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Effects of Poly-MVA on the rheological properties of blood after in-vivo exposure to gamma radiation

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ABSTRACT

This study aims to examine the radio-prophylactic effects of poly-MVA against exposure to acute dose of gamma radiation. Adult male rats, weighing 200 gm, were exposed to 6 Gy gamma radiation from Cs-137 source. The animals received daily oral administration of 2 ml/kg body weight of poly-MVA for different time intervals. The prophylactic effect was examined by two modes of administration: two weeks before irradiation and another group which received continuous administration for two weeks before and two other weeks after irradiation (total time of administration 28 days). Different parameters were performed, which include determination of cellular antioxidant enzymes (Glutathione (GSH), catalase and superoxide dismutase) in hepatic cells, the rheological properties of blood, osmotic fragility and scanning electron microscope photography of red blood cells. Exposure to radiation resulted in a significant decrease in cellular antioxidant enzymes (GSH, Catalase and SOD) and decrease in Bingham viscosity, yield stress and aggregation index of blood. Furthermore it induced slightly increase in average osmotic fragility of red blood cells accompanied by decrease in osmotic dispersion and remarkable modification of red blood cell morphology. Administration of Poly-MVA showed markedly elevation in GSH, Catalase and SOD content in liver cells in all treated groups. It also showed improvement in all observed parameters. The obtained results showed that oral uptake of poly MVA posses a radio-prophylactic effect that might be used in planned radiation exposure in diagnosis and radiotherapy.

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1. Introduction

Development of agents for prophylaxis, mitigation and treatment of radiation injury is an important task for radiological studies. Radio-prophylactics are agents that must be given before radiation exposure; to minimize the effect of radiation (Stone, Moulder, & Coleman, 2004).Many research works are directed towards finding effective agents that would successfully prevent the development of radiation syndrome and protect biological system from free radicals that appear as a consequence of the exposure to radiation. Many compounds, that had been considered potential chemical radioprotectors, have been tested. Only some of them have shown to have significant effects. Among the investigated compounds certain number of them, under specific circumstances, has shown a considerably protective effect in the experiments with the animals (Citrin et al., 2010; Greenberger, 2009; Hosseinimehr, 2007; Jagetia, 2007; Madhu & Kumari, 2014; Maurya Dharmendra, Devasagayam Thomas, & Krishnan Cherupally, 2006; Nair, Parida, & Nomura, 2001; Peebles, Soref, Copp, Thunberg, & Fahl, 2012; Shukla & Gupta, 2010; Weiss, 1997; Yamini & Gopal, 2010). Synthetic thiol Amifostine (Ethyol) is the only FDA approved radioprotective treatment available today (Cassatt, Fazenbaker, Bachy, & Hanson, 2002). However, it has significant shortcomings including relatively high toxicity, unfavorable routes of administration, and narrow protection time window (Hosseinimehr, 2007). Because of its adverse side effects (nausea, vomiting and hypotension) in humans, effectiveness of Amifostine in clinical trials is significantly diminished compared to that in animal studies (Weiss & Landauer, 2003).

However, there is a need for solving the problems concerning the unwanted effects and to find pharmaceutical formulation of radioprotectors for oral application. Palladium α-lipoic acid complex (PLAC) was formulated to act as a non-toxic chemotherapeutic agent for oral administration. It exists in a prescription version called DNA Reductase, and available commercially as dietary supplement called poly-MVA (Antonawich, Fiore, & Welicky, 2004).The active ingredient in this complex is the palladium–lipoic acid polymer, which exists as a trimer of palladium–lipoic acid joined to thiamine in an arrangement which allows it to be both water and lipid soluble, and the initials "MVA" stand for minerals, vitamins, and amino acids (Garnett, 1995). Palladium, which is a transition mineral, serves as highly efficient aerobic catalyst (Stahl, 2005). During oral administration of this material in the emergency treatment of certain brain tumors, it was found that patients receiving concurrent radiation did not develop the usual signs of radiation toxicity such as nausea, exhaustion, disorientation, and depression (Garnett and Remo, 2001). It was examined for its efficacy as a radioprotector; 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. Also, the radiation-induced DNA damage in these cells was reduced when PLAC was administered to animals exposed to a lethal dose of 8 Gy whole-body gamma-radiation (Ramachandran, Krishnan, & Nair, 2010). Administration of poly-MVA, for seven days prior to whole body gamma radiation significantly reduced the damage to cellular DNA in bone marrow and blood leukocytes, as well as preventing the radiation-induced lowering of tissue antioxidant levels (Menon, Krishnan, & Nair, 2009). 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 (Bunger, Stork, & Stalder, 1996).

As lipoic acid is a powerful antioxidant that is water and fat-soluble, it allows the Poly-MVA to penetrate the cell membranes and the blood brain barrier. Since it is a polymer (liquid crystal), rather than a single molecule, this liquid crystalline structure allows it to store a great deal of energy and thus serve as a semiconductor (Garnett and Garnett, 1996). Therefore, LAPC is not only a potent free radical scavenger, but it also provides cellular energy. It acts as a liquid electrical transistor that transfers electrical current from the cell membrane to the mitochondria which redistributes the electrical current throughout the cell via the existing electrical pathways (Garnett and Garnett, 1996). It oscillates between an oxidized and reduced form as it accepts unpaired electrons and donates them to its enzymatic site. In cancer cells, it has been demonstrated to be an oxidizer of membrane fatty acids, serving as a redox shunt to provide a continuous river of reducing equivalents to protect DNA against oxidation (Garnett, 2002).

