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Haematological alterations induced by the oral doses of iron oxide and aluminium oxide nanoparticles in Wistar rats

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Abstract

The present study was designed to know the haematological alterations caused by nano-iron oxide and nano- aluminum oxide in Wistar rats in a repeated dose study for 90 days. 35 Wistar rats were divided randomly in 2 group *viz.* control and test. Control group contain 20 and tests group contain 15 experimental animals. From day 0 and till 90 day of the experiment, control group was provided with standard feed and RO water and in treated group along with standard feed and RO water, nano-iron oxide and nano-aluminium oxide mixed in distilled water was also gavazed at the dose half of the NOAEL dose *viz.* 15mg/kg body weight and 3mg/kg body weight respectively. Various haematological parameters were studied at day 0, 30, 60 and 90 of the experiment. And the results showed that long term exposure of iron and aluminium nanoparticles at half of their dose cause mild to moderate decrease in the mean Hb, mean RBC count, mean TLC, mean MCH and mean MCV in rats of treated group as compared to control group.

Keywords: Nanoparticle, haematological, rats, nano-ironoxide, nano-aluminum oxide

Introduction

A nanomaterial is an object which has, at least, one dimension in the nanometer scale, which is conventionally ranging from one to a few hundred nanometers [1]. Nanotechnology involves the development of research and technology in the range of approximately 1-100 nanometers at the atomic, molecular or macromolecular levels to provide a fundamental understanding of nanoscale phenomena and materials. The word nano-technology was derived from the Greek word "nanos" meaning "dwarf." Nanotechnology is primarily used to create structures, devices and systems with novel properties and functions due to their tiny size. Manmade nanostructure materials are manufactured in large quantities worldwide due to their broad range of applications, such as industrial uses, great innovations, communication technology, drug discovery, drug delivery, drug targeting, drug formulations, pharmaceutics, cosmetics, chemical engineering, high-performance materials, electronics, textiles, ceramics, paints, optics, energy production, wastewater treatment, creams, ointments, lotions, metal ornament preparations, environmental sciences, nano-biofilm disinfectants for food processing and the list goes on.

Iron is a metal ion in the body that plays a critical role in different physiological functions, including DNA synthesis, mitochondrial respiration and oxygen transport [2]. In the human body, iron primarily exists in complex forms bound to protein (hemoprotein) as heme compounds (hemoglobin or myoglobin), heme enzymes, or non heme compounds (flavin-iron enzymes, transferring, and ferritin) [3]. The body requires iron to synthesize its oxygen transport proteins, particularly hemoglobin and myoglobin, and to form heme enzymes and other iron-containing enzymes involved in electron transfer and oxidation-reductions [4]. Nearly two-thirds of body iron is contained in hemoglobin in circulating erythrocytes, 25% in a readily mobilizable iron store and the remaining 15% is bound to myoglobin in muscle tissue and a number of enzymes involved in oxidative metabolism and many other cell functions [5].

Iron nanoparticles are used as food additives for human consumption in Fe-fortified drinks and cereals [6]. Fe overdose can damage the intestinal mucosa and increase its permeability [7]. It is also noted that nano-sized Zero-valent (FeO) has greater reactivity than micro-sized FeO particles [8]. Furthermore, some interesting facts about Fe metal are that it is an essential micronutrient required for many important biological processes as well as the most abundant transition metal in the body, but it can generate oxidative stress in aqueous solutions due to the production of reactive oxygen species (ROS) [9].

Aluminum (Al) is the third most abundant element in the world and is a well-known neurotoxin in the environment. Aluminum-based NPs are used in many fields, such as fuel cells, polymers, paints, coatings, textiles, biomaterials and so on. About their toxic effects, it has been reported that aluminum oxide NPs interfere with cell viability, alter mitochondrial function, increase oxidative stress, and also alter blood brain barrier (BBB) tight junction protein expression [10]. Aluminum oxide nanoparticles (Al_2O_3-NPs) have been applied in catalysis [11], structural ceramics for reinforcements [12], polymer modification [13], functionalization of textiles [14], heat transfer fluids [15] [16], and waste water treatment as one of the widely studied and used nanomaterials. Also, Al_2O_3-NPs have shown wide biological applications in biosensors [17], filtration [18], and antigen delivery for immunization purposes [19]. Thus, the environmental and health impact of Al_2O_3-NPs is of great interest. Al_2O_3-NPs have been commonly used as abrasive, wear-resistant coatings, in solid rocket fuel and as drug delivery systems [20]. Due to the enormous increase in the use of these nanoparticles, humans and animals exposure increasing day-to-day by different entry routes such as ingestion, inhalation and dermal penetration and therefore the health effects of these nanoparticles automatically generate a hot topic of research.

