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Radio-mitigation effect of poly-MVA after exposure to an acute dose of gamma radiation

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Abstract

Adult male rats were exposed to a 6 Gy single dose from a Cs-137 source. The radio-mitigation effect of poly-MVA was evaluated by daily administration of 2 ml/kg of body weight immediately after irradiation for two weeks. The morphological changes in the red blood cells were studied. The osmotic fragility and rheological properties of blood, the alteration in the contents of antioxidant enzymes (glutathione, catalase and superoxide dismutase) and lipid peroxidation in hepatic cells were determined. The results showed that exposure to radiation resulted in significant changes in cellular antioxidant enzymes (GSH, catalase and SOD) and a decrease in the blood Bingham viscosity, yield stress and aggregation index. Furthermore, it induced a slight increase in the average osmotic fragility of red blood cells accompanied by a decrease in osmotic dispersion, as well as a modification of red blood cell morphology. It also caused a significant increase (75%) in the lipid peroxidation 1 day after exposure to radiation, which persisted until the 14th day recorded after irradiation. Oral administration of poly-MVA after irradiation reduced the radiation-induced damage, as seen in the non-significant change in lipid peroxidation compared to the control. It also resulted in improvement in the observed parameters.

Keywords: Red blood cells; Gamma radiation; Rheological properties; Lipid peroxidation; Poly-MVA; Radio-mitigation effects

1. Introduction

Accidental exposure to radiation can arise due to factors beyond the control of the operating agencies, e.g., human error, system failure, sabotage, earthquake, cyclone, flood, etc. Incidence of radiological accidents, whether intentional, e.g., associated with military conflict and terrorism, or unintentional, e.g., power plant disasters such as Chernobyl and Fukushima, could lead to large-scale radiation exposure to occupational workers, patients and the public. Timely and effective medical response is a crucial component in reducing radiation harmful effects and mortality. The management of accidental radiation exposure is relatively complicated due to uncertainties in dose, duration, and organs involved in radiation exposure. Treatment of the victim in this case

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requires information and measurements that may take time to determine the suitable therapeutic strategy for each case. However, after the event of the radiation accident, it will be important to provide an agent that would mitigate the effects of ionizing radiation and can promote or increase the efficiency of the treatment. Ideally, this agent would be long lasting and easily administered (preferably orally) and would possess low toxicity.

Agents that possess radioprotective effects can be classified into three groups according to their action: radioprotectors, adaptogens and absorbents. Radioprotectors are constituted mainly of sulfhydryl compounds and other antioxidants [1]. They act as free radical scavengers that interact with aqueous free radicals or radicals of bio-molecules by donating hydrogen atoms to repair the radical species, thus preventing damage. Adaptogens are substances that can act as stimulators of radio-resistance and offer chemical protection under low levels of ionizing radiation. They include novel immuno-modulators (an agent that augments or diminishes immune responses) and cytokines (number of substances that are secreted by specific cells of the immune system, which carry signals locally between cells, and regulate various inflammatory responses). Some immuno-modulators are well-tolerated and reduce susceptibility to infectious agents, as well as reduce rates of neoplastic transformation. In recent years, radioprotective agents with a novel mode of action have been investigated, in particular, compounds that can affect haematopoietic stem cell regeneration to stimulate the function and regeneration of a stem cell population that has decreased due to radiation induced damage [2]. Absorbents are substances that can protect organisms from internal radiation and chemicals, such as drugs that prevent the incorporation of radioiodine by the thyroid gland and the absorption of radionuclides ^{137}Cs, ^{90}Sr, ^{239}Pu, etc. [3].

According to the administration time, the radioprotective agents have been classified into three categories: prophylactic, mitigators, and therapeutic agents [4]. Prophylactic agents are administered before radiation exposure to prevent radiation damage. A mitigator designates an agent that is administered during or immediately after radiation exposure with the aim of preventing or reducing the action of radiation on tissues before the appearance of symptoms. It is expected to regulate the downstream patho-physiological events of radiation injury. It should act on the radiation injury cascade and thereby prevent the development of further injury. Therapeutic agents are given after the development of clinical symptoms of radiation exposure [5]. Most radio-prophylactic agents are free radical scavengers, anti-oxidants, cytokines, thiols, and steroids [6,7]. They can be classified as radioprotectors and/or adaptogens. Therapeutic agents include suppressors of the renin-angiotensin system and chronic oxidative stress as well as agents such as pentoxifylline to treat radiation fibrosis and growth factors to facilitate recovery from haematological injury [8]. Most radio-protecting agents, whether applied clinically or under research study, are either for prophylaxis or treatment purposes. There are hardly few radio-mitigating agents. However, all radioprotective agents (antioxidants, adaptogens or absorbents) can represent suitable candidates to test their mitigating effects.

Palladium-α-lipoic acid is a complex formulated to act as a non-toxic chemotherapeutic agent for oral administration. It exists in a prescription version called DNA Reductase and is available commercially as a dietary supplement called poly-MVA [9]. The active ingredient in this complex is the palladium-α-lipoic acid polymer, which exists as a trimer of palladium-lipoic acid joined to thiamine in an arrangement that allows it to be both water and lipid soluble. The initials “MVA” stand for minerals, vitamins, and amino acids [10]. Palladium, as a transition metal, serves as a highly efficient aerobic catalyst [11]. Toxicological studies indicated that the LD_{50} of poly-MVA exceeded 5000 mg/kg, and no mutagenic effect of the combination was observed in the Ames test [12]. In a few recent studies, it showed significant radio-protective and mitigation effects [13–16]. It significantly reduced the γ-radiation-induced mortality in mice and aided recovery from the radiation-induced loss of body weight after 8 Gy exposures. Additionally, the radiation-induced DNA damage in these cells was reduced when poly-MVA was administered to animals exposed to a lethal dose of 8 Gy whole-body γ-radiation [14]. Its administration, for seven days prior to whole body gamma radiation, significantly reduced the damage to cellular DNA in bone marrow and blood leukocytes and prevented the radiation-induced decrease of tissue antioxidant levels [13]. Administration of poly-MVA for 14 days before exposure to 6 Gy gamma radiation, from a Cs-137 source, resulted in normal blood viscosity and yield stress compared to a control group 14 days after exposure, reducing the damage induced by radiation exposure. It also resulted in the normal mean osmotic fragility of red blood cells and reduced lipid peroxidation [15].

The mitigation effect of poly-MVA was tested in a previous work, and the results showed that the administration of poly-MVA for two weeks after whole-body exposure to 6 Gy gamma radiation alleviates the changes in dielectric properties of red blood cells [16]. In the