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An Evaluation of Biochemical and Hematological Parameters of Blood in Male Rats after Exposure to Nickel and Nickel Chloride Nanoparticles

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ABSTRACT

BACKGROUND AND OBJECTIVE: Nickel and its compounds are considered as carcinogenic agents. Considering the application of nickel and nickel nanoparticles in medicine, pharmaceutical industries, food, and cosmetics, it is important to study the destructive effects and toxicity of these nanoparticles on living organisms. The aim of this study was to investigate the toxicity of nickel nanoparticles compared with nickel chloride on biochemical and hematological parameters in rats.

METHODS: In this experimental study, 48 adult male rats were divided into 6 experimental groups and one control group and one sham group (n=6). The control group did not receive any treatment. The sham group received physiologic serum and the treatment groups received nickel and nickel chloride nanoparticles at concentrations of 5, 15 and 25 mg/kg intraperitoneally. One week after injection, blood samples were collected from the heart. Biochemical and hematological parameters were measured and compared for all groups.

FINDINGS: The results showed that the level of albumin in the nickel and nickel chloride nanoparticle group at concentration of 25 mg/kg decreased compared to the control (2.91±0.09 to 3.25±0.33, p=0.015) and (2.95±0.13 to 3.25±0.33, p=0.04), while the level of blood urea increased significantly (90.33±13.95 to 43.33±11.94, p<0.001) and (69.50±12.28 to 43.33±11.94, p=0.019). Creatinine and white blood cell count at 25 mg/kg concentration of nickel chloride showed a significant increase compared to the control (0.66±0.05 to 0.53±0.05, p=0.05) and (9.10±0.62 to 4.43±0.66, p=0.05).

CONCLUSION: The results of the study showed that nickel and nickel chloride nanoparticles stimulate the immune system, increase the number of white blood cells and change the biochemical parameters of the blood, which confirms the toxicity of the nickel nanoparticle.

KEY WORDS: *Nickel Nanoparticles, Nickel Chloride, Biochemical Parameters, Hematology Parameters, Male Rat.*

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Introduction

Nanotechnology utilizes the physical, chemical and biological properties of materials in sizes less than 100 nm in various sciences and industries (1). In recent years, nanotechnology has progressed rapidly in many branches of science. Nanoparticles are the basic elements in the framework of nanotechnology (2). These particles are used in a variety of applications because of the unique physical and chemical properties such as high surface-to-volume ratio and high quantum effects, solubility and mobility levels (3). The growing use of synthetic nanoparticles in human societies will undoubtedly lead to the release of such materials into a variety of environments and ecosystems. However, little research has been conducted on environmental behavior, the degree of release in various environments and its risk factors, and the safety of this compound for humans remains uncertain.

Nickel is a metallic and hard, malleable, white-silver element that is represented by the scientific symbol of Ni. Factories and burning waste are two main factors in the production of nickel and its entry into the air. Nickel chloride and nickel nanoparticles are used in medicine, pharmaceuticals, food, cosmetics and engineering. Therefore, it is important to know their toxicity in the body. Typical uses of nickel include the hydrogenation of vegetable oils, the production of heat-resistant dishes, the production of coins, the production of pharmaceutical compositions in pharmacy as carrier capacity for treatment and penetration of cellular barriers to drug delivery (4). According to the categorization of national toxicology of the United States, nickel and its compounds are considered to be carcinogenic and categorized by the International Agency for Research on Cancer (IARC) for nickel in Group 1 (4).

The digestive absorption of this metal is slow, but the inhalation of nickel fumes absorbs it. Most of its accumulation occurs in the lungs and brain and is excreted through the kidneys and bile. Nickel compounds pass through the pair and have teratogenic effects (5). Inhalation of nickel fumes causes nasal, larynx, lung, stomach and kidney cancer (6). Like most metals, nickel toxicity depends on the exposure pathway and the solubility of nickel compounds. The mechanism of the nickel is through the formation of non-reverse connections with vital macromolecules such as albumin, alpha2-macroglobulin, and L-histidine, which is why they interfere with the biological activity of the cells. The low molecular weight of the nickel complex and L-histidine makes it easy to pass through a biological membrane. Nickel is absorbed from the rhodium-gastric duct in the form of a lipophilic molecule of low molecular weight (7, 8). The molecular mechanism of the toxicity of nanoparticles is still not fully understood, but research has shown that active oxygen species play an important role in the toxicity of nanoparticles. Increasing the physico-chemical parameters of nanomaterials such as size, shape, structure and components of the nanomaterial has led to a complex and challenging study of the effects of cytotoxic nanomaterials (9).

