNFα significantly increased in groups 2 and 3 in comparison with control group (Figure 3).

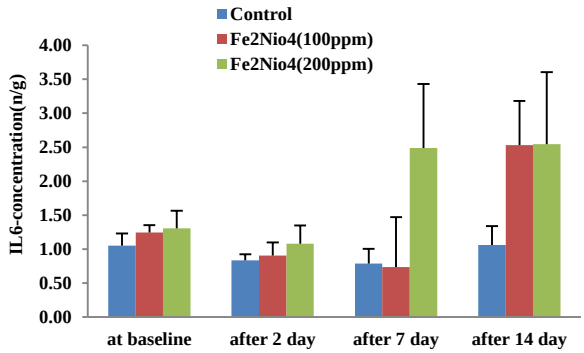

Figure 2. Comparison of IL-6(ng/l) concentration between group1, 2 and 3

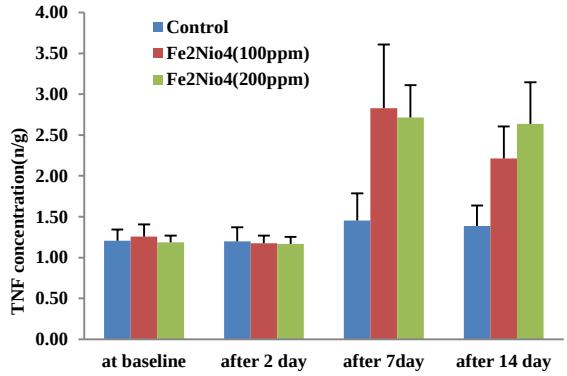

Figure 3. Comparison of TNF α (ng/l) concentration between group 1, 2 and 3

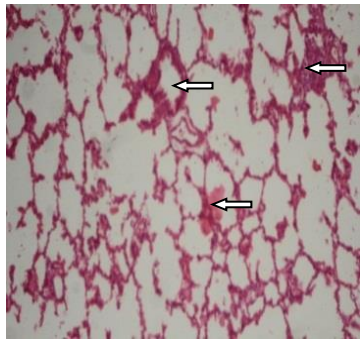

Figure 4. Light micrographs of lung sections in control group every day for 7 successive days (group 1)

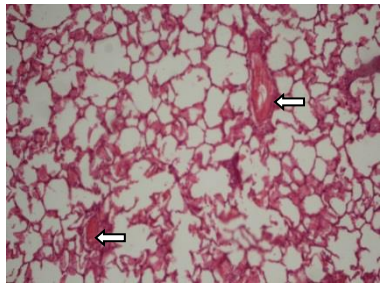

Figure 5. Light micrographs of lung sections in Fe2Nio4 -treated rat received 100 ppm every day for 7 successive days (group 2)

The histological photomicrographs of the liver sections are shown in figures 4-6.

In the control group, there were no pathological changes of lung tissue elements such as air bags and there were normal blood vessels insight (Figure 4). Although in group 2 there were not evident pathological changes in blood vessels but we saw slight hyperemia (Figure 5). In group 3, bronchioles were normal whereas air sacs wall thickening. Moreover collapse of air sacs, increased tissue fibrous and the sign segments was seen (Figure 6).

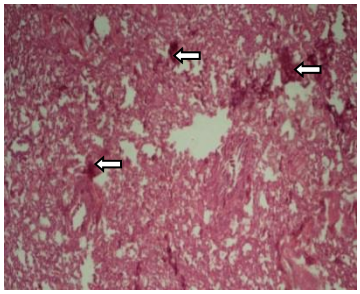

Figure 6. Light micrographs of lung sections in Fe2Nio4 -treated rat received 200 ppm every day for 7 successive days (group 3)

Discussion

The results of the present study indicated an increase in inflammatory cytokines in the treated groups with Fe2NiO4 and high dose of this nanoparticles caused drastic changes in lung tissue.

Studies have shown that nanoparticles could cause to toxicity includes: O xidativestress, inflammation, gene damage, body harness division and cell death (7-10). Production reactive oxygen species (ROS) and oxygen free radicals include superoxide an ion radical (O2·–), singlet oxygen (1O2), hydroxyl radical (·OH) and perhydroxyl radical (HO2·), which can be harmful in biological interactions and subsequent oxidative stress often have seen in nanoparticles toxicity (11).