In this study, the efficiency of poly MVA was examined as a radio-prophylactic agent against exposure to a single sublethal dose of gamma radiation.

2. Materials and methods

2.1. Chemicals

Poly-MVA is a liquid dietary supplement that contains 23.5 mg/ml of lipoic acid–palladium complexes as well as minerals (molybdenum, rhodium, ruthenium), vitamins (B_1, B_2 and B_{12}), and amino acids (N-acetyl cysteine and formyl methionine). The palladium lipoic acid formulation, used in this study, was obtained as a gift from Garnett McKeen Laboratory, Inc., USA.

2.2. Animals

Adult male Swiss Albino rats weighing 200 g were used. They were divided into 4 groups of 18 animals each: control group, treated group with poly-MVA, irradiated group and treated-irradiated group. Rats were kept under standard conditions along the experimental period. Food and water were supplied daily *ad libitum*. All animals were housed according to the ethical rules in compliance with institutional guidelines. The conditions were the same for all animals throughout the study. The animals were housed in standard cages (26 × 42 × 15 cm) with sawdust, at constant room temperature (25 ± 1 °C) and relative humidity (45–55%) with a 12 h light/dark cycle. They were dissected at three times intervals: 1, 7, 14 days after exposure to radiation.

2.3. Irradiation

Animals were placed in a specially designed well-ventilated acrylic pie cage which holds up to 20 rats. The whole body of the animals was exposed to 6 Gy gamma radiation from the

biological irradiator gamma cell-40, cesium-137 source with dose rate: 0.769 cGy/s (manufactured at the atomic energy agency, Canada) at the National Center for Radiation Research and Technology, Cairo. The dose rate was calibrated at the beginning of the experimental work by the Egyptian High-Dose Reference Laboratory. The animals were exposed to 6 Gy acute dose. The activity of the irradiation source allows the animals to receive the recommended dose in this study in 13 min.

2.4. Treatment

Poly-MVA was taken orally with daily dose of 2 ml/kg body weight. Rats were divided into (4) main groups:

1. Normal control group: it consisted of six rats, kept un-irradiated and un-treated as normal control group.
2. Irradiated group (group A): it includes 3 subgroups according to the dissection time: 1, 7, 14 days after irradiation. Each irradiated group of rats was composed of 6 rats.
3. The radio-prophylactic effect of poly-MVA was evaluated after two modes of administration:
   a) Uptake of poly-MVA before irradiation (Group B), it consisted of two subgroups treated with poly-MVA for two consecutive weeks; one of the subgroups was exposed to radiation at the end of administration period. The measurements were performed 1 day after stopping administration and/or irradiation, and continued to the 7^{th} and 14^{th} days. The other was kept un-irradiated as positive control, administration of poly-MVA was stopped after two weeks then the measurements were performed at 1, 7, 14 days.
   b) Continuous administration of poly-MVA before and after irradiation (Group C), it consisted of two subgroups: one subgroup treated with poly-MVA for two consecutive weeks before irradiation and the administration continued for two other weeks. The measurements were performed 1 day after irradiation, and continued at the 7^{th} and 14^{th} days during poly-MVA administration. The other subgroup received administration of poly-MVA for four consecutive weeks (total time of administration 28 days). The measurements started after two weeks of administration (at the 14^{th} day) and continued to the 21^{st} and 28^{th} days.

2.5. Preparation of samples

Animals were anesthetized by exposure to diethyl ether in a closed container by open-drop method. The blood samples were withdrawn from the left ventricle of the heart using heparinized needles. After dissection, the liver washed with isotonic 0.9% NaCl. 10% of liver sample in saline was homogenized using a Tri-R STIR-R model K41 homogenizer, and then the homogenate was centrifuged at 3000 rpm for 10 min at 4 °C. The supernatant was separated for use in analysis.

2.6. Determination of antioxidants enzymes

2.6.1. Glutathione (GSH) assay

The hepatic level of glutathione (GSH) was measured spectrophotometrically using Ellman's reagent with 5-5′, dithiobis-2-nitrobenzoic acid [DTNB] as a coloring reagent, according to the method of (Beutler, 1963). The absorbance was read at 412 nm using a UV–VIS spectrophotometer CECIL-3041.

2.6.2. Catalase estimation

The catalase activity was measured in liver cells by catalytic reduction of hydrogen peroxide using the method of Sinha (1972).

2.6.3. Superoxide dismutase (SOD)

Superoxide dismutase activity can easily be measured by using the method of Minami and Yoshikawa (1979).