Some of the paradigms for nanoparticle-induced toxicity include oxidative stress, inflammation, genetic damage, cell division and cell death (10-12). Active oxygen species are involved in cellular signaling and immune systems. By changing the surface of the reactive oxygen species (ROS), nanoparticles cause DNA damage, changes in the gene transcription process, changes in cytokines and damage to protein and fat, and can cause adverse effects in the cell (13). Inflammatory cells such as neutrophils and macrophages with nanoparticle phagocytosis produce a high level of ROS through the NADPH-oxidase enzyme system. Thus, nanoparticle-induced ROS cause an inflammatory cascade of chemokine and cytokine expression through the activity of cell signaling pathways such as MAPK, NF-kB, AKT, and RTK (15, 14).

Nanoparticles can be absorbed through the intestines and they are distributed in various tissues such as the brain, heart, liver, kidney and etc. and affect these organs. Nanoparticles can penetrate the depths of the tissues and can reach the lymph system and increase inflammatory responses (16). The cytotoxic information of nickel compounds, such as changes in the blood system and serum biochemical parameters, is less known at different intervals. The aim of this study was to investigate the toxicity of nickel nanoparticles in comparison with nickel chloride on blood cells and investigate the biochemical parameters of rat serum via intraperitoneal injection.

Methods

In this experimental study, 48 male Wistar rats aged 12-14 weeks and weighing 170-220 g were purchased from the Pasteur Institute of Amol. Rats were kept in the animal room of University of

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Mazandaran under standard conditions, temperature of 23±2 ° C and humidity of 60±10% in 12 hours of light and 12 hours of darkness, and water and food were always available to them in the form of pellets. The experiments were conducted in all groups under the same conditions and in accordance with the ethics of working with laboratory animals at University of Mazandaran and with the Code of Ethics UMZ.REC. 396001. For this study, the nickel nanoparticle was purchased from Sigma-Aldrich and nickel chloride was purchased from the Merck Co. (Germany), and their specifications are shown in Table 1.

In this experimental study, 48 adult male rats were randomly divided into 8 groups of 6, including a control group, a sham group and 6 experimental groups. Daily injectable compounds were prepared and in each stage before injection, were dissolved in physiologic serum for 15 minutes. One milliliter of each concentration was injected intraperitoneally for one week using an insulin syringe. The mice in the sham group were injected with one ml of 0.9% physiological serum daily.

The six experimental groups received nickel chloride and nickel nanoparticles at concentrations of 5, 15 and 25 mg / kg. After the last injection, with fasting conditions, blood sampling was performed under deep anesthesia. First, the rat was anesthetized with chloroform, the animal was fixed and blood collection from the heart was performed using a 5cc syringe. The blood sample was then centrifuged for about 15 minutes at 3000 rpm to separate the serum from the clot. Serum samples were collected until the biochemical parameters were measured at -20 °C. To measure the albumin, uric acid, total protein, urea, creatinine and CRP, a fully-automatic alpha-classic autoanalizer was utilized using Pars Azmoon kits on serum samples. Trucal U was used to calibrate and Trucal P was used to control the parameters. To measure total protein in serum, photometric method and enzymatic kit of biochemical CO. (Pars Azmoon Co.) were used. This test is based on calorimetry. In this experiment, the protein in the alkali environment with copper ions forms an azure complex. The color intensity is proportional to the protein content of the sample. Serum albumin was measured by photometric method and biochemical CO (Pars Azmoon). In this experiment, the albumin contained in the serum creates a green-blue colored complex with the bromocresol green in acidic pH. The intensity of the color is proportional to the amount of albumin in the sample. For diagnosis of urea in serum, photometric method and biochemical CO. (Pars Azmoon) were used. In this test, urea is hydrolyzed in the presence of urease and converted to ammonia and carbon dioxide.

