The Mechanism and Treatment of Coagulopathy in Proton Irradiated Ferrets

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ABSTRACT

A solar particle event (SPE) involves the release of particles with energies greater than 10 MeV/n. Protons are a major component of SPE radiation; therefore, ground-based SPE radiation research is focused on the biological consequences of proton radiation at the appropriate energies, doses and dose-rates occurring during an SPE. Effects of SPE radiation on cardiovascular functions are of interest in space radiation research due to the fact that a number of charged particles from an SPE have the ability to penetrate an astronaut's spacesuit and body. The estimated radiation doses could be deleterious to the vasculature as they exceed the NASA space radiation permissible exposure limits. One of the understudied areas of radiation research involves the effects of radiation on blood coagulation. The coagulation pathway is comprised of interlocking components that generate a fibrin-rich blood clot, which halts bleeding. Previous experiments were performed in ferrets exposed to 110 MeV protons at doses and dose rates that mimic SPE-like proton radiation (50 cGy/hour or 50 cGy/minute). At 4-8 hours post-irradiation, we have reported increased prothrombin times (PT) and activated partial thromboplastin times (aPTT). 100 cGy (LDR) exposure resulted in a number of ferrets with clinically significant international normalized ratio (≥ 2.0). We have hypothesized that SPE radiation activates the coagulation cascade, leading to an SPE-induced hypocoagulable state.

In these current studies ferrets were exposed to LDR and evaluated for coagulopathy. Factor deficient plasma samples were mixed with the plasma samples isolated from the irradiated ferrets and PT/aPTT values were determined; the 100 cGy dose group (LDR) resulted in radiation-induced factor deficiencies in Factor II, V, VII, VIII, IX, X, XI, and XII. These factor deficiencies led to the hypocoagulable state with clinically significant radiation-induced coagulopathy. Using a soluble fibrin assay that measures the endpoint of fibrin production, fibrin concentration increased 10-fold over the course of 24 hours while sham-irradiated fibrin concentration remained unchanged indicating an activated coagulation cascade. An activated coagulation cascade causes a two fold dilemma including the production of clots but also leaves the blood deficient in clotting factors preventing future clotting; therefore depleting factor concentration and giving the appearance of an increased PT/aPTT. We have assessed increasing factor concentration with pre-irradiation treatment with either Aquamephyton or BeneFIX. Both treatments were able to modify the radiation response, however further research is necessary to determine necessary dosing.