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Original Article

Acceleration of skin wound healing by low-dose indirect ionizing radiation in male rats

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Abstract A recent hypothesis has revealed that low-dose irradiation (LDI) with ionizing radiation might have a promoting effect on fracture healing. The aim of this study was to investigate the influence of direct (electron beam) and indirect (gamma-ray) low-dose ionizing irradiations on the wound healing process in male rats. In 72 male rats, a full-thickness wound was incised. The animals were randomly assigned to three groups, each with 24 rats. The first two groups were named IG—I and IG—II and respectively exposed to electron and gamma-radiations (75 cGy) immediately after the surgical procedure. The third group was considered as the control (CG) and remained untreated. Skin biopsies from the subgroups were collected on days 3, 7, 15, and 21 after the operation and evaluated using histological and biomechanical methods. Data were analyzed by one-way ANOVA, followed by Tukey's post hoc test using SPSS 20 software. Histological studies of tissues showed that the mean number of fibroblasts, macrophages, blood vessel sections, and neutrophils on the third and seventh days after the surgery in the gamma-treated group was higher than that in both other groups. In contrast, on day 21, the mean number of mentioned cells in the gamma-treated group was lower than in the other two groups. In addition, the mean maximum stress value was significantly greater in the gamma-treated group. Results of this study showed that gamma-ray irradiation is effective in the acceleration of wound healing.

Conflicts of interest: All authors declare no conflicts of interest.
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Introduction

A wound is a break in the epithelial layer of skin that may be accompanied by the disruption of structures and function of normal tissues. A wound may result from an incision, a trauma, burns, lacerations, or an abrasion [1]. Around three to six million skin wounds occur in patients only in the USA every year [2]. Wound healing involves a complex series of interactions between different cell types, mediators, and extracellular matrix [3] and has four characteristic phases, including hemostasis or bleeding, inflammation, proliferation, and remodeling [4,5]. Wound healing is an essential factor for successful healthcare; therefore, studies on the methods that accelerate wound healing are of high importance. Apart from the biological factors that influence the healing process [6], biophysical interventions, including ultraviolet, pulsed radiofrequency radiation, low-energy laser, ultrasound waves, pulsed electromagnetic fields, and electrical stimulation may also impact the healing process of wounds or fractures [4,7,8]. In 1994, the wound healing process was evaluated by Wang et al. [9] in electron-irradiated rat skin using electron microscopy. Rat's skin was locally irradiated with 9.6 Gy electron radiation seven days before the creation of the skin wound. The result indicated that healing was delayed due to electron irradiation.

A recent hypothesis suggested by Song and coworkers [4] was a milestone in low-dose irradiation (LDI). They revealed that LDI with ionizing radiation might have increasing effect on fracture healing. Several investigations have been performed in the effects of low-dose ionizing radiation on biological systems; nevertheless, compromised wound healing in irradiated tissues is a common and challenging clinical problem [10—12]. In a study, it has been indicated that the callus formation and mineralization in a rat model can be promoted by LDI at 100 cGy without being able to explain the fundamental mechanism [10]. In another study, the effect of low-dose electron radiation on the wound healing process of rat skin was evaluated. The histological evaluations showed that a low dose of electron beam delayed rat skin repair [11]. Conversely, Chen et al. [12] have reported that low-dose X-ray irradiation (50 cGy) induces beneficial effects, such as the stimulation of osteoblast proliferation, differentiation, and fracture healing. Some other studies have revealed that the low-dose X-ray irradiation (100 cGy) is able to promote fracture healing [5,10], but the same dose of electron irradiation has adverse effects on wound healing [11]. Since the linear energy transfer (LET) of photon and that of electron beams are different from each other, we suppose that the 100 cGy dose of electron beams may be sufficient to delay rat skin repair. Frey et al. [13] have demonstrated that whole-body low-dose radiotherapy (30—100 cGy) can be useful in clinical settings for treatment of patients with chronic and degenerative diseases. In the current study, a relevant clinical whole-body low-dose of electron beam and gamma-ray (75 cGy) was evaluated in skin wound healing.

However, evidence has demonstrated that LDI, as whole-body irradiation, stimulates many physiologic functions such as increased immune competence without toxic effects, lower morbidity and mortality, longer lifespan, enhanced reproduction [14,15], and promotion of fracture healing [12]; and protects cells and tissues against oxidant damages mediated by their antioxidant property [16], and so on. Thus, the present study is an attempt to evaluate the systemic effects of whole-body LDI on wound healing. In the literature, some different doses of LDI (50 cGy, 100 cGy, 75 mGy, and so on) have been examined [4,10—12]. In the current study, dose selection was carried out based on the results of the mentioned previous studies: positive or promoting effects in the case of photons (X- and gamma-rays) and negative or delaying effects in the case of electrons. Moreover, we were encouraged to evaluate the systemic effects of low-dose ionizing radiation on wound healing using 75 cGy whole-body irradiation, instead of its biological effects on the target or skin dose.

Since the term LDI has been used widely in scientific literatures, we decided to focus on evaluating the systemic effects of photon and electron beams on wound healing, considering LDI, and types of ionizing radiations. Therefore, the present study was designed to investigate the influence of direct (electron beam) and indirect (gamma-ray) low-dose ionizing irradiations on the wound-healing process in male rats using histological and biomechanical evaluation methods.

Methods

Animal experiments

All the experimental procedures were approved by the Ethical Committee of Urmia University of Medical Sciences (Urmia, Iran). Seventy-two healthy male adult Sprague—Dawley rats (Pasteur Institute of Iran, Tehran), weighing 200—250 g, were housed under normal conditions and acclimatized for two weeks. On day 0, the rats were anesthetized by the intraperitoneal injection of ketamine and xylazine (90 mg/kg and 10 mg/kg, respectively; both from Sigma-Aldrich, USA). Dorsal hair of each rat was shaved and cleaned by betadine, approximately 10 mm on the left side of the spine. A full-thickness wound with the approximate length of 2.5 cm from the first thoracic vertebrae, which extended into the dermis to involve subcutaneous tissues, was incised to the level of subcutaneous adipose tissue by means of a surgical blade under aseptic conditions. The skin was closed with 4-0 nylon sutures (Teb Keyhan, Iran). The animals were then randomly assigned to three groups, each with 24 rats. The first two groups were named IG—I and IG—II and were respectively exposed to electron and gamma-radiations immediately after the surgical procedure (on day 0). The third group was considered as the control (CG) and remained untreated. The IG—I group was irradiated with 8 MeV electron beam using a Siemens Primus medical linear accelerator (Siemens® Medical Solutions, Inc., Germany) at the source-to-skin distance (SSD) of 100 cm. The dose rate of electron beam irradiation was 300 MU/min. The IG—II group was exposed to gamma-ray irradiation using a Cobalt—60 (Co—60) source (Theratron Phoenix, Theratronics Inc., Ottawa, Canada) with the approximate dose rate of 52 cGy/min at the SSD of 80 cm.