Ammonia produced with 2-oxoglutarate and NADH react in the presence of glutamate-dehydrogenase and produce NAD and glutamate. Reduced adsorption of solutions is due to a decrease in the concentration of NADH per time unit relative to the urea concentration. The concentration of urea was reported in mg / dl. Quantitative detection of uric acid in serum was done by photometric method and biochemical CO. (Pars Azmoon). This assay was based on the enzyme and calorimetry using the Toos method (17). To detect creatinine in serum quantitatively, photometric method and biochemical CO. (Pars Azmoon) were used. In this experiment, creatinine formed a colored complex with alkaline picrate. The intensity of the color is proportional to the amount of creatinine in the sample. Creatinine concentration was reported in mg/dl. In this test, to detect quantitative CRP in the serum, anti-CRP-sensitive latex particles are agglutinated when adjacent to the sample containing CRP. The agglutination of Latex particles causes a change in optical absorption, which is measured by the amount of CRP present in the test sample, while comparing its optical absorption by the optical absorption of CRP calibrator. CRP concentration was reported in mg / dl. The measurement of all parameters was done by the International Federation of Clinical Institute (IFCC), using the COBAS MIRA autoanalyzer (18).

Table 1. Specifications of Nickel Nanoparticle and Nickel Chloride

Manufacturer	Product code	Percentage of purity	Color	Molecular Weight	Appearance	Density	Type of Material
Sigma-Aldrich	577995	99%	Black	58.69 g/mol	Spherical	8.9 g/cm^3	Nickel nanoparticle
Merck Co. (Germany)	106717	99%	Green	129.59g/mol	Crystalline	92.1g/cm^3	Nickel Hexahydrate Chloride

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Blood cell count: To conduct a complete cell counting test, the blood sample taken in a CBC vial containing EDTA anticoagulant was placed on a hematologic roller mixer for 29 minutes to mix and homogenize the sample, then the samples were transferred to the cell counter (Sismex) and blood cells, hemoglobin, hematocrit, and MCV levels were measured.

Statistical analysis method: After data collection, SPSS and One Way ANOVA were used for statistical analysis and Tukey test was used to compare the means. P<0.05 was considered significant.

Results

The results of the effect of different concentrations of nickel and nickel nanoparticles on blood biochemical parameters: Serum samples were used to measure biochemical parameters. Investigating the blood biochemical parameters, the results of this study showed significant changes in urea, uric acid and albumin. Statistical analysis of the groups showed significant changes in the amount of albumin (p = 0.001). The amount of albumin in the nickel chloride group was 25 mg/kg (2.91±0.09, p=0.015) and nickel nanoparticle at a concentration of 25 mg/kg (2.95±0.13, p=0.04) showed a significant decrease compared to control (3.25±0.33) (Table 2). The amount of albumin in the nickel nanoparticle group at a concentration of 5 mg/kg (p=0.053), nickel nanoparticle at a concentration of 15 mg/kg (p=0.003) and nickel nanoparticle at a concentration of 25 mg/kg (p=0.009) showed a significant difference compared to sham group. There was no significant difference in the amount of albumin among the rest of the experimental groups. Statistical analysis showed a significant increase in creatinine concentration in the studied groups (p=0.023). Creatinine showed a significant increase in the nickel chloride group at a concentration of 25 mg/kg (0.66±0.05) compared to control (0.53±0.05) (p=0.05).

There was no significant difference between the sham and other groups and also between the groups (Table 2). The results showed that blood urea significantly increased in treated groups (p<0.001). Blood urea showed significant increase compared to control in 5 mg/kg nickel chloride group (70.50±10.52 vs. 43.33±11.94, p=0.013) in 25 mg/kg nickel chloride group (90.33±13.95 vs. 43.33±11.94, p<0.001), and in 25 mg/kg nickel nanoparticle group (69.50±12.28 vs. 43.33±11.94, p=0.019) (Table 2). In addition, there was a significant difference between the sham group and 25 mg/kg nickel chloride group (90.33±13.95 vs. 56.2±11.18, p=0.002). 5 mg/kg nickel chloride group showed a significant difference with 5 mg/kg nickel nanoparticle group (p=0.03) and 15 mg/kg nickel nanoparticle group (p=0.027). 25 mg/kg nickel chloride group showed a significant difference with 5 mg/kg nickel nanoparticle (p<0.001) and 15 mg/kg nickel nanoparticle group (p<0.001).

