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In vivo ameliorative effect of cerium oxide nanoparticles in isoproterenol-induced cardiac toxicity

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ABSTRACT

Background: Cerium oxide nanoparticles have gained much more attention especially in the field of nanomedicine. This work represents cerium oxide nanoparticles as a new prophylactic model for heart failure progression.
Objective: To investigate the potential protective effect of cerium oxide nanoparticles on Isoproterenol (ISO)-induced cardiac toxicity in rats.
Methods: Cerium oxide nanoparticles (5 ± 1 nm) were synthesized by reverse micelle method and characterized using High Resolution Transmission Electron Microscopy, X-Ray Diffraction and particle size analyzer. The experiments were performed on 96 male Wistar rats. The rats were randomly allocated into eight groups. Namely; two Negative and positive control groups, captopril administered group, Nano-ceria (low dose) group, Nano-ceria (high dose) group, Captopril- Isoproterenol group, Nano-ceria (low dose)-Isoproterenol group and Nano-ceria (high dose)-Isoproterenol group. Cardio toxic rat model was induced by subcutaneous administration of Isoproterenol (ISO) (30 mg/kg) for two consecutive days in adult male rats. Two doses (0.5 and 5 μg/kg/week) of cerium oxide nanoparticles were applied for five weeks and 50 mg/kg/day of Captopril was used as a reference drug. Cardiac marker enzymes, Cortisol and Aldosterone hormones were assessed in serum. Oxidant-antioxidant parameters and histopathological examination in heart tissues were also determined.
Results: These dose of nano-ceria, showed a promising ameliorative and prophylactic effect against cardiac toxicity compared to Captopril reference drug. Serum cardiac markers were decreased by noticeable percentage, CK-MB (50% and 57%), LDH (47% and 57.7%), AST (38% and 36.5%) and ALT (33.5% and 30.6%) for both doses respectively, while increased tissues level of the antioxidant enzymes, catalase (48% – 26%) and superoxide dismutase (64%, 143%).
Conclusion: These consistent biochemical and histopathological results suggest that, nano-ceria could be used as effective antioxidant in prophylactic protocols for management of cardiac disorders associated with oxidative stress.

1. Introduction

Heart failure (HF) has gradually became one of the most prevalent cardiovascular disorders not only in the elderly but in youth. It is a complex clinical disorder that can come about because of any useful or auxiliary heart issue that impedes the ventricle's capacity to load with or launch blood (Juenger et al., 2002). It is likewise connected with a fundamentally diminished physical and emotional wellness, bringing about a diminished personal satisfaction (Juenger et al., 2002; Hobbs et al., 2002). In spite of the fact that survival in clinical trials is enhancing, heart disappointment remains a deadly condition in the group with an expected yearly mortality of roughly 21% in men and 17% in women (Schocken et al., 2008). In created nations, the pervasiveness of HF is around 1%–2% of the grown-up populace, with the commonness ascending to ≥10% among people 70 years old or more seasoned (Mosterd and Hoes, 2007). Isoproterenol (ISO) is an engineered catecholamine and beta-adrenergic receptor agonist

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that has been found to instigate myocardial damage through severe necrosis damage in cardiac tissue of rats that shows MI induction (Jazi et al., 2017) The instrument of myocardial harm is still not totally saw, but rather some confirmation from exploratory and clinical reviews demonstrates that myocardial hypertrophy was reenacted by ISO (Lin et al., 2014) and its pathogenesis is for the most part connected with oxidative anxiety, calcium overburden, apoptosis and incendiary reaction (Bi et al., 2015). It exhibits many metabolic and morphological abnormalities in the heart tissue of experimental animals similar to those found in humans with myocardial infarction as injected ISO undergoes auto-oxidation, and generates highly cytotoxic free radicals that stimulate the peroxidation of membrane phospholipids causing severe damage (Kannan and Quine, 2013; Khalil et al., 2015) A number of therapeutic agents are presently employed in heart failure; but they are not sufficient to control symptoms of heart failure. Moreover, the prevalence of chronic heart failure is progressively increasing and thus there is a continuing need to create compelling treatments for the administration of this malady (Pacher et al., 2006). Advances in nanotechnology have led to the development of new materials and devices for various scientific and therapeutic purposes (Spivak et al., 2013). Several antioxidant nano formulations have been built and explored for remedial effect in cardiovascular infections, including Ischemic reperfusion injury and stroke (Kim et al., 2012). Cerium oxide nanoparticles are considered as a potent remedial option for the treatment of smoking related maladies, where pretreatment of cardiomyocytes as well as cardiac progenitor cells cause critical hindrance of tobacco smoke-incited ROS generation (Niu et al., 2011; Pagliari et al., 2012), in addition to reducing ischemic cardiomyopathy in mice by decreasing serum levels of monocyte chemo attractant protein-1, C-reactive protein, and total nitrated proteins (Niu et al., 2007). Administration of nano-ceria in monocrotaline induced hepatotoxicity rat models results in significant increases in hepatic catalase and superoxide dismutase (SOD) activities and thus serves as an effective hepatoprotective agent (Amin et al., 2011). Nano-ceria may acts as immediate cell reinforcements, block reactive oxygen species (ROS) production by inhibiting a step in the programmed cell death pathway (Becker et al., 2002). Furthermore, CeO_2NPs can induce cellular resistance to exogenous sources of oxidative stress (Xia et al., 2008). This remarkable and interesting ROS scavenging ability results from the speedy and convenient transformation of the oxidation state amongst Ce + 4 and Ce + 3. The cerium particle can without much of a stretch and definitely changes its electronic design to best fit its prompt surroundings derive from the quick and expedient mutation of the oxidation state between Ce^{+4} and Ce^{+3}. The cerium atom has the ability to easily and drastically adjust its electronic configuration to best fit its immediate environment (Skorodumova et al., 2002). The present study meant to investigate the antioxidant efficiency of cerium oxide nanoparticles as a cardio prophylactic protocol in Isoproterenol-induced cardio toxicity rat model compared to Captopril as a reference ameliorative drug. Captopril has a binary function, it is an angiotensin converting enzyme inhibitor (Inhibits the arrangement of angiotensin II, a bioactive peptide that fortifies angiogenesis and increments small scale vessel thickness) and has antioxidant activities due to presence of free sulfhydryl group (-SH).

