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ORIGINAL ARTICLE

The influence of growth factors on skin wound healing in rats☆

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KEYWORDS
Wounds in rats;
Growth factor;
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Abstract
Introduction: Healing is a process that restores the physical integrity of body structures. It is a dynamic, complex, multicellular process that involves the extracellular matrix, cytokines, blood cells, and growth factors. Growth factors are proteins that activate and stimulate cell proliferation through the activation of angiogenesis, mitogenesis, and gene transcription, accelerating the healing process.
Objective: To assess the influence of growth factors on the healing process of wounds made on the backs of female rats compared to the control wound, through macro and microscopy.
Methods: This study used 45 female Wistar rats, in which three wounds were made on the back. The first was the control wound, the second received epithelial growth factor injection, and the third received a combination of factors. Macroscopic and microscopic assessments were performed on the third, seventh, and 15th days of the experiment. For microscopic analysis, hematoxylin–eosin staining was utilized to assess the inflammatory process; vimentin, for assessment of blood vessels and fibroblasts, and Sirius Red for collagen assessment.
Results: In the macroscopic assessment, the use of growth factors resulted in faster healing and decrease of granulation tissue on days seven and 15; (80.31% reduction in the control wound *vs.* 83.24% in the epithelial wound *vs.* 100% in the mixed wound). Utilizing microscopy, at the three stages of the experiment, there were no significant differences between the three wounds; however, when comparing the day of euthanization for each type of wound, there was a favorable outcome for epithelial and mixed wounds (between the third *vs.* 15th day, $p < 0.001$, and in the comparison of the seventh *vs.* 15th day; $p = 0.002$ and $p = 0.001$ for epithelial and

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mixed wounds, respectively) with a higher number of fibroblasts, angiogenesis, and collagen type I.
Conclusion: The use of growth factors accelerates healing, stimulates greater angiogenic activity, and accelerates fibroplasia and collagen maturation.

PALAVRAS-CHAVE
Feridas em ratas;
Fator de crescimento;
Cicatrização

A influência de fatores de crescimento na cicatrização de feridas cutâneas de ratas

Resumo
Introdução: A cicatrização é um processo de restauração da integridade física das estruturas do corpo. É um processo dinâmico, complexo, multicelular que envolve matriz extracelular, citosinas, células sanguíneas e fatores de crescimento. Os fatores de crescimento são proteínas que estimulam e ativam a proliferação celular mediante a ativação da angiogênese, mitogênese, transcrição genética, acelerando o processo de cicatrização.
Objetivo: Avaliar a influência dos fatores de crescimento no processo cicatricial de feridas realizadas no dorso de ratas em comparação com a ferida, controle através da macro e microscopia.
Método: Foram utilizadas 45 ratas *Wistar*, submetidas à criação de três feridas no dorso. A primeira controle a segunda com injeção de fator de crescimento epitelial e a terceira com fator misto. As avaliações macroscópicas e microscópicas foram realizadas no 3°, no 7° e no 15° dia do experimento. Para análise microscópica, utilizou-se coloração de Hematoxilina-Eosina para avaliar o processo inflamatório; vimentina, para a avaliação dos vasos e fibroblastos, e *Sirius Red*, para avaliar o colágeno.
Resultados: Na avaliação macroscópica, o uso de fatores de crescimento proporcionou cicatrização mais rápida e diminuição do tecido de granulação no 7° e 15° dia; (80,31% de redução na ferida controle *vs*. 83,24% na ferida epitelial *vs*. 100% na ferida mista). Na microscopia, nos três momentos do experimento, não foram encontradas diferenças significativas entre as três feridas; entretanto, quando comparados os dias de morte em relação a cada tipo de ferida, observou-se resultado favorável para as feridas epiteliais e mistas (entre 3°×15° dia apresentou $p < 0,001$ e na comparação entre 7°×15° dias; $p = 0,002$ e $p = 0,001$ para as feridas epiteliais e mistas) com maior número de fibroblasto, angiogênese e colágeno tipo 1.
Conclusão: a utilização de fatores de crescimento acelera a cicatrização, estimula maior atividade angiogênica, acelera a fibroplasia e maturação do colágeno.

Introduction

Healing is a process that restores the internal and/or external physical integrity of body structures and involves complex interactions between cells and several other factors. It is a dynamic and complex process, consisting of three phases: tissue inflammation, proliferation, and remodeling.[1] The healing process comprises the extracellular matrix, cytokines, blood cells, and growth factors. Growth factors are proteins that stimulate and activate cell proliferation through activation of angiogenesis, myelogenesis, and gene transcription, among other reactions, which activate and accelerate the healing process.[1,2]

Among the growth factors, the most important ones for wound healing include: epithelial growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF-b), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and insulin growth factor (IGF); the latter stimulates cell proliferation, tissue remodeling, and collagen and elastin increase. VEGF acts on angiogenesis and tissue granulation at the early stage of healing. PDGF is crucial for inflammation, granulation, re-epithelialization, and remodeling in the three stages of wound healing.[3,4]

Due to the pathological and physiological complexity of the healing process, the perfect regeneration of tissues is difficult to achieve.[4,5] Therefore, the assessment of new treatments is needed, as well as the use of new strategies. The use of growth factors and their combinations have been suggested as promising treatments, because they accelerate the healing process. However, a major obstacle is that the growth factors are degraded by proteinases or removed by exudates before they reach the wound bed.[5]