شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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قسم

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HANAA ALY

“The Effect of Topical Phenytoin on Chemically Induced Oral Mucosal Ulcer in Albino Rats; Histological and Immunohistochemical study”

Thesis

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Abbreviation	Meaning
CNS	central nervous system
ECM	extracellular matrix
FGF	fibroblast growth factor
EGF	epidermal growth factor
VEGF	vascular endothelial growth factor
PDGF	platelet-derived growth factor
TNF-a	Tumour Necrosis Factor alpha
MHC	major histocompatibility complexes

KHG	Keratohyalin granules
BM	basement membrane
PVP	polyvinylpyrrolidone
PCNA	proliferating cell nuclear antigen
PBS	phosphate buffer saline
ANOVA	analysis of variance
LSD	least significant difference
B.Vs	blood vessels
C.T	connective tissue
PIGE	phenytoin induced gingival enlargement

Abstract

Background: Buccal mucosal ulcers are common oral lesions that may arise from chemical damage to oral mucosa. Appropriate treatment and wound care speed up the healing process, avoid chronicity and wound infection. Phenytoin is considered one of the promising wound healing agents that may have the ability to decrease the duration of the healing process of wounds.

Objectives: The aim of the present study was to evaluate the effect of topical application of phenytoin on chemically induced buccal mucosal ulcer in albino rats.

Material and methods: After chemical induction of ulceration on left side buccal mucosa, sixty three adult male albino rats were divided equally into 3 main groups (21 rats each) as follows: Control group: The right side buccal mucosa was left intact to act as negative control group (Group I), while the ulcerated left buccal mucosa of rats was left untreated to heal normally and serve as a positive control (Group II), rats in control group were sacrificed in parallel with its corresponding experimental groups. Group III (plain gel) ulcerated buccal mucosa in albino rats received topical application of plain gel twice daily on the ulcer from the day following ulcer induction (day 1) till the day of sacrification at 4, 7 and 12 days. Group IV (phenytoin gel) rats received topical application of 1% phenytoin gel twice daily on the ulcer from the day following ulcer induction (day 1) till the day of sacrification at 4, 7 and 12 days. Each group was equally subdivided into 3 subgroups according to sacrification periods. Buccal mucosa was dissected free and examined histologically and immunohistochemically.

Results: Histologically, group II showed complete epithelial degeneration at day 4, re-epithelization at day 7 and complete regeneration at day 12. Group III showed complete epithelial degeneration day 4, re-epithelization started at day 7 and partial regeneration at day 12. Group IV showed beginning of re-epithelization at day 4, continuous epithelial lining at day 7 and complete regeneration at day 12. Immunohistochemically and statistically, group IV showed the highest anti-PCNA expression regarding immunopositive epithelial cells followed by group III then group II. Group I showed the lowest mean.

Conclusions: Topical application of phenytoin 1% can help accelerate healing of chemically induced ulcers through increased vascularization, relatively decreased inflammatory cell count and hastened re-epithelization.

Introduction

Traumatic ulcers are common oral lesions in all age groups that can arise from chemical damage to oral mucosa. Ulcers may be acute or chronic and are commonly located in the buccal mucosa **(Neville et al., 2009**).

The histological structure of the buccal mucosa of rats consists of keratinized stratified squamous epithelium that is formed of basal, prickle, granular and amorphous keratin layer with few, regular, broad and short epithelial rete pegs. The lamina propria is formed of regular arrangement of collagen fibers, fibroblasts, progenitor cells and small sized blood vessels (B.Vs) **(Ahlfors & Larsson, 1988)**.

Histopathologically, traumatic ulcers appear as a mixture of fibrin and neutrophils, while epithelial edges can be normal or hypertrophic with or without hyperkeratosis. Granulation tissue in the core of the ulcer shows proliferation of endothelium and a mixture of inflammatory cells that may extend to adjacent muscles **(Khounganian et al., 2020)**.

Researches for improved wound-healing agents is considered a challenge in medical practice and avoiding the chronicity of wounds remain a serious healthcare problem. One of the effective methods that have been used to decrease the duration of the healing process of wounds is phenytoin **(Inchingolo et al., 2017)**.

For over 80 years, phenytoin has been evaluated in many researches and has had a remarkable track record of drug repositioning in many disorders, apart from the initial indication of epilepsy specially in wound healing. However, advances in the field of phenytoin still appear to be possible particularly in wound healing **(Hesselink et al., 2018)**.

Previous studies recommended further controlled studies to confirm the benefits of topical phenytoin in wounds of various etiologies, as well as to determine the optimal dose and method of drug delivery.

Review of literature

Phenytoin:

Phenytoin was first introduced as an antiepileptic drug in 1937 **(Al-Mashhadane, 2012)**. Phenytoin is one of the central nervous system (CNS) drugs. Its use in clinical settings has taken place for over 80 years now. Distant from the original indication in epilepsy, phenytoin repositioning has taken place in many disorders such as; depression, bipolar disorder, aggression, impulsivity and wound healing. Noticeably the most explored repositioning indication was the wound healing **(Hesselink et al., 2018)**.

Mechanism of action:

There has been considerable debate over the mechanism by which phenytoin acts locally on wounds. Phenytoin may improve wound strength through its ability to increase proliferation of fibroblasts and myofibroblasts, extracellular matrix (ECM) and protein production inside the wound as well as activation of growth factors and their mediators, which eventually leads to increased collagen production and deposition. In addition to decrease in wound edema, exudate, bacterial load and reduction of collagenase activity **(Shaw et al., 2007)**.

Growth factors have a major role in wound healing. Several types are secreted during the process of wound healing, such as, fibroblast