Advances in Medical Sciences 63 (2018) 347–352

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original research article

Topical folinic acid enhances wound healing in rat model

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ARTICLE INFO

Keywords:
Folinic acid
Wound healing
Rat

ABSTRACT

Purpose: Folic acid is an essential vitamin participating in DNA synthesis and repair. Recently folic acid has been shown to stimulate DNA-repair capacity in dermal fibroblasts in response to injury. Thus, the present study aimed to investigate the effects of topical folinic acid, a 5-formyl derivative of tetrahydrofolic acid, on wound healing using rat wound model.

Materials and methods: A rat wound model was established, and the wound healing was evaluated by macroscopic and histological analyses among vehicle control, 2.5% folinic acid, 1% folinic acid, and dexpanthenol treatment groups. While an image-analysis program was used to evaluate macroscopic wound closure, connective tissue properties, mast cell numbers, and the expressions of matrix metalloproteinase 1 (MMP-1) and 9 (MMP-9) were evaluated by microscopy.

Results: The 2.5% folinic acid-treated group exhibited enhanced wound healing by increased reepithelialization, neo-vessel formation, inflammatory cell migration, collagen deposition and progressive mast cell increase. Furthermore, 2.5% folinic acid induced higher expressions of MMP-1 and MMP-9.

Conclusions: Folinic acid enhances both macroscopic and microscopic wound healing in rat wound model.

1. Introduction

Folic acid is a water-soluble vitamin B mainly involved in DNA synthesis and repair and is essential for normal cell metabolism [1]. Insufficient folic acid intake has been associated with impaired normal growth and development, neural tube defects, DNA instability, cardiovascular diseases, and various cancers [2]. The knowledge about the role of folates on the skin is limited, however, there are ongoing promising studies on folate status and human skin diseases [3].

In mammalian cells and tissues including skin, major transport system of folic acid is folate-carrier [1]. It has been shown that skin fibroblasts, which are essential components of connective tissue metabolism and predominant cell type in the course of wound repair in the skin, increase folate-carrier 1 expression, and their intracellular folic acid uptake in response to UV radiation [3]. Also, it has been shown that treatment of cultured dermal fibroblasts with folic acid stimulates DNA repair capacity of dermal fibroblasts suggesting a promising treatment option for photoaged skin [3,4]. In-vitro and in-vivo efficacies of topical folic acid-and creatine-containing formulation on epidermal skin regeneration were previously reported, indicating a role of folic acid in the treatment of photoaged skin [4]. In addition, treatment of cultured dermal fibroblasts with folic acid and creatine increased collagen gene expression and procollagen levels, and improved collagen fiber density [1].

Given all these study findings, we suggested that topical folic acid might play a role in promoting skin wound repair.

Folinic acid is a 5-formyl derivative of tetrahydrofolic acid. In contrast to folic acid (a synthetic form of folate), folinic acid is one of the forms of folate found naturally in foods. In the body, folinic acid can be converted into the other active forms of folate and has the full vitamin activity of folic acid. And, in contrast to folic acid, its function is unaffected by the inhibition of dihydrofolate reductase [5]. Thus, in this

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https://doi.org/10.1016/j.advms.2018.04.011
Received 17 August 2017; Accepted 26 April 2018

Fig. 1. Wound model used in the study.

study, we aimed to investigate the effects of topical folinic acid on wound repair using in vivo rat wound model.

2. Material and methods

2.1. Animals and wound repair model

Forty adult male Sprague-Dawley rats, with average weight 200–250 g were included in the study. The study protocol was in compliance with current guidelines for the care of the laboratory animals and was approved by the Afyon Kocatepe University Animal Experimentation Ethics Committee (approval number: AKUHAD-YEK-414-15). The animals were maintained in the standard laboratory conditions (temperature: 22 ± 2 °C, humidity: 55 ± 5%, 12/12 reversed light cycle). Each rat was housed in a separate cage and provided with standard diet and water ad libitum.