2.7. Rheological properties of blood

The rheological properties were measured by means of Brookfield DV-III Programmable Rheometer. It is a cone-plate viscometer that measures fluid parameters of shear stress and viscosity at given shear rates. The body temperature varies from 29 °C at the surface to 37 °C in the blood stream. Red blood cells (RBCs) properties are well known to be temperature-dependent, so that statistically significant differences were present in a wider range of temperatures between 25 and 37 °C (Baskurt & Mat, 2000). In this study, the temperature was set at 35 °C. The applied shear rate was 7.5–375 s^{-1}. The data was collected from the rheometer by means of software program "Rheocalc for Windows". The change in viscosity with shear rate gives the flow curve (Fig. 1), which is characterized by two regions: in the low shear rate up to 100 s^{-1}, and high shear region; from 100 s^{-1} up to the shear rate at which no change in viscosity is obtained.

For analysis of the flow curve, the Bingham plastic model was applied to calculate the yield stress (F_0) and viscosity (η) as follows:

$$F = F_0 + \eta D$$

where F is the shear stress (dyne/cm^2) and D is the shear rate (s^{-1}).

Since the blood viscosity at low shear rate is greatly affected by the RBCs aggregation, the ratio of viscosities at 20 and 100 s^{-1} can be regarded as quantitative characteristic of RBCs aggregation efficiency (Aggregation index) (Dobrovol'skii et al., 1997).

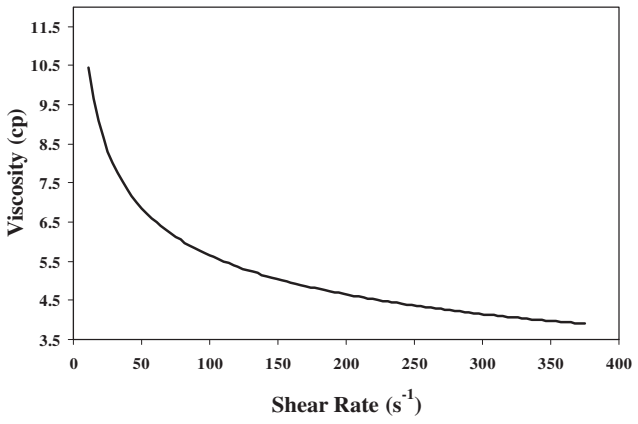

Fig. 1 – Blood flow curve for control group.

$$\text{Aggregation index} = \frac{\eta_{at20s^{-1}}}{\eta_{at100s^{-1}}}$$

2.8. Osmotic fragility measurements

The process of osmosis was studied by placing red blood cells (RBCs) in solutions of different tonicity. The osmotic lysis of RBCs is easily detected by the release of hemoglobin (Hb) into the extracellular fluid. The amount of Hb appearing in media of different ionic strength was determined spectrophotometrically at 540 nm to characterize the degree of hemolysis according to the method reported by Dacie and Lewis (2006). The quantitative measurements (degree of hemolysis versus decreasing NaCl concentration) are plotted on a graph called the fragility curve as shown in Fig. 2 (Mazeron, Didelon, Muller, & Stoltz, 2000). The experimental curves were normalized to 100% hemolysis to facilitate the comparison between different samples without the interference of the hematocrit changes. The fragility curve can be evaluated by the following parameters:

1 Average osmotic fragility (H_{50}): the NaCl concentration producing 50% homolysis.
2 Dispersion of hemolysis (S): it is defined as the difference between the maximum and minimum values of NaCl concentration at which the rate of hemolysis (dH/dC) = 0. High values of S correspond to isohemolysis (homogenous RBCs population), and low values of S to anisohemolysis (heterogenous RBCs population) (Kergounou, Thiriot, Braquet, Ducousso, & Rocquet, 1986).

2.9. Morphological analysis

The morphology of RBCs was studied using scanning electron microscope (SEM) according to Ross, Wang, and Jelinek (2007) as follows: Three drops of RBCs suspension were added directly to 5 ml of 2.5% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.4. Fixation was allowed to proceed for at least 1 day before processing. The cells were washed twice in cacodylate buffer, dehydrated with two washes in 70% ethanol, washed twice in 95% ethanol, twice in absolute ethanol and twice in acetone. One drop of the cell suspension was applied to an acetone-washed coverslip and allowed to dry. The coverslip was fixed to an aluminum stub using a colloidal silver adhesive and gold coated using a sputter coater (SPI). Electron microscopy was carried out using a Jeol Model JSM-5400 scanning electron microscope at the National Center for Radiation Research and Technology (NCRRT).

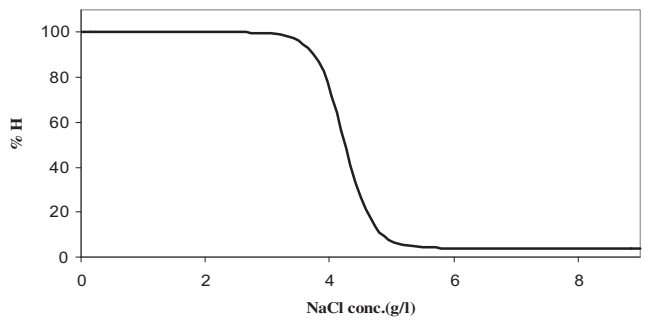

Fig. 2 – Fragility curve of RBCs.

