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Original Article

Remote ischemic preconditioning enhances fracture healing



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ABSTRACT

Purpose: We hypothesized that RIP accelerates fracture healing.

Methods: Rats (n = 48) were used for the technique of ischemic preconditioning involved applying 35 min of intermittent pneumatic tourniquet for 7 cycles of 5 min each to the fractured hind limb.

Results: We observed greater callus maturity in RIP group at first week after fracture when compared to controls (p < 0,0001). The serum MDA levels demonstrated statistically lower values at the RIP group at the first week after fracture; however, there were not significant differences at 3rd and 5th weeks (p = 0.0001, p = 0.725, p = 0.271, respectively).

Conclusions: Greater callus maturity was obtained in RIP group.

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1. Introduction

Diaphyseal long bone fractures have a bimodal distribution, having a peak incidence in young men and in elderly women, creating a great burden on societies by their economic aspects.^{1,2} Thus, satisfactory management of such injuries is crucial to prevent morbidity, to lower medical costs and to enhance quality of life.³ A steep rise investigation to accelerate fracture healing can be detected in the literature in the last decade and many attempts have been made to accelerate

fracture healing time. Percutaneous autogenous bone marrow injection, low-intensity pulsed ultrasound, sclerostin antibody administration, inhibition of 5-lipoxygenase, mesenchymal stem cell augmentation and insulin-like growth factor-II were shown to accelerate healing.^{4–9} Also, Sarban et al, in their precious study, have evaluated the effect of rhBMP-2 soaked collagen sponges on fracture healing and found higher fracture healing scores.² A progressive increase for alternate methods in biologic fracture management seems to become evident in the future.

The experimental protocol was approved by the Animal Study Committee of the hospital (Ref. No. 2013/32). The study was performed in Dışkapı Yıldırım Beyazıt Education and Research Hospital.

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Recently, the effect of remote ischemic preconditioning (RIP) on vascularized bone grafts has been assessed and found that both survivability of skin flaps and callus formation during the healing process of the graft were increased.¹⁰ However, the idea of preparing the ischemic tissue to ischemia, namely ischemic preconditioning was first defined by.¹¹ They designed an animal study and their main purpose was whether multiple brief episodes of ischemia of the myocardium resulted in less necrosis. Alike this pioneer study, studies on bone marrow-derived mesenchymal stromal cells showed that ischemic preconditioning promotes trophic signal expression and migration of these cells leading to improved healing.^{12–15} Although these studies demonstrated that RIP could stimulate fracture healing, the effect of RIP on fresh long bone fracture healing has not been evaluated before.

Taking into account positive effects of RIP on mesenchymal precursor cells on the healing process of the fractures, we asked whether RIP would radiographically and histologically enhance fracture healing of the long bones. For this purpose, (1) the radiologic healing maturity of each fracture, (2) histologic evaluation of fracture healing and (3) malondialdehyde (MDA) levels to estimate oxidative stress at the fracture site were compared in an animal model.

2. Material and methods

The experimental protocol was approved by the Animal Study Committee of the hospital (Ref. No. 2013/32). All the animals were handled in accordance with the Guidelines for Animal Experimentation. Forty-eight Wistar-Hannover rats weighing a mean 184 gr and aged a mean 20 weeks were housed in cages and maintained under suitable temperature ($23\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$), humidity ($55\% \pm 15\%$), ventilation (continuous circulation of fresh air), and illumination conditions (a 12-hr light/dark cycle). Rats were divided into two groups: study group and sham-operated group and each group consisted of 12 males and 12 females. RIP was performed to the study group prior to surgery.

2.1. Experimental design

The technique of ischemic preconditioning involved applying 35 min of intermittent pneumatic tourniquet for 7 cycles of 5 min each to the hind limb. In the sham-operated group, tibias were left hypoxic for 30 min by a pneumatic tourniquet prior to surgery. All left tibia fractures were produced in a standard manner as previously described.¹⁶ All fractures were fixed using an intramedullary Kirschner wire (diameter 1.5 mm) (Fig. 1). All wires were cut level with the condyles to avoid restriction of motion of the knee joint. After recovery from anesthesia, unrestricted activity was allowed.

2.2. Radiological analyses

At first, third and fifth weeks, eight rats from each group were sacrificed and after anteroposterior and lateral X-ray examination of each hind limb, tibias were bisected along sagittal plane after disarticulation of the hind limb. The Goldberg



Fig. 1 – Intramedullary K-wire fixation of the tibial fracture after standard closed fracture in laboratory animal bone.

radiological classification of fracture callus in 3 stages was used.¹⁷ Fracture callus without bridging bone was accepted as stage 1, with bridging bone was accepted as stage 2 and without a visible fracture line was accepted as stage 3.

2.3. Quantitative histology and serum MDA analyses

For histological evaluation, tibias were fixed with 4% paraformaldehyde overnight at room temperature, and decalcified in 14% EDTA for 6 weeks (liquid refreshed weekly). After sufficient decalcification was achieved (judged by the easy penetration of a needle), the sample was dehydrated through an ethanol series, embedded in paraffin, and 5 μm sections were cut longitudinally. The sections were stained with hematoxylin and eosin for light microscopic examination. A numerical scoring scheme for histologic evaluation of fracture healing was used to identify phases of fracture repair and a ten-point scale from 10 (union of fracture fragments by mature bone) to 1 (fibrous tissue) was assigned to each fracture in a blinded manner by an independent investigator.¹⁸ MDA levels were investigated in blood samples of the rats at the time of sacrifice from abdominal aorta.

2.4. Statistical analyses

Data were expressed as mean \pm standard deviation (SD). Statistical computation of data was performed using the statistical package SPSS 10.0 (SPSS, Chicago, IL, USA). The significance of the difference of MDA levels between the two groups was investigated by Student's t-test. Differences between histologic grading and Goldberg scores were tested by Mann Whitney-U test. A P value less than 0.05 was considered significant.

3. Results

Radiological analysis at first, third and fifth weeks after fracture demonstrated no significant difference between the RIP and sham-operated groups (Table 1) ($p = 0.148$). In these animals, osseous bridging of the fracture gap as defined by Goldberg had revealed similar scores and all had stage 2 osseous bridging at the end of fifth week at the lateral

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