Materials and methods

Animals, nanomaterials and feeding schedule: The experiment was performed for a complete period of 90 days in Wistar rats of both sexes of age 18 weeks. 35 wistar rats were randomly divided into 2 groups i.e. control and test group containing 20 and 15 rats respectively. Nanoparticles used in research are Iron oxide and Aluminium Oxide (Boehmite) nano dispersion. The iron oxide nanodispersion is used in this study having molecular weight 159.69, (Sisco Research Laboratories Pvt. Ltd), orally administered at half of the NOAEL dose 15mg/kg BW/day. The aluminium oxide (beohmite) nanodispersion is used in this study having nanodispersion of 50 nm and molecular weight 59.99, specific gravity: 1.19, pH 4, Viscocity: 10 cps (Sisco Research Laboratories Pvt. Ltd), orally administered at half of the NOAEL dose 3mg/kg BW/day. From the beginning of the experiment the experimental rats were fed with standard ration and will be provided with ad-libitum RO drinking water till 90 days i.e. last day of experiment. Before the start of the experiment, all the rats were accustomed with the experimental animal house for 7 days.

Collection and Examination of Blood: From the retro-orbital plexus blood samples were collected from both test and control groups at day 0, 30, 60 and 90 of the experiment for the haematological examination. Blood was collected in EDTA vials and all these hematological parameters were determined by standard procedures [21]. Hematology includes various blood parameters mentioned below.

Hemoglobin: Hemoglobin concentration was determined by Sahli's hemoglobinometer. Blood sucked up to 20 marks in pipette and was mixed with 5 drop of N/10 HCl. It was left undisturbed for 5 minute in the dark and then distilled water was added drop wise till the color matches with the standard. Hemoglobin concentration was determined by reading the scale on tube.

Total Erythrocyte Count: TEC was determined using RBC diluting pipette and hemocytometer. First the blood was sucked upto 0.5 mark and then RBC diluting fluid up to 101 marks and both were mixed properlyby keeping the pipette in horizontal position in between the palms and after discarding few drops, the Neubauer's chamber is charged with a drop from the pipette. Cells from 5 central secondary squares were counted after charging and settling the cells in the Neubauer's chamber and total no. of cells were then multiplied with 10000 to get the TEC value/µlof blood.

Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration: These parameters were calculated according to the formula.

Total Leucocyte Count: TLC was determined using WBC diluting pipette and hemocytometer. First the blood was sucked upto 0.5 mark and then WBC diluting fluid up to 11 marks and both were mixed properly by keeping the pipette in horizontal position in between the palms and after discarding few drops, the Neubauer's is charged with a drop from the pipette. Cells from 4 outer primary squares were counted after charging and settling the cells in the Neubauer's chamber and total no. of cells were than multiplied with 50 to get the TLC value/µl of blood.

Absolute Lymphocyte and Neutrophil Count: These parameters were calculated according to the formula.

Result and discussion

During the course of experiment various hematological parameters were evaluated. Decrease in the mean concentration of hemoglobin was observed in the rats of treated group on 30, 60 and 90DPT as compared to the rats of control group **(**Tab. 1) (Fig. 1). Although the hemoglobin concentration in both the group is within the normal range and no significant difference is observed between the groups. However, the results are in contrast with Elshemy, (2018) recorded that the alone administration of iron oxide nanoparticles induced a significant increase in hemoglobin concentration, RBCs count and packed cell volume when compared to ferrous sulfate group in treatment of anemia in wistar rats. In our study, the decrease in the hemoglobin concentration may be observed due to joint administration of iron and aluminium nanoparticles. As, in previous studies it was documented that after exposure of rats to aluminum a functional iron deficiency may result from the blockade of reticuloendothelial iron release or disturbed activity of ferrochelatase, an enzyme that catalyzes the addition of iron to protoporphyrin [23]. Also, studies showed, a decrease in iron concentration in the blood, erythrocytes, and spleen was observed after intragastric administration of Aluminium [24] also seem to confirm the interaction between iron and aluminium. It is known that Al may affect iron metabolism by direct binding with transferrin receptors, blocking the release of accumulated iron, inhibiting ceruloplasmin-dependent Fe oxygenase, or reducing intracellular NADPH and hence, potentially blocking the reduction of Fe, which is indispensable for its incorporation into heme [25]. This decrease in the hemoglobin is also said to be linked with the oxidation of hemoglobin caused by nanoalumina [26]. Where as, some studies showed, that in long term aluminium oxide nanoparticles altered the quaternary structure of the hemoglobin molecule [27]. The results are also in commensurate with the results of research conducted on Wistar rats administered with nano-aluminium oxide [28].

