Use of bleomycin in keloids and hypertrophic scars: a literature review

Uso de bleomicina em queloides e cicatrizes hipertróficas: revisão da literatura

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ABSTRACT

Keloids and hypertrophic scars result from abnormal wound healing with excessive growth of fibrous tissue. Despite the high incidence in the population, the high rates of relapse and the significant psychosocial impairment, treatment remains a challenge for dermatologists. The objective of this study was to review literature on clinical, etiological and therapeutical aspects of keloids and hypertrophic scars, emphasizing its therapy with bleomycin, demonstrating its effective and safe use. The search was conducted in Scopus and MEDLINE databases, for the period from 1995 to 2016, using the key words: queloide/keloid; cicatriz hipertrófica/cicatrix, hypertrophic; and bleomicina/bleomycin.

Keywords: keloid; cicatrix, hypertrophic; bleomycin

RESUMO

Queloides e cicatrizes hipertróficas resultam da cicatrização anormal de feridas, com crescimento excessivo de tecido fibroso. Apesar da elevada ocorrência na população, das altas taxas de recidivas e do importante comprometimento psicossocial, o tratamento continua sendo um desafio para os dermatologistas.

O objetivo deste trabalho foi revisar publicações sobre aspectos clínicos, etiológicos e terapêuticos de queloides e cicatrizes hipertróficas, com ênfase em sua terapêutica com bleomicina, demonstrando seu uso eficaz e seguro.

A busca foi realizada nas bases de dados Scopus e MEDLINE, utilizando-se, para o período de 1995 a 2016, as palavras-chave: queloide/keloid; cicatriz hipertrófica/cicatrix, hypertrophic; e bleomicina/bleomycin.

Palavras-chave: *queloide; cicatriz hipertrófica; bleomicina*

Authors:

Marcela Baraldi Moreira[1]
Caroline Romanelli[2]
Marina de Almeida Delatti[1]
Marcel Alex Soares dos Santos[1]
Daniela Melo Siqueira[1]
Bogdana Victória Kaduncˆ[3]

[1] 3rd year dermatology resident physician, Pontifícia Universidade Católica de Campinas (PUC-Campinas) – Campinas (SP), Brazil.

[2] Preceptor at the Medical Residency; Coordinator at the Trichology and Dermatopediatric Outpatient Clinic, Dermatology Service, PUC-Campinas.

[3] PhD in Dermatology, Head of the Dermatology Service, PUC-Campinas.

Correspondence:
Marcela Baraldi Moreira
Rua Sacramento, 463 /apto. 33
13010-210 – Campinas – SP
Brazil
E-mail: marcelabmoreira@hotmail.com

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INTRODUCTION

Hypertrophic scars and keloids are forms of abnormal wound healing.[1] Both entities are the result of exuberant fibroblast response in the dermis, what lends them certain similarities. Nevertheless, their clinical and histopathological characteristics, as well as their pathogenesis, are different.[2]

The present literature review covers publications on etiology, clinical, genetic and epidemiological aspects, clinical and laboratory diagnostic, and therapeutic options in keloids and hypertrophic scars, with emphasis on bleomycin, demonstrating its effective and safe use.

The article search was conducted on the Scopus and MEDLINE databases, encompassing the period 1995-2016, using the keywords *queloide/keloid*; *cicatriz hipertrófica/cicatrix, hypertrophic;* and *bleomicina/bleomycin*.

The pathogenesis of keloids is associated with autosomal dominant inheritance, with incomplete clinical penetration and variable expression.[3]

They can develop following any aggression in the deep dermis, including abscesses, acne, surgery, abrasions, lacerations, injuries, piercings, burns and vaccines.[4] There is significant impairment of quality of life for patients, with physical, motor, aesthetic and psychosocial sequels.[5]