All rats were anesthetized with an intramuscular injection of ketamine/xylazine (87 mg/kg/13 mg/kg). Dorsal skin hair of the rats was shaved bilaterally and 2 circular full-thickness skin wounds were obtained using a 6-mm punch biopsy tool (Fig. 1). The wounds were not sutured and left open. The rats were then randomly divided into four groups based on treatment applied on wounds: pure vaseline (negative control, G1), 1% folinic acid cream (G2), 2.5% folinic acid cream (G3), and dexpanthenol (positive control, G4). Ten animals were included in each group, and starting from the day of biopsy, topical creams were applied two times daily in sufficient amounts to cover the entire wound until the epithelisation was complete. Animals were observed closely for any signs of infection and excluded from the study in case of infection.

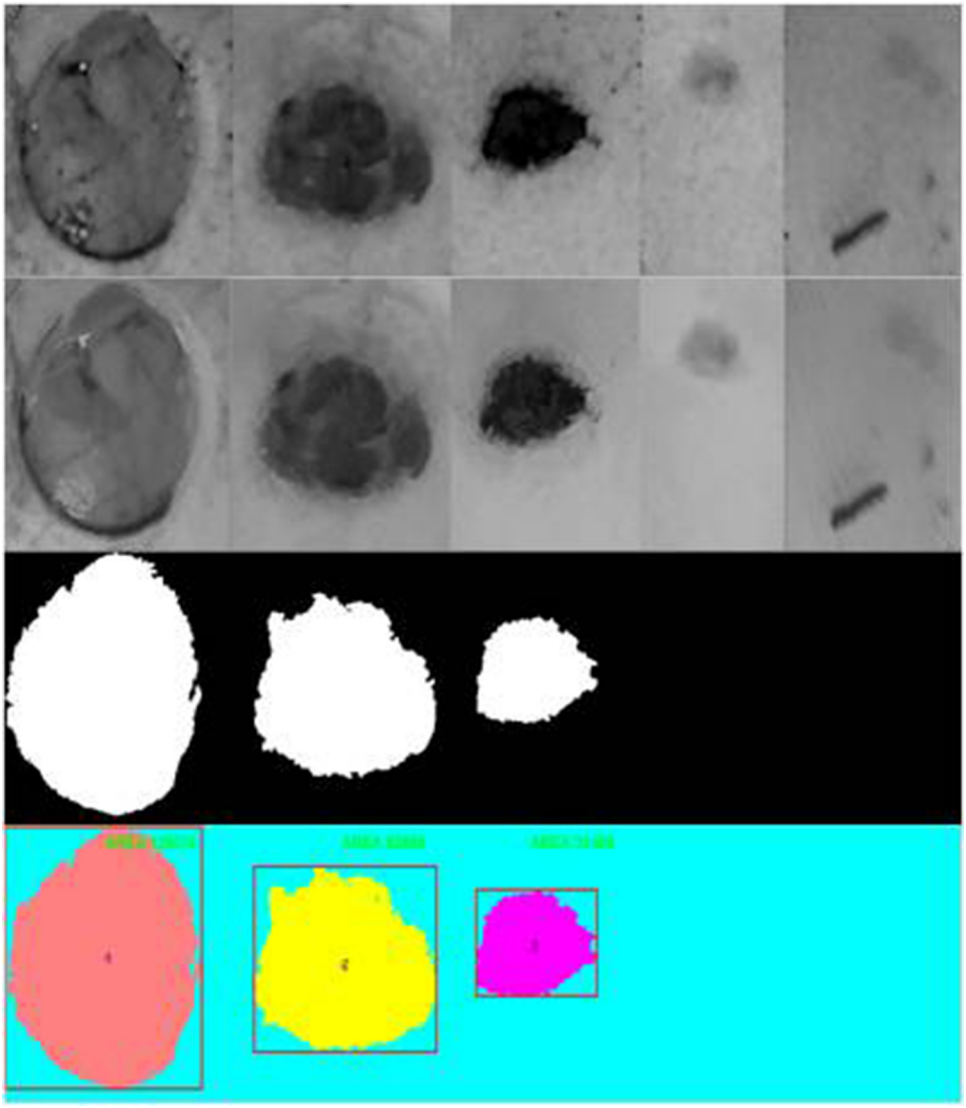

Fig. 2. Implementation of image processing on the images.