Total erythrocyte count was also found decreased at 60 and 90 DPT of the experiment in comparison to control group **(**Tab. 2) (Fig. 2). However the decrease was not satistically significant. The results are in confirmation with the results by Gaharwar and Paulraj, (2015) on wistar rats treated with iron oxide nanoparticles**.** Red blood cells are derived from hemopoietic stem cells in bone marrow. After maturation or erythropoiesis, red cells enucleate and enter in to the circulatory system. Thus, the variation in red blood cells can be related to the dysfunction of hematopoietic system. Also, the free radicals produced by nanoparticles may be the main cause for destruction of red blood cells [30]. It may be explained by alteration in erythrocyte rheology caused by binding of aluminium to the transferrin receptor present on the surface of RBCs which triggers the lipid peroxidation reaction which further damage membrane function [31].

The experiment demonstrated a significant increase in the MCV value in the treated group at 30th DPT as compared to control group where as the increase was non significant at 60^{th} and 90^{th} DPT (Tab. 3) (Fig. 3). This can be interpreted as macrocytic erythrocytes. The significant decrease in the MCH value in the treated group in comparison with the control group at 30^{th} DPT indicating decrease in the average hemoglobin mass per RBC in blood, where as the decrease was non significant at 60^{th} and 90^{th} DPT (Tab. 4) (Fig. 4). This decrease in their values can be attributed to the decrease in hemoglobin content as recorded in our experiment. This is also in confirmation with the study by Gaharwar and Paulraj, (2015) on wistar rats treated with iron oxide nanoparticles. Although the MCHC remained almost normal.

Decrease in Total leucocyte count, absolute lymphocyte count is observed in treated rats at day 30, 60 and 90 of the experiment as compared to control rats. And decrease in TLC and ALC at day 90 was statistically significant (Tab.5) (Fig.5).

After entering in the body, nanoparticles present in the blood interact with various component of blood especially various proteins like albumin, tansferrin and several other components (poly ethylene glycol or PEGylated particles). These proteins get instantly adsorb on the surface of nanoparticles and mask the clearance of these nanoparticles by the leucocytic phagocytosis and leads to their accumulation in the leucocytes [32]. Once nanoparticles get absorb into the leucocytes they induce free radicals or reactive oxygen species production which elicit the oxidative stress, affect their viability [33] and induces programmed cell death mainly in T and B lymphocytes [34]. On the other hand, the negative relationship between the leucocyte count and experimental time can be suggested by the shortage of the components necessary for the synthesis of leucocytes such as proteins and lipids that significantly decreased [26]. During the experiment percent increase in the ANC was recorded.

It may be due to the proinflammatory effect of the nanoparticles. Nanoparticles also activate the NLRP3 inflammasomes and increase production of the TGFβ [35]. This is also in confirmation with the results by Srinivas *et al*., (2012) recorded increase in percentage of neutrophils following acute inhalation to iron oxide nanoparticles in rats and with the study by Keshwan and Fadeel, (2020) reported that nano size particles can modulate and activate the neutrophils. These activated neutrophils cause biodegradation of nanomaterials through expression of myeloperoxidases (MPO) and related enzymes.

Table 1: Hemoglobin concentration (g/dl) of experimental rats at different time intervals of the experimental period.

Day of Experiment	Haemoglobin in gm/dl (Mean ± SE)	
	Group I (Control)	Group II (Fe_2O_3+Al_2O_3NP)
0	15.6±0.50^{C}	15.6±0.50^{C} (0%)
30	14.6±0.50^{A}	13.8±0.48^{AB} (-5.47%)
60	15.4±0.50^{B}	14.6±0.50^{BC} (-5.19)
90	15.2±0.37^{aB}	12.8±0.58^{bA} (-7.89%)

*Alphabetical letters (a and b) indicate significant (P<0.05) difference between groups at a particular DPT whereas different alphabetical letters (A, B and C) indicate significant (P<0.05) difference within days in a particular group.