Significant differences were observed between 15 mg/kg nickel chloride group and 25 mg/kg nickel chloride group (p=0.018). There was a significant difference between 15 mg/kg nickel nanoparticle group and 25 mg/kg nickel nanoparticle group (p=0.038). Statistical analysis showed a significant decrease in uric acid in the study groups (p<0.001). Uric acid in the control group showed a significant difference with all study groups except sham group (p<0.001) (Table 2). In addition, there was a significant difference between the sham and the rest of the groups (p<0.001). There was no significant difference between the control group and sham group, as well as among the other groups. CRP increased in the studied groups, but this difference was not significant compared to control. The results showed that total protein decreased in the studied groups, but this decrease was not significant compared to control (Table 2).

The results regarding the effect of different concentrations of nickel nanoparticle and nickel chloride on blood cells: CBC samples were collected from rats after blood sampling, and a full-automatic Sysmex device was used for counting blood cells and hemoglobin and hematocrit values and measuring MCV. The results of this study showed that the number of white blood cells in the studied groups increased significantly (p<0.027). The number of white blood cells in the 25 mg/kg nickel chloride group (9.10±0.62) showed a significant increase in comparison with the control (4.43±0.66) (p=0.05) (Table 2). The rest of the groups did not show any significant difference compared to each other and also to the sham group.

The changes in the number of red blood cells in the studied groups was significant (p<0.05). There was no significant difference between the number of red blood cells in treated groups and different concentrations of nickel chloride and nickel nanoparticle compared to control and sham. The number of red blood cells in the 25 mg/kg nickel chloride group decreased compared to control, but this difference was not significant.

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Significant difference was only observed between 25 mg/kg nickel chloride (6.46±0.40) and 15 mg/kg nickel chloride at p<0.017. The number of platelets in the studied groups did not change significantly. The results of this study showed that the hemoglobin levels in the studied groups changed significantly (p=0.01). The level of hemoglobin in treated groups with different concentrations of nickel chloride and nickel nanoparticles was not significantly different from the control. However, the level of hemoglobin showed significant change in the 15 mg/kg nickel chloride group (15.6±1.04) in comparison with the 15 mg/kg nickel chloride group (13.03±1.03, p=0.003) and 5 mg/kg nickel nanoparticle group (13.8±0.30, p=0.034) (Table 3). The percentage of hematocrit in the studied groups did not change significantly (p=0.096). Statistical analysis showed that the mean level of red blood cell in the studied groups changed significantly (p=0.018). The mean level of red blood cells in the treated groups with nickel nanoparticles decreased compared with the control group, but did not show significant difference (Table 3).

Table 2. Biochemical parameters of blood after intraperitoneal injection of different concentrations of nickel chloride and nickel nanoparticle in rats

Parameters / Groups	Albumin(g/dl) Mean±SD	Total Protein(g/dl) Mean±SD	Creatinine (mg/dl) Mean±SD	Urea (mg/dl) Mean±SD	Uric acid(mg/dl) Mean±SD	CRP(mg/dl) Mean±SD
Control	3.25±0.33	6.46±0.23	0.53±0.05	43.33±11.94	6.6±1.4	0.101±0.08
Sham	3.32±0.08	6.84±0.48	0.54±0.05	56.20±11.18	7.2±1.4	0.142±0.09
group 1	3.05±0.08	6.28±0.14	0.61±0.07	70.50±10.52*	3.4±0.58 ***	0.175±0.16
group 2	3.20±0.08	6.51±0.36	0.6±0.06	64.00±8.67	3.3±0.10	0.170±0.11
group 3	3.14±0.05	6.54±0.43	0.66±0.05 *	90.33±13.95***	3.4±0.30 ***	0.196±0.20
group 4	3.01±0.14	6.33±0.40	0.56±0.05	45.66±4.03	3.9±0.58 ***	0.125±0.13
group 5	2.91±0.09	6.15±0.36	0.56±0.08	45.33±10.34	3.7±0.65 ***	0.176±0.15
group 6	2.95±0.13 *	6.23±0.30	0.64±0.08	69.50±12.28 *	3.9±0.57 ***	0.194±0.10

The findings are shown as mean±standard deviation (n=6). The sign of star indicates a significant level compared to control. * p<0.05, **p<0.01, ***p<0.001, Experimental groups 1, 2 and 3 were 5, 15 and 25 mg/kg nickel chloride concentrations, respectively, and experimental groups 4, 5 and 6, were 5, 15 and 25 mg/kg nickel nanoparticles, respectively.