Physicochemical properties such as particle size and chemical composition of nanoparticles (NPs) have significant impact on tissue damage and ROS production (12). NP-mediated ROS responses are accompanied by series of pathological events such as genotoxicity, inflammation, fibrosis and carcinogenesis. Many nanoparticles activate inflammatory cells such as macrophages and neutrophils that lead increased production of ROS (13,14,15).

ROS producing mechanism for each nanoparticleis different and the exact mechanism for ROS production has not yet been fully understood.

Red ox cycles could activate by many metal nanoparticles through reactions that are the most important sources of ROS in biological systems such as decomposition of chemical reactions and fenton reactions (16,17).

Phagocytes such as neutrophils and macrophages can induce oxidative burst after activation as a defense mechanism against environmental pollutants, cancer cells and microbes. Some nanoparticles such as metal oxide particles can lead to ROS production by phagocytes as one of the cytotoxicity mechanisms (18).

It has been reported that nanoparticles change the intracellular calcium concentration, activate transcription factors and cytokine production through production of free radicals (19,20). In addition to cellular damage, ROS production can be observed during interactions nanoparticle with biological targets (21). Significantly, oxidative stresses induced by nano-processed materials (NM) can lead to inflammation and fibrosis (22-24).

Another possible mechanism is the absorption of chemicals such as organic material by the surface of nanoparticles that is followed by the induction of inflammatory responses (25). Under moderate oxidative stress conditions, pre-inflammatory pathways are activated in an attempt to maintain redox balance. Inflammatory cascade consists of biochemical events including production of inflammatory cytokines such as TNF-α, TGF-β, IL-1β which participate in the pathogenesis of fibrosis.

Cellular response to oxidative stress can operate by increasing the production of cytokines (such as interleukin-1andTNF-α), the activation of kinases and inhibition of phosphatases that could affect phosphorylation cascade. Protein phosphorylation is involved in theregulation of many critical events such as mitogenesis, cell adhesion and apoptosis (26).

The studies (27-29) with reference to iron oxide Fe3O4 (magnetite) have shown that in given equal doses by mass, NPs considerably higher cytotoxicity for lung macrophages with higher sub-chronic systemic toxicity than micrometric particles of the same chemical composition. Moreover, it was indicated that, within the established nanometric range, the relationship between particle size and toxicity is complicated and non-unique, which may be due to its distinct properties such as differences in the toxicokinetics. This relationship is controlled by active physiological mechanisms that are responsible for both elimination and retention of NPs with various diameters according to their unequal penetrability through biological barriers and unequal solubility.

The results of this study indicated an increase in inflammatory cytokines in the rats treated with Fe2NiO4 and high dose of these nanoparticles caused drastic changes in lung tissue. Although the iron oxide consider as a non-hazardous compound but homeostasis imbalance can cause toxic effects. Thus, before the application of magnetic nanoparticles, a review of toxic and non-essential structures of nanoparticles is necessary.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Gupta AK, Gupta M. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications.Biomaterials. 2005;26(18): 3995-4021.

2. Mirkovic B, LahTurnsek T, Kos J.Nanotechnology in the treatment of cancer. ZdravVestn. 201079: 146-55.

3. Pankhurst Q. A, Connolly J, Jones S. K, Dobson J. Applications of magnetic nanoparticles in biomedicine.J. Phys. D. Appl. Phys. 2003;36: R167-81.

4. Saiyed Z. M, Telang S. D, Ramchand C. N.Application of magnetic techniques in the field of drug discovery and biomedicine.Biomagn Res Technol.2003; 1: 2.

5. Shubayev V. I.,Pisanic T. R., Jin S.,(2009),Magnetic nanoparticles for theragnostics. Adv Drug Deliv Rev.61: 467-77.

6. NTP Toxicology and Carcinogenesis Studies of Nickel Oxide (CAS No. 1313-99-1) in F344 Rats and B6C3F1 Mice (Inhalation Studies), 1996.

7. V. Stone, H. Johnston, M. J. D. Clift. Air pollution, ultrafine and nanoparticle toxicology: cellular and molecular interactions. IEEE Transactions on Nanobioscience. 2007; 6(4): 331-340.

8. H. J. Johnston, G. Hutchison, F. M. Christensen, S. Peters, S. Hankin, and V. Stone.A review of the in vivo and in vitro toxicity of silver and gold particulates: particle attributes and biological mechanisms responsible for the observed toxicity.Critical Reviews in Toxicology. 2010; 40(4): 328-346.

9. Z. Zhang, A. Berg, H. Levanon, R. W. Fessenden, and D. Meisel.On the interactions of free radicals with gold nanoparticles.Journal of the American Chemical Society. 2003; 125(26): 7959-7963.