Table 2: Total erythrocyte Count in 10^6/µl of experimental rats at different time intervals

Day of Experiment	Total Erythrocyte Count in 10^6/µl (Mean ± SE)		% incease or decrease than control
	Group I (Control)	Group II(Fe_2O_3+Al_2O_3NP)	
0	6.54±0.28^{A}	6.54±0.28	(0%)
30	8.85±0.43^{B}	9.44±0.22	(6.66%)
60	7.95±0.20^{B}	7.12±0.30	(-10.44%)
90	8.02±0.22^{B}	7.3±0.34	(-8.97%)

*Alphabetical letters (A and B) indicate significant (P<0.05) difference within days in a particular group

Table 3: Mean Corpuscular Volume (fL) of experimental rats at different time intervals

Day of Experiment	MCV in fL (Mean ± SE)	
	Group I (Control)	Group II(Fe_2O_3+Al_2O_3NP)
0	70.86±2.97^{C}	70.86±2.97^{B} (0%)
30	46.50±3.32^{Aa}	56.26±2.57^{bA} (20.9%)
60	56.94±2.10^{B}	57.22±3.31^{A} (0.49%)
90	55.07±2.32^{B}	57.04±3.72^{A}(3.57%)

*Alphabetical letters (a and b) indicate significant (P<0.05) difference between groups at a particular DPT whereas different alphabetical letters (A and B) indicate significant (P<0.05) difference within days in a particular group

Table 4: Mean Corpuscular Hemoglobin (pg) of experimental rats at different time intervals (Mean ± SE).

Day Post- Treatment	MCH in pg (Mean ± SE)		% incease or decrease than control
	Group I (Control)	Group II (Fe_2O_3+Al_2O_3NP)	
0	24.09±1.64^{B}	24.09±1.64^{B}	(0%)
30	20.32±1.05^{aA}	15.71±0.87^{bA}	(-22.68%)
60	22.12±0.95^{AB}	19.56±1.21^{A}	(-11.57%)
90	19.12±0.27^{A}	19.73±1.26^{A}	(3.19%)

*Alphabetical letters (a and b) indicate significant (P<0.05) difference between groups at a particular DPT whereas different alphabetical letters (A and B) indicate significant (P<0.05) difference within days in a particular group

Table 5: Total Leucocyte Count (10^3/µl) of experimental rats at different time intervals of the experimental period (Mean ± SE)

Day Post- Treatment	Total Leucocyte Count in 10^3/µl (Mean ± SE)		% incease or decrease than control
	Group I (Control)	Group II(Fe_2O_3+Al_2O_3NP)	
0	15.24±1.22	15.24±1.22^{C}	(0%)
30	14.7±0.39	13.90±1.05^{BC}	(-5.44%)
60	13.48±0.98	11.68±0.81^{AB}	(-13.33%)
90	12.73±0.5^{a}	9.68±0.26^{bA}	(-23.95%)

Alphabetical letters (a and b) indicate significant (P<0.05) difference between groups at a particular DPT whereas different alphabetical letters (A, B and C) indicate significant (P<0.05) difference within days in a particular group.

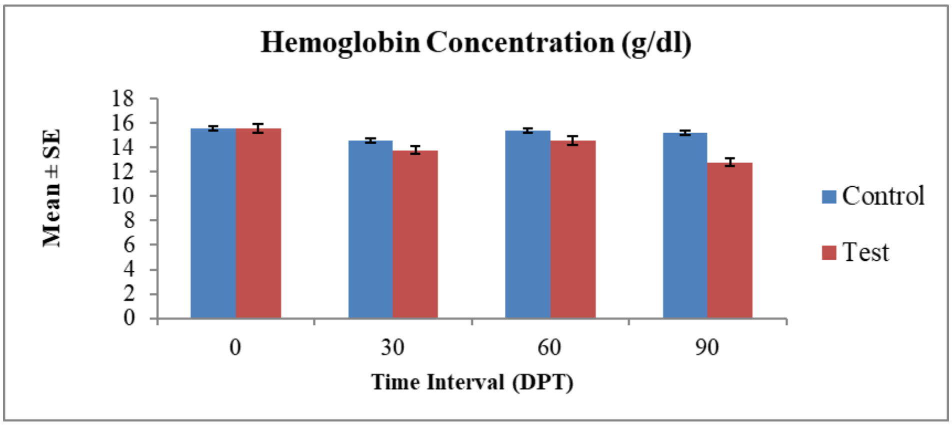

Fig 1: Hemoglobin concentration in g/dl of experimental rats at different time intervals