Table 3. Evaluation of blood cells after intraperitoneal injection of different concentrations of nickel chloride and nickel nanoparticle in rats

Parameters / Groups	WBC(10^3/µl) Mean±SD	RBC(10^6/µl) Mean±SD	PLT (10^3/µl) Mean±SD	Hb(g/dl) Mean±SD	MCV(fL) Mean±SD	HCT% Mean±SD
Control	4.43±0.66	7.06±0.35	930.33±179	14.4±0.50	59.3±1.52	44.16±3.4
Sham	5.03±1.19	7.33±0.26	1040.17±118	14.6±0.35	61.00±1.1	44.53±2.50
group 1	8.76±1.96	7.20±0.24	906.67±116	14.5±0.50	58.00±1.1	42.00±1.73
group 2	7.56±2.33	8.06±0.99	879.60±371	15.6±1.04	59.6±1.51	45.25±1.89
group 3	9.10±0.62 *	6.46±0.40	937.67±57	13.03±1.00	59.6±0.57	39.66±3.21
group 4	8.15±1.78	7.05±0.28	925.00±108	13.8±0.30	57.7±0.5	41.00±1.41
group 5	7.35±1.97	7.16±0.47	908.32±59	14.4±0.80	57.6±0.57	41.66±2.88
group 6	7.70±1.59	7.20±0.30	926.33±100	14.2±0.99	57.3±2.33	41.66±2.51

The findings are presented as mean±standard deviation (n=6). The sign of star indicate a significant level compared to control. *p<0.05, **p<0.01 RBC (red blood cells, millions per microliter), WBC (white blood cells, thousands per microliter), MCV (average volume of red blood cells, femtoliter), Hb (hemoglobin, g / dl), PLT (platelet, thousand per microliter), HCT (hematocrit percentage). Experimental groups 1, 2 and 3 were 5, 15 and 25 mg / kg nickel chloride concentrations, respectively, and experimental groups 4, 5 and 6, were 5, 15 and 25 mg / kg nickel nanoparticles, respectively.

Discussion

The results of this study showed that intraperitoneal injections of nickel chloride and nickel nanoparticles in different concentrations have different effects on the biochemical and hematological parameters of blood in rats. To use paraclinics in the diagnosis of diseases, the normal activity of the organs and tissues and the normal values of the parameters in the serum must first be carefully determined and measured to obtain abnormal values, so that the evaluation of abnormal activity of organs and tissues during illness would be

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possible. Therefore, measuring and obtaining normal values of biochemical parameters is very important. In this study, the level of albumin showed significant changes, so there was a significant decrease in the concentration of nickel chloride and nickel nanoparticles compared to control.

Albumin is the major protein in the liver that actually acts as an antioxidant and protects tissues and cells from damage to free radicals. Albumin binds to excreta products, toxins and harmful drugs that may damage the body and disposes of them. In addition, albumin is responsible for the transfer of many vitamins, minerals and hormones in the blood. Serum albumin concentration can also be directly affected by renal glomerular damage (19). Several factors play a role in reducing serum albumin, which can be due to an impairment in the synthesis of albumin in liver disease and catabolism enhancement in infections and malignancies, which is associated with reduction in the transmission capacity of associated compounds and has a significant effect on the metabolism of drugs, hormonal compounds and endogenous substances like calcium and bilirubin.

A study by Magaye et al. showed that intravenous injection of 1 mg / kg nickel nanoparticle into mice increased albumin levels, but no significant changes were found in concentrations of 2 and 4 mg / kg (20), which is not consistent with our study. Measuring the total protein ratio is a useful tool for detecting many deficiencies. The normal level of total serum proteins results in their synthesis and catabolism in the body. Reduction of total serum protein is associated with a moderate deficiency of globin and albumin, as well as a decrease in total proteins in cases of decreased albumin, which can be seen in severe liver disease (which reduces the synthesis of proteins) and increases catabolism. Reduction of the total protein concentration due to incomplete protein synthesis in the liver, inadequate intestinal absorption, and loss of protein occur due to inadequate renal function (21, 22).