Pathophysiology

The wound healing process is divided into three phases: inflammatory, proliferative and remodeling.[6] When an injury takes place, complex interactions with pro-fibrotic molecules, proteolytic enzymes, interleukins and cytokines, epidermal growth factor (EGF), platelet derived growth factor (PDGF), insulin growth factor (IGF) and transforming growth factor beta (TGF-β) cause the recruitment of neutrophils, macrophages, epithelial cells, endothelial cells, mast cells and fibroblasts aiming at starting the inflammatory phase of wound healing. Later on, when repair tissue is produced, the collagen synthesis – which is mainly formed by extracellular matrix (ECM) – is followed by the remodeling of the tissue, completing all stages of the wound healing process. Any imbalance between destruction and deposition of the extracellular matrix's metabolism can lead to excessive scarring.[5, 7-10]

Clinical picture

Keloids are mostly found in African, Asian and Hispanic population, in patients with elevated hormone levels (such as puberty or pregnancy) and are prevalent among young individuals in the 10 to 30 years of age group, which is most subject to traumas, with increased collagen synthesis, which in turn results in more tensioned scars.[11, 12] Keloids have a strong family correlation, which reinforces the concept of genetic predisposition in this pathology, a less frequently reported factor in hypertrophic scars.[6]

Clinically, keloids are defined as cicatricial lesions that extend beyond the limits of the trauma, with invasion of adjacent healthy tissue.[8] They take from three months to years to develop and do not lend future malignant potential.[13] Additionally, they do not spontaneously regress and tend to recur even after surgical excision.[8, 14] They arise as firm, lobulated tumorations with shiny surface, often marked by telangiectasias and ulcerations, initially with erythematous color, evolving into red-brownish as they age.[7, 13] Keloids are located in skin areas more subject to trauma, such as the pre-sternal region, arms, shoulders, earlobes and cheeks. They can be associated with pruritus, pain and hyperesthesia, meaning an important functional and aesthetic impairment for patients.[13, 15]

Hypertrophic scarring is more common in the population; however it is less associated with the skin color and usually arises earlier after the trauma (one month after the lesion has been inflicted).[5, 14] It can occur in any location of the integument and has the clinical appearance of elevated, erythematous tumorations confined to the original lesion's site, with a tendency to fade over time, and is sometimes associated with pruritus. In this manner, it has a better prognosis as compared to keloids.[7]

Histology

The common histological finding to in keloids and hypertrophic scars is excessive dermal collagen. In the first, there is a flattening of the epidermis, presence of hyaline type I and III collagen bundles, and a great number of fibroblasts with disorganized orientation along the reticular dermis; the papillary dermis is preserved and there are few blood vessels vertically oriented. In the second, there is flattening of the epidermis and replacement of the dermis with hypertrophic collagen fibers, predominantly type III, with a great number of fibroblasts and acid mucopolysaccharides, oriented parallel to the skin's surface.[7, 16]

Treatment

There are multiple treatment methods for keloids and hypertrophic scars. Surgical excision, cryosurgery, radiation therapy, laser therapy and different drugs for topical use or delivered through punctures or intralesional injections (interferons, imiquimod, verapamil, mitomycin, rapamycin, triamcinolone, 5-fluorouracil, botulinum toxin, bleomycin sulfate) are described in the literature.[15-18] More recently, Manca [19] published his experience in the treatment of keloids using intralesional injections of bleomycin associated with electroporation.

Bleomycin sulfate belongs to the family of the glycopeptides, which are classified as antibiotic, antitumor or cytotoxic agents. It is isolated from a *Streptomyces verticillus* strain and has been approved by the US Food and Drug Administration (FDA) as a chemotherapeutic agent for treating malignancies.[20, 21] It induces DNA damage, cell apoptosis and inhibits the synthesis of collagen due to a decrease in TGF-β.[17]

In dermatology, intralesional bleomycin is used on an off-label basis in multiple skin conditions, including keloids, hypertrophic scars, warts, hemangiomas, vascular and lymphatic malformations, telangiectasia, skin cancer and condyloma.[22-25]

Each bleomycin sulfate vial contains 15mg (15U) lyophilized powder, and can be stored at low temperature (from 2°C to 8°C) for 24 months. The standard dilution is carried out

with 5ml 0.9% saline solution, sterile water for injection or lidocaine, [21] reaching a 3mg/ml concentration. According to most authors, the diluted medication should be stored at low temperature (4°C) and used in the following four-week period.[22, 26]