2.10. Statistical analysis

In this study, the values are expressed as mean values ± - standard deviation. The significance of the difference between the values of the treated groups and control was evaluated by the Student *t*-test and values with $p < 0.05$ were considered as statistically significant (Snedecor & Cochran, 1989).

3. Results

The radio-prophylactic effect of poly MVA against exposure to acute dose of gamma radiation (6 Gy) was studied by its daily administration for two weeks before exposure to gamma radiation for two different groups. In the first group the administration of poly MVA was stopped after irradiation (group B) and the second group the administration continued after irradiation for two more weeks (group C).

A significant decrease in cellular antioxidant enzymes (GSH, Catalase and SOD) was shown in irradiated animals (group A) compared to control group, and it is more noticeable at 14th day after exposure (Table 1). Also radiation exposure resulted in significant decrease in Bingham viscosity, yield stress and aggregation index of blood, which persist until 14th day as shown in Fig. 3. Furthermore it induced slightly increase in average osmotic fragility of red blood cells (Fig. 4) accompanied by decrease in osmotic dispersion S after 1 day of exposure then the dispersion non-significantly increased at 7th and 14th day.

Uptake of poly-MVA showed non-significant change in glutathione content with elevation in cellular catalase and SOD enzymes activity (Table 1), while it produced a significant decrease in blood Bingham viscosity and yield stress with a non significant change in aggregation index, accompanied by a significant increase in average osmotic hemolysis and osmotic dispersion which continued increasing with time of poly-MVA administration (Figs. 3 and 4).

Poly-MVA raised the concentration of antioxidant enzymes in liver cells in both treated groups (B and C) as shown in Table 1. In group B, administration of Poly-MVA resulted in slightly decrease in Bingham viscosity, yield stress and aggregation index compared to control group, reducing the damage induced by radiation exposure. While it showed a significant decrease in osmotic dispersion with non-significant change in mean osmotic fragility H_{50}.

Continuous administration of Poly-MVA before and after irradiation (Group C) shows significant decrease in Bingham viscosity, yield stress and aggregation index at 1, 7 days after radiation exposure, while at 14th day their values were close to control value. Furthermore, it showed a significant increase in H_{50} and non-significant change in osmotic dispersion.

The changes in RBCs shape was investigated by scanning electron microscope (SEM). Figs. 5 and 6 shows scanning electron micrographs of RBCs samples of control, irradiated and the treated groups with Poly-MVA (B and C), at different time intervals (1, 7 and 14 days), prepared immediately after withdrawal. It shows the normal biconcave shape (a) of a

Table 1 – The antioxidants content (Glutathione μ/g tissue, Catalase U/g tissue and Superoxide dismutase enzymes U/g tissue) in control, treated, irradiated and treated-irradiated groups at different time intervals (1, 7 and 14 days).

Treatment with poly MVA	Groups	Statistics	GSH content			Catalase activity			SOD activity		
			1 day	7 days	14 days	1 day	7 days	14 days	1 day	7 days	14 days
Without treatment	Control	Mean	14.72	14.72	14.72	1.27	1.27	1.27	35.67	35.67	35.67
		S. D.	±1.19	±1.19	±1.19	±0.29	±0.29	±0.29	±8.73	±8.73	±8.73
	6 Gy	Mean	13.48*	12.99*	12.96*	1.40	1.05	1.03	28.74	19.67*	8.69*
		S. D.	±0.96	±0.38	±0.53	±0.39	±0.17	±0.11	±5.86	±2.76	±1.90
Before irradiation (group B)	Poly-MVA	Mean	15.62	14.80	14.07	2.00	2.27*	2.61	49.69*	57.87*	56.38*
		S. D.	±3.14	±1.56	±2.02	±0.30	±0.21	±0.69	±0.86	±5.91	±4.87
	6 Gy + Poly-MVA	Mean	14.12	15.56	13.86	2.04*	1.91*	1.93*	48.92*	47.61*	44.21
		S. D.	±1.39	±2.22	±1.25	±0.26	±0.33	±0.11	±9.31	±8.77	±4.02
Continuous treatment (group C)	Poly-MVA	Mean	14.05	14.17	15.29	2.17*	2.36*	2.25*	56.22*	61.25*	69.61*
		S. D.	±0.69	±0.47	±0.64	±0.59	±0.03	±0.35	±7.49	±0.81	±2.73
	6 Gy + Poly-MVA	Mean	13.81	14.12	14.43	1.65*	1.43	1.66	36.10	38.94	48.00*
		S. D.	±0.66	±0.22	±0.22	±0.15	±0.28	±0.26	±9.18	±5.98	±4.10

S.D.: standard deviation.
*: statistically significant.