Our study showed that total serum proteins were reduced in all studied groups, which is consistent with the results of Magaye et al. (20). C-reactive protein is a type of serum protein and is one of the most prominent members of the acute phase protein group that is increased by the inflammation caused by infections, stress, injuries, necrosis and malignancy. One of the tasks of this protein is to encourage the phagocytosis of blood leukocytes against pathogens. Increased CRP in infectious diseases and inflammation occurs along with red blood cell sedimentation and increased blood leukocytes. The level of CRP in the body is low in normal people, but it increases by several hundred times during the inflammatory response in the body. The study of Deng et al. showed that serum CRP levels in different concentrations of nickel sulfate increased compared to control, and these changes were significant only at high concentrations (23).

Our study showed that serum CRP increased in treatment with nickel nanoparticle and nickel chloride, but this increase was not significant compared to control. Uric acid is the final product of purine catabolism in humans, which is caused by the xanthine oxidase enzyme from intermediate metabolites such as hypoxanthine and xanthine. In humans, uric acid is the most abundant soluble antioxidant, which is considered as a source of intracellular free radicals in the conditions of oxidative stress (24).

After the decomposition of the proteins used in the body cells, the liver produces ammonia, which contains nitrogen. Most diseases that affect the liver and kidneys potentially affect the level of blood urea as well. If the level of urea increases in the blood due to the activity of the liver, but the rate of its excretion from the kidney decreases, blood urea concentration increases. Creatinine is mainly made up of arginine, glycine and methionine in the liver. Low levels of creatinine are due to inadequate protein intake, liver disease, and pregnancy. Any increase in its amount occurs in renal problems (25).

The study of Sheydaei et al. showed that the effect of zinc oxide nanoparticles on some renal factors in experimental mice increased serum creatinine and urea levels in the 80 mg / kg group, indicating a serious damage to the kidney (26). The results of this study are in line with our study. The results of this study showed that the amount of blood urea nitrogen and creatinine increased significantly compared to control. The kidneys are responsible for cleaning up certain toxic substances from the metabolism. Creatinine and blood urea nitrogen test was also used to evaluate renal function. Therefore, the results of this study indicate that intraperitoneal injection of nickel nanoparticles and nickel chloride affects kidney performance and shows renal damage.

In the study of Naghsh et al., increase in white blood cells and decrease in the number of red blood cells after the effect of silver nanoparticles was observed. The reason is high concentration, possible lysis of red blood cells and potential stimulation of the

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cellular immune system (27). In the present study, with intraperitoneal injection of different concentrations of nickel chloride and nickel nanoparticles for one week, the number of white blood cells at all concentrations of nickel chloride and nickel nanoparticles increased compared to control. No significant changes were observed in the number of red blood cells in the study, which was observed in the 25 mg / kg concentration of nickel chloride compared to control, but it was not significant. Intraperitoneal injection of nickel chloride and nickel nanoparticles stimulated the immune system and increased white blood cell production in rats.

White blood cells play an important role in immunity. Various studies have shown that the increase in white blood cell count can be due to the high concentrations of nanoparticles, which, due to more contact surface and the effect on cell membranes, contribute to the mitochondrial transmission of white blood cells and alter the activity of their enzymes (28). It also reduces the antioxidant activity of the cell and thus reduces the amount of white blood cells. Ultimately, the body increases the amount of white blood cells at high concentrations to compensate (29). Therefore, the increase in the number of white blood cells is a natural physiological reaction to inflammation of foreign substances into the bloodstream, and the decrease in the number of white blood cells indicates excessive penetration of the nanoparticle and infection. Free radicals produced by nanoparticles cause inflammation of the red cells as a result of hemolysis (30).

Reducing the number of red blood cells at high concentrations may also be due to the effect of nanoparticles on hematopoietic stem cells in bone marrow (28). Research showed that nanoparticles reduces the number of red blood cells and thus result in anemia by diminishing the life span of red blood cells or suppressing the activity of bone marrow stem cells (30). Decreased hemoglobin, hematocrit, and blood cell volume after exposure to various forms of nickel have been observed (31) which is consistent with the findings of our study in rats. Various studies have shown that free radicals produced by nanoparticles can cause inflammation of red cells as a result of hemolysis (31, 32). In the present study, nickel chloride and nickel nanoparticles reduced the number of red blood cells, hematocrit, hemoglobin, and average volume of red blood cells and platelets. Rezaei-Zarchi et al. showed that the nanoparticles reduced the platelet count by altering the integrin level of platelets and phosphoprotein levels in the platelets (33). These findings are consistent with the results of the present study. Penetration of nanoparticles into platelets and occupying vacuoles and granules prevent the spread of hyaloplasm and reduce platelet aggregation (34).