Its mechanism of action in keloid is still not fully known.[9] It is known that bleomycin induces necrosis of keratinocytes in warts through an inflammatory process, with the expression of various adhesion molecules.[25, 27] In hemangiomas, it causes damage to endothelial cells, resulting in the collapse, shrinkage, fibrosis and subsequent tumor regression.[28]

The cutaneous toxic effects that may arise from bleomycin's use depend on the dose uemployed (from 200 to 300U) and include: neutrophilic eccrine hidradenitis, necrosis of keratinocytes, flagellate erythema, acute exanthematous pustulosis, hyperpigmentation, Raynaud's phenomenon, gangrene, fibrosis, edema, alopecia and ungual alterations. Systemic side effects, such as hepatotoxicity, bone marrow suppression, pulmonary and kidney fibrosis, are reported at high doses (greater than 400U).[21, 23]

In 1996, Bodokh and Brun[29] were the first to report the use of bleomycin as therapy for scars. They performed 3 to 5 intradermal injections in [31] keloids and 5 hypertrophic scars during a one-month period. The outcome obtained with the first 2 injections was complete regression in 84% of the scars, with a significant reduction of keloid volume and improvement of the functional loss in most patients.

In another study, España et al.[30] evaluated 13 patients with keloids and hypertrophic scars. Bleomycin was administered through multiple superficial punctures, with the dose applied in 2cm^2 areas, at a concentration of 1.5 IU/ml, and a maximum of 6ml per lesion. Patients received 1 to 5 applications, in a period ranging from 1 to 4 months. After the first session, all patients reported relief regarding the pruritus. Complete flattening of the scar was reported in 7 cases (53.8%), and the remaining 6 cases (46.2%) had a decrease greater than 75% in the thickness of the scar. At the one-year follow-up, there were 2 cases of recurrence (15.4%). As for complications, there were 2 cases of hyperpigmentation (15.4%).

In 2005, Saray and Gülec, [31] treated 15 patients with 15 keloids or hypertrophic scars, who had not previously responded to a minimum of 3 intralesional triamcinolone applications. Monthly bleomycin injections were performed in each lesion with a 0.1ml solution at a concentration of 0.15 UI. The delivery of the medication was performed with a jet injector (MadaJet XL, Mada Inc., Carlstadt, NJ, USA), observing a 0.5 mm spacing between the points of applications. A dose of 0.4 ml/cm^2 was applied to each lesion, for a total maximum volume of 3.5ml per session After an average of 4 sessions, all treated scars had a reduction of more than 50% in height; 73.3% had complete flattening; being highly significant in 6.7% of cases, significant in 13.3% and moderately significant in 6.7%. These outcomes were more relevant when compared to the rates shown previously by Bodokh and España. The complications found were hyperpigmentation and dermal atrophy.

In a study by Naeini et al.,[32] 45 patients with keloids and hypertrophic scars were separated into two groups to underwent a therapeutic test. Group A was treated with bleomycin via the tattooing technique, while Group B was treated with cryotherapy associated with intralesional triamcinolone infiltrations.

In the combination therapy, lesions with an area smaller than 100mm2 showed significant response when compared to larger lesions, whereas in the bleomycin group the lesion size did not affect the resolution rate. There was no statistical difference between the two groups for lesions smaller than 100mm^2. In larger lesions, however, the therapeutic response to bleomycin was significantly higher.[32]

In 2008, Aggarwal et al. [33] revealed interesting results after treating 50 patients with keloids and hypertrophic scars with 3 applications of bleomycin at 15-day intervals. Of the 50 patients included in the study, 22 (44%) had complete remission of the lesions, 11 (22%) showed significant response with the reduction in the size of the lesions, 7 (14%) had adequate flattening, and 10 (20%) did not respond to the treatment.