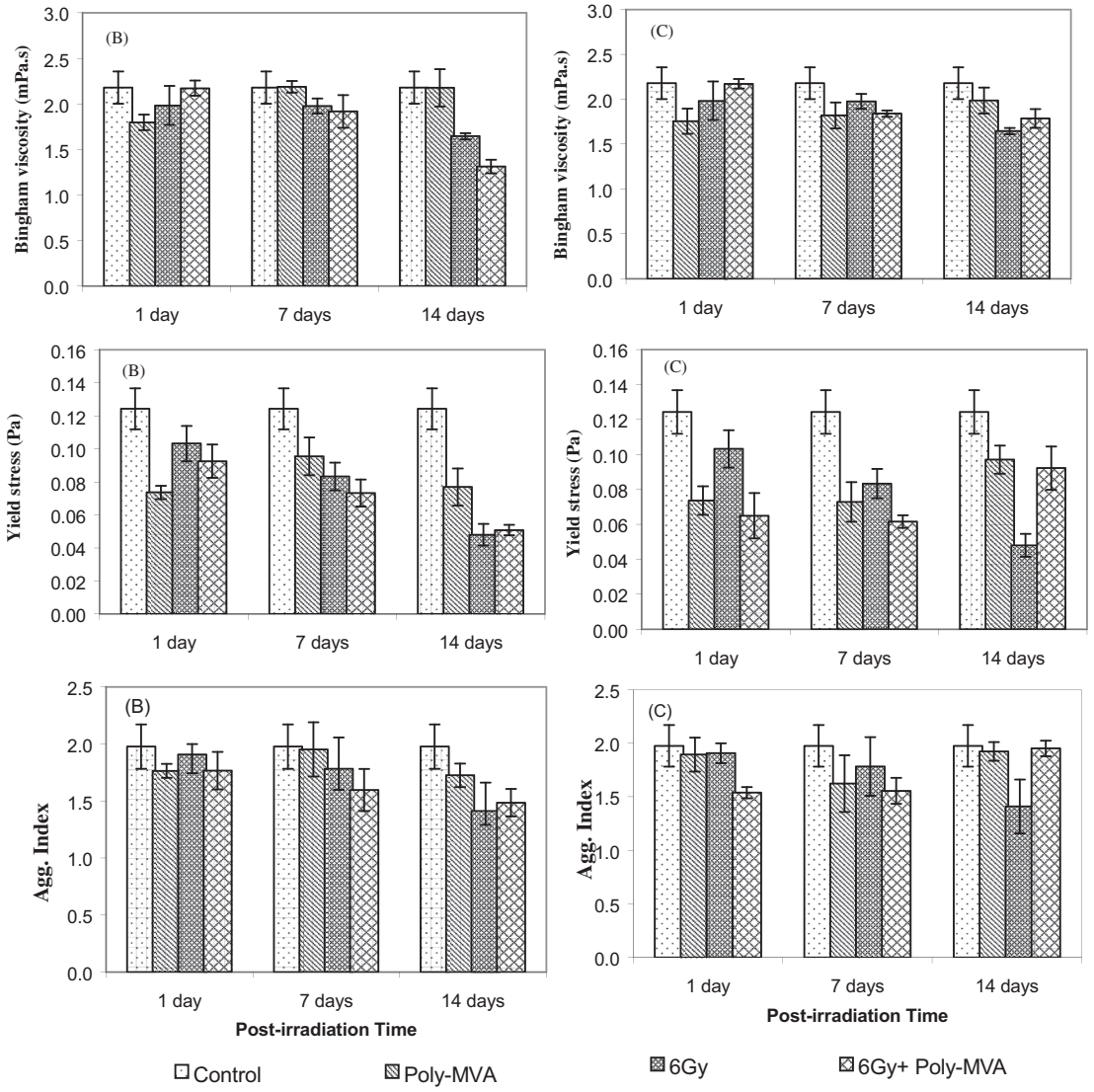

Fig. 3 – The Bingham viscosity, Yield stress and Aggregation index of control, irradiated and treated groups with poly-MVA, (B) group B (administrated before irradiation) and (C) group C (continuous administration), at different time intervals (1, 7 and 14 days).