The body increases the production of white blood cells in order to cope with low concentrations of nanoparticles, but by weakening the body at high concentrations, we are confronted with a decrease in the white blood cell count. As a result, severe cell deaths appear to decrease in number of cells. Nanoparticles with high activity probably penetrate into target tissues and increase inflammatory responses to the lymph system.

The results showed that nickel chloride and nickel nanoparticles at high concentrations had a higher toxic effect on blood and serum parameters compared to low concentrations. Reductions in parameters such as hematocrit and red blood cells, hemoglobin, and moderate red blood cells are a sign of anemia. This study showed that intraperitoneal Injection of nickel nanoparticles and nickel chloride stimulated cellular immune system and increased the number of white blood cells at all concentrations of the study compared to control. In general, the results of this study confirm the toxicity of nickel chloride and nickel nanoparticles, and accuracy in the use of high concentrations of these compounds in the field of health is necessary.

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References

1.Buzea C, Blandino I, Robbie K. Nanomaterials and nanoparticles: sources and toxicity. Biointerphases. 2007;2(4):170-2.

2. Moreno-Vega AI, Gómez-Quintero T, Nuñez-Anita RE, Acosta-Torres LS, Castaño V. Polymeric and Ceramic Nanoparticles in Biomedical Applications. J Nanotechnol. 2012;2012.

3. David B. How meaningful are the resuls of nanotoxicity studies in the absence of adequate material characterization?. Toxicol Sci. 2008;101(2):183-5.

4. Cempel M, Nikel G. Nickel: A Review of Its Sources and Environmental Toxicology. Polish J Environ Stud. 2006;15(3):375-82.

5. Saini S, Nair N, Saini MR. Embryotoxic and teratogenic effects of nickel in Swiss albino mice during organogenetic period. Biomed Res Int. 2013 (2013).

6. Das KK, Buchner V. Effect of nickel exposure on peripheral tissues: Role of oxidative stress in toxicity and possible protection by ascorbic acid. Rev Environ Health. 2007;22(2):157-73.

7.Sunderman FW Jr, Hopfer SM, Sweeney KR, Marcus AH, Most BM, Creason J. Nickel absorption and kinetics in human volunteers. Proc Soc Exp Biol Med. 1989;191(1):5-11.

8. Sunderman FW Jr. Biological monitoring of nickel in humans. Scand J Work Env Hea. 1993;19(1):34-8.

9. Pojlak-Blazi M, Jaganjac M, Zarkovic N. Cell oxidative stress, : risk ofmetal nanoparticles, inHandbook of nanophysics: Nanomedicine and Nanorobotics; NY, USA, 2010. pp:1–17.

10. Ju-Nam YR, Lead J. Manufactured nanoparticles: an overview of their chemistry, interactions and potential environmental implications. Sci Total Environ. 2008;400(1-3):396-414.

11. Li N, Xia T, Nel AE. The role of oxidative stress in ambient particulate matter-induced lung diseases and its implications in the toxicity of engineered nanoparticles. Free Radic Biol Med. 2008;44(9):1689-99.

12.Johnston HJ, Hutchison G, Christensen FM, Peters S, Hankin S, Stone V. 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. Crit Rev Toxicol. 2010;40(4):328-46.

13.Manke A, Wang L, Rojanasakul Y. Mechanisms of nanoparticle-induced oxidative stress and toxicity. Biomed Res Int. 2013;942916:1-15.

14.Donaldson K, Poland CA. Inhaled nanoparticles and lung cancer—what we can learn from conventional particle toxicology. Swiss Med Wkly. 2012;142(13547):1-9.

15.Smith KR, Klei LR, Barchowsky A. Arsenite stimulates plasma membrane NADPH oxidase in vascular endothelial cells. Am J Physio. 2001;280(3):442-9.

16.Hillyer JF, Albrecht RM. Gastrointestinal persorption and tissue distribution of differently sized colloidal gold nanoparticles. J Pharm Sci. 2001;90(12):1927-36.