10. I. M Kennedy, D. Wilson, and A. I. Barakat.Uptake and inflammatory effects of nanoparticles in a human vascular endothelial cell line.Research Report. 2009; 136: 3-32.

11. A. Nel T. Xia, L. Mädler and N. Li.Toxic potential of materials at the nanolevel. Science . 2006; 311(5761): 622-627.

12. A. A. Shvedova, A. Pietroiusti, B. Fadeel, and V. E. Kagan.Mechanisms of carbon nanotube-induced toxicity: focus on oxidative stress.Toxicology and Applied Pharmacology.2012; 261(2): 121-133.

13. Z. Zhang, A. Berg, H. Levanon, R. W. Fessenden., and D. Meisel.On the interactions of free radicals with gold nanoparticles.Journal of the American Chemical Society. 2003;125(26): 7959-7963.

14. I. M. Kennedy, D. Wilson, and A. I. Barakat.Uptake and inflammatory effects of nanoparticles in a human vascular endothelial cell line.Research Report. 2009;136: 3-32.

15. H. Lee, D. Shin, H. Song et al. Nanoparticles up-regulate tumor necrosis factor-α and CXCL8 via reactive oxygen species and mitogen-activated protein kinase activation.Toxicology and Applied Pharmacology. 2009; 238(2): 160-169.

16. Y. Huang., C. Wu., and R. Aronstam. Toxicity of transition metal oxide nanoparticles: recent insights from in vitro Studies.Materials. 2010; 3(10): 4842-4859.

17. B. Fubini, and A. Hubbard.Reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation by silica in inflammation and fibrosis.Free Radical Biology and Medicine. 2003; 34(12): 1507-1516.

18. L. Risom, P. Møller, and S. Loft.Oxidative stress-induced DNA damage by particulate air pollution.Mutation Research. 2005; 592(1-2): 119-137.

19. J. J. Li, S. Muralikrishnan, C. T. Ng, L. Y. Yung, and B. H. Bay. Nanoparticle-induced pulmonary toxicity.Experimental Biology and Medicine. 2010; 235(9):1025-1033.

20. C. Huang, R. S. Aronstam, D. Chen, and Y. Huang. Oxidative stress, calcium homeostasis, and altered gene expression in human lung epithelial cells exposed to ZnO nanoparticles. Toxicology in Vitro.2010; 24(1): 45-55.

21. K. Donaldson, and C. L. Tran. Inflammation caused by particles and fibers.Inhalation Toxicology. 2002;14(1): 5-27.

22. Donaldson, V. Stone, A. Clouter, L. Renwick, and W. MacNeeUltrafine particles. Occupational and Environmental Medicine. 2001;58(3): 211-216.

23. Donaldson K, Stone V, Tran CL, Kreyling W, Borm PJA. Nanotoxicology. Occupational and Environmental Medicine.2004; 61(9): 727-728.

24 A. Nel.Air pollution-related illness: effects of particles.Science. 2005; 308(5723): 804-806.

25. H. Sies. Oxidative stress: introduction, in Oxidative Stress Oxidants and Antioxidants, H. Sies, Ed., pp. 15-22, Academic Press, London, UK.1991.

26. M. Genestra.Oxyl radicals, redox-sensitive signalling cascades and antioxidants.Cellular Signalling. 2007; 19(9):1807-1819.

27. Katsnelson B.A, Privalova L.I, Sutunkova M.P, Tulakina L.G, Pichugova S.V, Beykin, J.B., Khodos,M.J.,(2012), The “in vivo” interaction between iron oxide Fe3O4 nanoparticles and alveolar macrophage.Bull. Exp. Biol. Med. 152: 627–631.

28. Katsnelson B.A., Privalova L.I., Sutunkova M.P., Khodos M.Y., Shur V.Y., Shishkina E.V., Tulakina L.G., Pichugova S.V., Beikin J.B., (2012), Uptake of some metallic nanoparticles by, and their impact on pulmonary macrophages in vivo as viewed by optical, atomic force, and transmission electron microscopy.J. Nanomed. Nanotechnol.3: 1-8.

29. Katsnelson B.A., Privalova L.I., Kuzmin S.V., Gurvich V.B., Sutunkova M.P., Kireyeva E.P., Minigalieva I.A., (2012), An approach to tentative reference levels setting for nanoparticles in the workroom air based on comparing their toxicity with that of their micrometric counterparts: A case study of iron oxide Fe3O4, Nanotechnology.12.