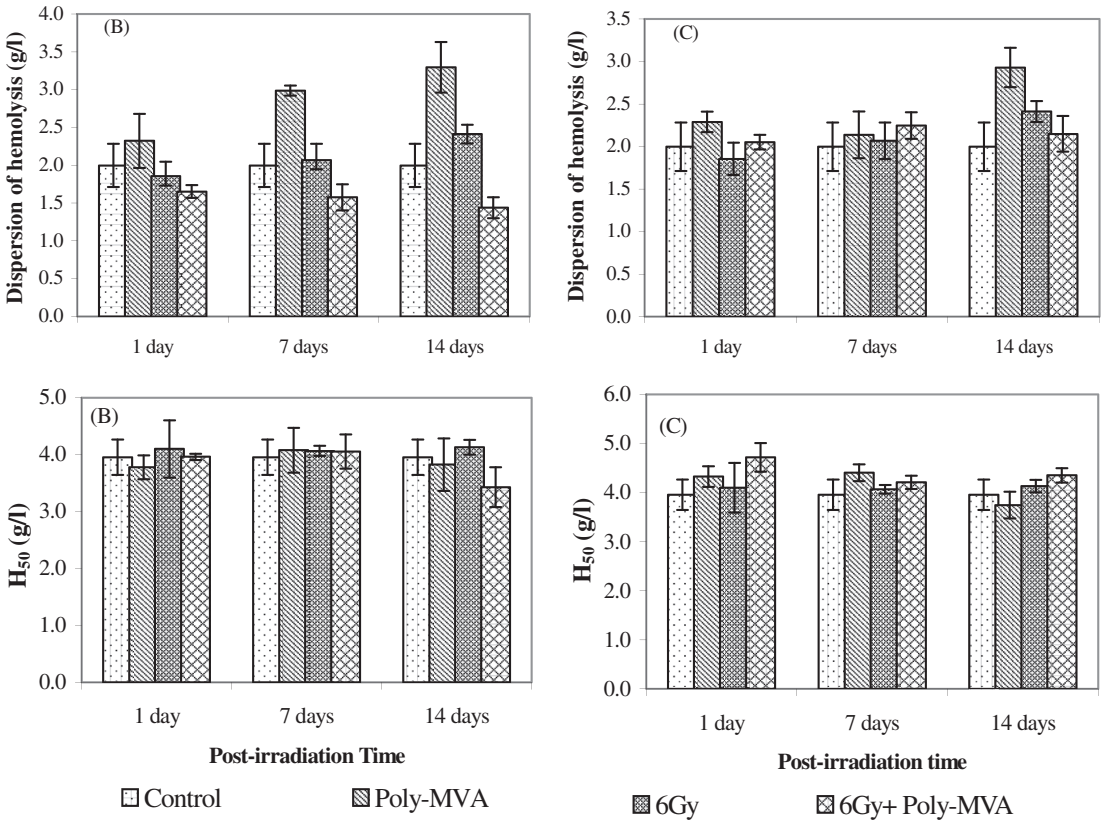

Fig. 4 – The dispersion of hemolysis and average osmotic fragility of control, irradiated and treated groups with poly-MVA, (B) group B (administrated before irradiation) and (C) group C (continuous administration), at different time intervals (1, 7 and 14 days).

control. A remarkable modification of red blood cell morphology with distinct echinocyte and stomatocytes formation was observed in irradiated groups as shown in (b). Oral uptake of Poly-MVA diminishes the formation of abnormal shapes, reducing the radiation induced damage in all groups (B and C) as shown in figures (d). Scanning electron micrographs showed that continuous administration of poly-MVA resulted in a better radio-prophylactic effect.

4. Discussion

Red blood cells (RBCs) constitute 99% of blood cellular components, so they govern its rheological properties (Pal, 2003). The RBC membrane consists of the phospholipid bilayer containing integral membrane proteins and the underlying membrane cytoskeleton (Svetina, Kuzman, Richard, Ziherl, & Zeks, 2004). Blood rheology is altered in various conditions: Changes at the level of hematocrit notably lead to variations in hemorheological parameters. Also modifications of the membrane skeletal proteins, the ratio of RBC membrane surface area to cell volume, cell morphology, and cytoplasmic viscosity influence deformability of RBCs. Also, RBC aggregation is mainly determined by plasma protein composition and surface properties of RBCs (Baskurt & Meiselman, 2003). Red cell rheological abnormalities due to alterations of these factors can thus be expected to lead to both disturbances of the microcirculation and also to changes of red cell survival in vivo. In the present study exposure to 6 Gy acute dose causes decrease in Bingham viscosity accompanied by increase in average osmotic fragility that is might be due to the oxidative changes occurred in cell membrane as a result of radiation exposure. Previous studies showed that cell membranes are particularly sensitive to the effects of radiation-induced oxidative damage and that lipid peroxidation which can alter membrane structure and function (Schroeder, 1984). In addition, numerous experiments have suggested that radiation may modify the transport mechanisms, react with membrane-bound proteins (Stark, 1991). Importantly, several membrane biophysical parameters may also be altered by radiation induced oxidative stress (e.g., shape, permeability, and osmotic fragility) (Joseph et al., 2000).

Scanning electron micrographs showed distinct deformations in RBCs membrane as a result of radiation exposure. Free radicals generated during radiation result in destructive processes within both layers of RBCs membrane lipids (Shadyro et al., 2002) and structural changes in the RBCs membrane proteins and a decrease in its intramolecular dynamics (Dreval, Sichevskaia, Doroshenko, & Roshal, 2000). Conformational change of integral membrane proteins could lead to an expansion of one leaflets of the membrane double layer relative to the other one and in turn results in a shape change (Gimsa & Ried, 1995). Poly-MVA reduced the radiation induced deformation in RBCs membrane.