17.Kageyama N. A direct colorimetric determination of uric acid in serum and urine with uricase-catalase system. Clin Chim Acta 1971; 31:421-6.

18.Hedlund P. Clinical and experimental studies on C-reactive protein (acute phase protein). Acta Med Scand Suppl. 1961; 361:1-71.

19.Venkatesan N, Punithavathi D, Arumugam V. Curcumin prevents adriamycin nephrotoxicity in rats. Brit J Pharmacol. 2000;129(2):231-4.

20.Magaye R, Yue X, Zou B, Shi H, Yu H, Liu K. Acute toxicity of nickel nanoparticles in rats after intravenous injection. Int J Nanomed. 2014;9:1393-402.

21.Thomas L. Clinical laboratory diagnostics: use and assessment of clinical laboratory results, 1st ed. Frankfurt/Main: TH-Books-Verl.-Ges 1ed;1998.pp. 644-7.

[DOR: 20.1001.1.15614107.1396.19.11.8.9]
[DOI: 10.18869/acadpub.jbums.19.11.58]

22. Johnson A, Rohlfs M, Silverman EM, Protein LM. Tietz Textbook of Clinical Chemistry, 3rd, WB. Saunders Co, Philadelphia;1999. Pp.477-540.

23.Deng F, Guo X, Xia P, Liu H. Damage on lung and systemic inflammation induced by nickel sulfate intratracheal instillation in rats. J Hyg Res. 2009;38(3):269-72.

24.Hellsten Y, Tullson PC, Richter EA, Bangsbo J. Oxidation of urate in human skeletal muscle during exercise. Free Radic Biol Med. 1997;22(1-2):169-74.

25. Jacobs SD, DeMott RW, Oxley KD. Laboratory test handbook,3rd ed. Lexi comp; 2004 .p.474-7.

26.Sheydaei P, Bayrami A, Azizian Y, Parvinroo S. Study on the toxicity effects of zinc oxide nanoparticles on hematological and serum parameters in mice. Arak Med Univ J. 2017;19(10):39-47. [In Persian].

27.Naghsh N, Nuri A, Aghababa H, Amirkhani-Dehkordi S. The effect of nanosilver particles on alanin aminotransferase (alt)aactivity and white blood cells level in male wistar rats, in vivo condition. Zahedan J Res Med Sci. 2012;13(9):1-7. [In Persian].

28.Razmara P, Heyrati PF, Dorafshan S. Effect of silver nanoparticles on some hematological indices of rainbow catfish (pangasiusn hypophthalmus). JCT autumn. 2014;5(3):263-72. [In Persian].

29.Vasantharaja D, Ramalingam V, Aadinaath Reddy G. Oral toxic exposure of titanium dioxide nanoparticles on serum biochemical changes in adult male Wistar rats. Nanomed J. 2015;2(1):46-53.

30.Faiz H, Zuberi A, Nazir S, Rauf M, Younus N. Zinc Oxide, zinc sulfate and zinc oxide nanoparticles as source of dietary zinc:comparative effects on growth and hematological indices of juvenile grass carp (Ctenopharyngodon idella). Int J Agric Biol. 2015;17(3):568-74.

31.Das kk, Das SN, Dhundasi SA. Nickel, its adverse health effects & oxidative stress. Indian J Med Res. 2008;128(4):412-25.

32.Alkaladi A, El-Deen NAMN, Afifi M, Zinadah OAA. Hematological and biochemical investigations on the effect of vitamin E and C on Oreochromis niloticus exposed to zinc oxide nanoparticles. Saudi J Biol Sci. 2015;22(5):556-63.

33. Rezaei-Zarchi S, Taghavi-Foumani M, Razavi Sheshdeh S, Negahdary M. The effect of silver nanoparticles on blood cells in male rats. Sci J of Iran Blood Transfus Organ. 2013;10(2):147-53. [In Persian]

34.Najafzadeh H, Ghoreishi SM, Mohammadian B, Rahimi E, Afzalzadeh MR, Kazemivarnamkhasti M, et al. Serum biochemical and histopathological changes in liver and kidney in lambs after zinc oxide nanoparticles administration. Vet World. 2013;6(8):534-7.

[DOR: 20.1001.1.15614107.1396.19.11.8.9]

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