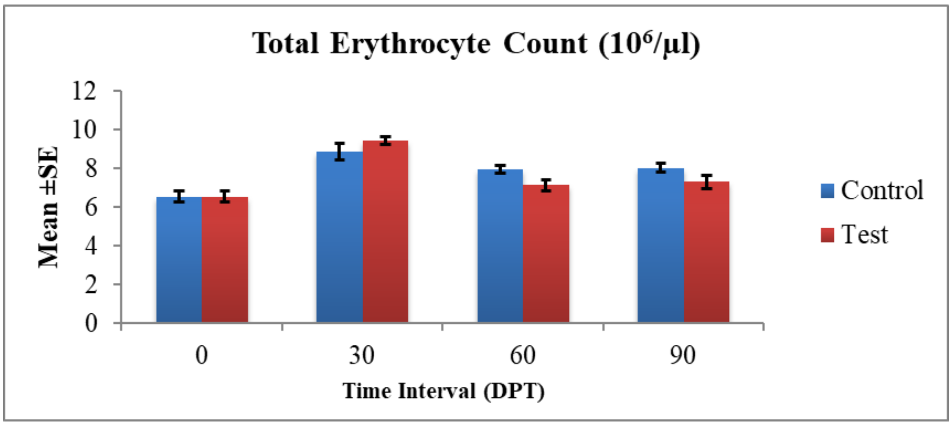

Fig 2: Total erythrocyte count in 10^6/µl of experimental rats at different time intervals.

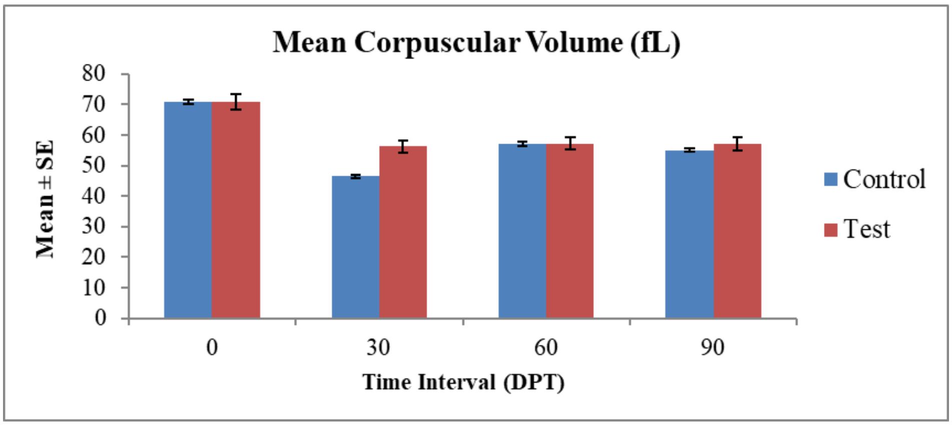

Fig 3: Mean Corpuscular Volume (fL) of experimental rats at different time intervals

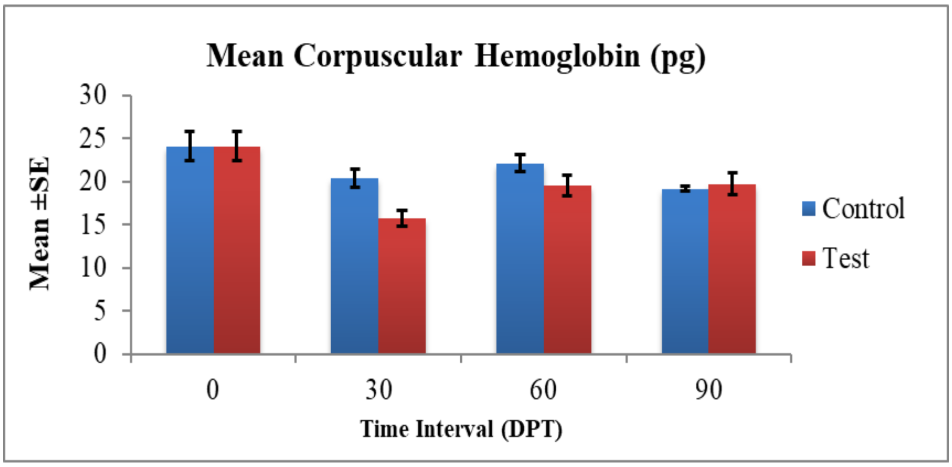

Fig 4: Mean Corpuscular Hemoglobin (pg) of experimental rats at different time intervals

Conclusion

Based on the above findings, it can be concluded that combination of iron and aluminium NPs at the rate of half of their NOAEL dose i.e. 15mg/kg BW and 3mg/kg BW caused mild to moderate decrease in hemoglobin concentration, red blood cell count and mean corpuscular hemoglobin which may be due to the combined effect of iron and aluminium nanoparticles. And there was also decrease in the total leucocyte count and absolute lymphocyte count.

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