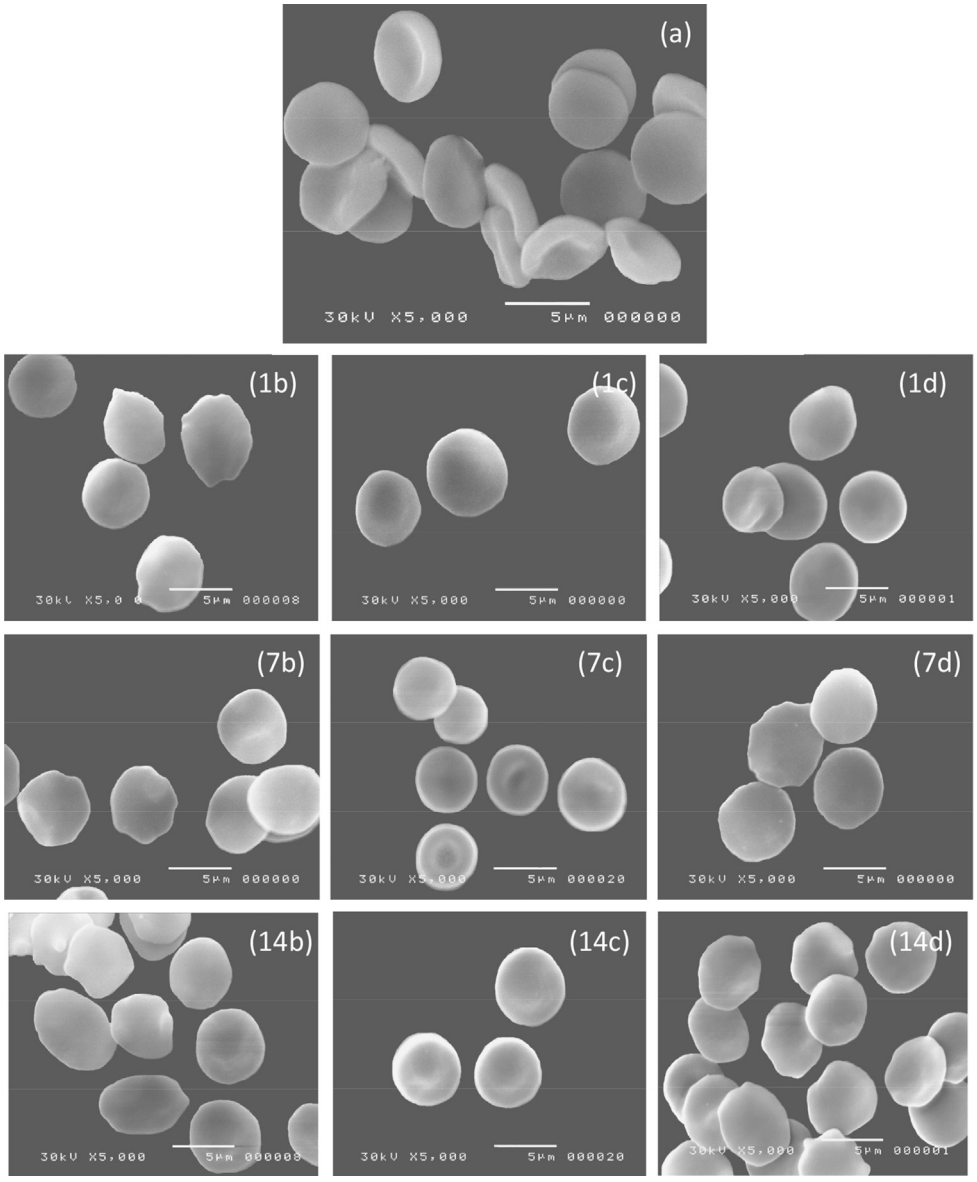

Fig. 5 – The scanning electromicrogragh of RBCs of control (a), irradiated (b), treated with Poly-MVA (c) and treated with irradiation (d) of the first mode of administration of poly-MVA (Group B) at different time intervals (1, 7 and 14 days).

Poly-MVA is a nano-complex liquid crystal complex (Garnett and Garnett, 1996). The interaction of polymer nanoparticles with biological membranes is a complex process due to the heterogeneity of both the nanoparticles and the cell membranes (Leroueil et al., 2007). Recent studies indicated that nanoparticles can strongly interact with cell membranes, either by adsorbing onto the membrane or compromising its integrity (Binder, Sachsenhofer, Farnik, & Blaas, 2007; Li, Chen, & Gu, 2008). Li et al., 2008 reported that a hydrophobic nanoparticle can result in the inclusion into the bilayer, whereas a semihydrophilic nanoparticle is only found to adsorb into the membrane. Also, the deformation of the lipid bilayer induced by the addition of nanoparticles is short-range, and the rearrangement of lipid molecules plays a significant role for morphological variations of nanopaticles-containing lipid membrane. Being soluble in water and lipid, poly-MVA can be found in both cell membrane and cytosol. Adhesive interactions due to electrostatic forces, van der Waals, or steric interactions are suspected to be involved in these processes (Rothen-Rutishauser, Schürch, & Gehr, 2007). The entering mechanism of nanoparticles into RBCs is different from phagocytosis and endocytosis, since they have neither phagocytic receptors on their surface nor the structures necessary for phagocytosis. It may occur by unspecific means, including diffusion, trans-membrane channels, and electrostatic, van der Waals, hydration forces, or adhesive interactions (Rothen-Rutishauser, Schürch, Haenni, Kapp, & Gehr, 2006). Although oral uptake of Poly-MVA minimizes the radiation effect it resulted in obvious changes in blood Bingham viscosity and average osmotic hemolysis as a result of the interaction of the nano-complex with cell membrane.