Complications included: 8 cases (16%) of ulceration after the second application, with resolution in ten days; 15 cases of pain after the first application; 7 (14%) cases of hyperpigmentation, resolved one year later; 7 (14%) cases of recurrence within 18 months. There was absence of cases of systemic side effects of bleomycin.[33]

In 1998, Heller[34] tested the electrochemotherapy technique in a group of 34 patients. Intralesional bleomycin was applied in combination to electrical pulses (electroporation) in solid cutaneous tumors (basal cell carcinomas, squamous cell carcinomas, melanomas and Kaposi's sarcomas). The electroporation technique corresponds to a local antitumor therapeutic modality that temporarily increases the permeability of cell membranes, facilitating the entry of chemotherapeutic agents, therefore enhancing the drug's local effect. The obtained outcomes showed the efficacy of the treatment for skin cancer, with a sparing effect in the tissue and minimal scarring. In 2013, based on the study by Heller, Manca et al.[19] performed electroporation combined with intralesional bleomycin for the first time in a group of 20 patients with keloids and hypertrophic scars. In this study, they tested bleomycin diluted in 0.9% sodium chloride solution, at a concentration of 1,000 IU/ml, delivered intralesionally, followed by electric pulses 10 minutes after the application. The outcomes contemplated a significant reduction of the lesions, as well as in their volumes in 87% of the sample. Of these, 94% had a decrease of more than 50% of their volumes. Hyperpigmentation was observed in 10% of cases, with 1 case of recurrence after 18 months of the first application.

More recently, Kabel et al.[35] evaluated the efficacy and safety of the intralesional infusion of 5-fluorouracil (5-FU) and bleomycin in the treatment of keloids and hypertrophic scars in 120 patients. The sample was divided into three groups: Group IA (30 patients tested with 50 mg/ml 5-FU), Group IB (30 patients tested with 5-FU combined with 40 mg/ml triamcinolone), Group II (60 patients tested with 1.5 UI/ml bleomycin). The variables evaluated were: vascularity, pigmentation, elasticity and height. As for the number of application sessions, it was possible to observe a range of 4 to 6 that in Group IA; 5 to 6

sessions in Group IB; and 2 to 6 sessions in Group II. The results obtained were: presence of a statistically significant difference between groups I and a significant improvement in group II (73%) when compared to groups I (IA: 54% and IB: 55%).

Recurrence was observed only in Group I: 12 patients (40%) in Group IA and 14 patients (46.67%) in Group IB.

The side effects found in all groups were: hyperpigmentation, ulceration and pain. In Group IA, hyperpigmentation was present in 20 (66.67%) patients, ulceration in 18 (60%) patients, and pain at the injection site in 22 (73.33%) patients. In Group IB, hyperpigmentation was verified in 18 (60%) patients, ulceration in 18 (60%) patients, and pain in 10 (33.33%) patients. Side effects in Group IB were similar to those in Group IA, except for pain, which decreased significantly in Group IB group. In Group II, hyperpigmentation was present in 42 (70%) patients, ulceration in 14 (21.33%) patients, and pain, in all patients.

It was possible to conclude that the injection of bleomycin was better and more effective when compared to the intralesional injection of 5-FU, either isolated or associated with triamcinolone acetonide, in the treatment of hypertrophic scars and keloids. [35]

CONCLUSION

Keloids and hypertrophic scars are pathological scars. They occur after any cutaneous lesion due to the exaggerated and inadequate proliferation of fibroblast tissue in the dermis. They often cause functional and cosmetic deformities, discomfort, psychological stress and a worsening in the quality of life of patients.

The understanding of their similarities and differences is of utmost importance for their therapeutic management.

Currently, it is possible to find several therapeutic options in the literature for treating hypertrophic scars and keloids. Recent studies, however, have shown the importance of the injection of bleomycin as compared to other treatments. Various statistical analyzes suggest minimal complications (pain, superficial ulceration and transient hyperpigmentation), low recurrence rates, excellent lesion regression rates, significant symptomatic reduction and improvement in the patients' quality of life.

The straightforward application, effectiveness and low side effect of bleomycin challenge dermatologists to use it as the first therapeutic option in keloids and hypertrophic scars.[1] ❑

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