2. Materials and methods

2.1. Preparation and characterization of cerium oxide nanoparticles

Cerium oxide nanoparticles were integrated from watery arrangements of cerium nitrate hexahydrate, $CeNO_3.6H_2O$, (99.5%, Sigma, US) and phosphatidylcholine (≥99%, Sigma, US) by the reverse micelle method as reported by Tsai et al. (Tsai et al., 2007). In brief, 5 ml 0.1 M $CeNO_3{\cdot}6H_2O$ watery arrangement was pipetted into the colloidal micelle solution of 2.285gm phosphatidylcholine (99.5%, Sigma, US) in 100 ml toluene with stirring until the system appears homogenous. 1.83 ml of 32% NH_4OH was pipetted into the system and left 1 h until CeO_2 NPs slowly shaped in the reversed micelles. Cerium oxide nanoparticles were washed with ethanol/water (1:1) for 3 times, then centrifuged for 5 min at 1721*g*, collected and dried at 50–60 °C. Physico-chemical properties of cerium oxide nanoparticles were characterized using High-Resolution Transmission Electron Microscope (HR-TEM, FEI, Tecnia G20, Netherlands), X-ray Diffraction (XRD, PanAnalytical, X'pert Pro, Netherlands) and Particle size analyzer (Zeta sizer nano series'zs', Malvern, UK). Cerium oxide nanoparticles concentration was determined by Inductively Coupled Plasma optical emission spectrometry ICP-OES (Thermo Scientific iCAP 7000, USA).

2.2. Experimental animals design

Ninety-six male albino rats of wistar origin weighing 180 ± 10gm and aged 10–12 weeks were acquired from the animal house of National Organization for Drug Control and Research (NODCAR), Egypt. Animals were housed in polycarbonate boxes with steel-wire tops (not more than six animals for every box) and slept with wood shavings. The encompassing temperature was controlled at 25 °C ± 3 °C with a relative humidity of 50% ± 10% and a 12-h light/dark photoperiod. Rats were allowed to adapt to the new environment for two weeks before starting the experiment. Cardio toxicity rat's model was constructed by subcutaneous (S.C.) injection of 30 mg/kg Isoproterenol hydrochloride (sigma, USA) disintegrated in ordinary saline twice at an interim of 24 h into adult male (El-Tantawy, 2014). Captopril (≥98%, Sigma, USA) was used as a reference drug.

Rats were randomly assigned into eight groups, 12 rats each. **Group I**, served as **Negative control** (daily administered saline, 0.5 ml saline/rat for 5 weeks). **Group II**, served as **Positive control** (S.C. administered Isoproterenol, 30 mg/kg/day for two consecutive days) (El-Tantawy, 2014). **Group III**, **captopril** (orally administered captopril drug, 50 mg/kg/day for 5 weeks) (El-Tantawy, 2014). **Group IV**, **Nano-ceria, low dose** (Intraperitonially administered nano-ceria, 0.5 μg/kg/week, for 5 weeks) (Amin et al., 2011). **Group V**, **Nano-ceria, high dose** (Intraperitonially administered nano-ceria, 5 μg/kg/week, for 5 weeks; tested dose). **Group VI**, **Captopril- Isoproterenol** (Orally administered captopril, 50 mg/kg/day for 5 weeks, then Isoproterenol, S.C. administered, 30 mg/kg/day for the last two days). **Group VII**, **Nano-ceria-Isoproterenol, low dose** (Intraperitonially administered nano-ceria, 0.5 μg/kg/week, for 5 weeks, then Isoproterenol, S.C. administered, 30 mg/kg/day for the last two days). **Group VIII**, **Nano-ceria-Isoproterenol, high dose** (Intraperitonially administered nano-ceria, 5 μg/kg/week, for 5 weeks, then Isoproterenol, S. C. administered, 30 mg/kg/day for the last two days). The dose of Isoproterenol, Captopril and Nano-ceria, low dose and the period of treatment were selected on the basis of previous studies (Amin et al., 2011; El-Tantawy, 2014), while the high dose Nano-ceria and other combined treatments are suggested as to be tested by our study.

2.3. Blood samples and tissue preparation

At the end of experimental period (5 weeks) and after twenty four hours, blood samples from all groups were collected from the retro orbital plexus vein using glass capillary tubes, samples were left to clot then centrifuged at 1721*g* for 20 min and serum was separated for biochemical analysis. Rats were anesthetized; hearts were dissected, rinsed in ice-cold saline to remove excess blood