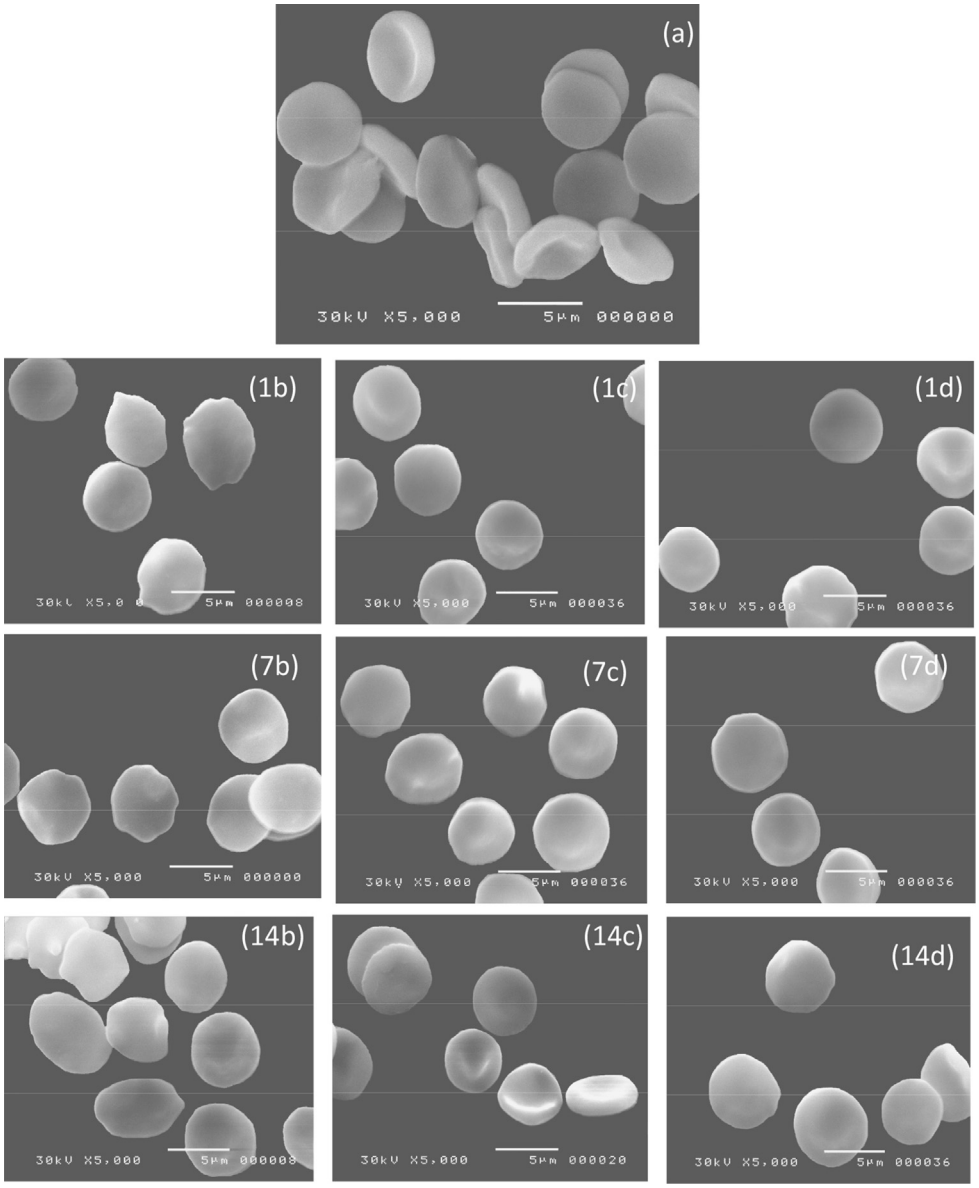

Fig. 6 – The scanning electromicrogragh of RBCs of control (a), irradiated (b), treated with Poly-MVA (c) and treated with irradiation (d) of the second mode of administration of poly-MVA (Group C) at different time intervals (1, 7 and 14 days).

The obtained results in this study agrees with the previously reported by Menon et al. (2009), who demonstrated that the administration of poly-MVA for seven days prior to whole body gamma radiation exposure (2.4 and 8 Gy) significantly reduced the damage to cellular DNA in bone marrow and blood leucocytes, as well as preventing the radiation induced lowering of tissue antioxidant levels. The same author also found that oral administration of the formulation to mice for 15 days showed an increase in GSH and glutathione peroxidase (GPx) levels and decrease in MDA level in the kidney and liver. At the same time the oral administration of POLY-MVA to mice prior to whole body radiation (8 Gy) exposure offered protection to cellular DNA as revealed by Comet assay of bone marrow cells and peripheral blood of the irradiated mice. Furthermore, Sudheesh, Ajith, Janardhanan, and Krishnan (2010) concluded that the POLY-MVA significantly enhance the activities of Krebs cycle dehydrogenases and respiratory complexes in the heart of aged rat. It also enhanced the activity of catalase, manganese–superoxide dismutase, glutathione peroxidase, and the level of lipid peroxidation was decreased significantly compared to the aged control.

5. Conclusion

Poly-MVA provide a satisfied radio-prophylactic effect, as it enhances the level of antioxidant enzymes and helps in reducing the radiation induced abnormalities in red blood cell morphology in both treated groups (before and continuous administration with radiation exposure). However administration before and after irradiation showed better results than administration before only. These results propose

useful application for planned radiation exposure during diagnosis and radiotherapy. Continuous administration of poly-MVA shows a better radio-prophylactic effect.

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