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Discussão: enfatizar os novos e importantes resultados encontrados pelo estudo e que farão parte da conclusão. Relatar observações de outros estudos relevantes. Mencionar as limitações dos achados e as implicações para pesquisas futuras.

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Sumário / *Table of contents*

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*

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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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Questions for continuing medical education CME

1) The differences between hypertrophic scars and keloids are:
A. Keloids typically arise in the first weeks after the wound has been inflicted, while hypertrophic scars appear in the third or fourth month after the wound has been inflicted.
B. Hypertrophic scarring is more common in dark skinned individuals and keloids are more common in fair skin individuals.
C. Both have spontaneous regression.
D. Keloids extend beyond the limits of the original tissular lesion, while hypertrophic scars remain within this limit.
E. Keloids are more frequent than hypertrophic scars.

2) In abnormal wound healing the following cytokines are involved, except:
A. EGF
B. IGF
C. PDGF
D. TGF-β
E. TGF-β

3) All of the below are keloid features, except for:
A. it affects African, Asian and Hispanic populations.
B. it affects only adults over 30 years of age.
C. there is greater involvement with local trauma.
D. it is a scar with high tension.
E. genetic predisposition is heavily involved.

4) Regarding hypertrophic scars, it can be stated that it:
A. is less prevalent than keloids.
B. is associated with higher phototypes.
C. occurs in areas of trauma.
D. does not tend to spontaneous regression.
E. occurs before the trauma.

5) Regarding the keloid's histology, it is correct to state that:
A. type III collagen is predominant.
B. collagen fibers are arranged in parallel.
C. the fibers are arranged in a disorderly pattern.
D. there is excess of collagen in excess in the epidermis.
E. there is a large number of fibroblasts arranged parallel to the skin.

6) Bleomycin is:
A. an anti-inflammatory.
B. an analgesic.
C. a chemotherapeutic agent.
D. an anesthetic.
E. an immunobiological agent.

7) Intralesional bleomycin can be used in the following disorders, except for in:
A. keloids and hypertrophic scars.
B. warts.
C. hemangiomas.
D. acuminated condyloma.
E. melanoma.

8) Bleomycin has the following adverse effects, except for:
A. neutrophilic eccrine hidradenitis.
B. necrosis of keratinocytes.
C. flagellate erythema.
D. acute exanthematous pustulosis.
E. hypopigmentation.

9) Electrochemotherapy corresponds to the following options, except for:
A. intralesional bleomycin combined with electrical pulses (electroporation).
B. it is indicated in the treatment of solid cutaneous tumors, basal cell carcinoma, squamous cell carcinoma, melanoma and Kaposi's sarcoma.
C. local antitumor therapeutic modality that temporarily reduces the cell membranes' permeability.
D. facilitates the entry of chemotherapeutic agents and strengthens the local effect of the drug.
E. avoidance of high doses of the drug.

10) Which of the below treatments can be performed in hypertrophic scars and keloids?
A. 5-fluorouracil
B. Verapamil
C. Intralesional bleomycin
D. Tacrolimus
E. All of the above

Key

Surgical treatment of scars. 2015;8(1):11-20.

1D, 2B, 3E, 4A, 5D, 6B, 7C, 8D, 9B, 10E

Answers must be submitted online using the website www.surgicalcosmetic.org.br.
The deadline for submitting answers will be available on the journal's website.

Original Articles

Stromal vascular fraction, a new therapy in photoaging: a comparative controlled study

Fração vascular estromal, uma nova terapêutica no fotoenvelhecimento: estudo comparativo e controlado

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ABSTRACT

Introduction: Stromal vascular fraction derived from adipose tissue is a rich source of different cells, containing large amounts of stem cells, which ability for diferentiation into various strains. In dermatology, there are several studies on the effectiveness of stem cells, which present antioxidant and rejuvenating effects. However, there are few reports about the anti-aging effects of stromal vascular fraction.
Objective: To evaluate the effectiveness of stromal vascular fraction in facial rejuvenation.
Methods: A prospective, comparative, controlled study was carried out, wit, with 10 patients divided into two groups and subjected to treatment of nasolabial folds with: Group 1: stromal vascular fraction and Group 2: conventional filler (calcium hydroxyapatite). Clinical, photographic and histological evaluations were conducted, with statistical analysis of data.
Results: Both techniques produced satisfactory results and were similar.
Conclusion: Application of stromal vascular fraction is a relatively new technique that presents good clinical results and is a promising option for rejuvenation.
Keywords: adult stem cells; skin aging; rejuvenation

RESUMO

Introdução: *A fração vascular estromal derivada do tecido adiposo é fonte rica de diferentes células, contendo grande população de células-tronco, que tem capacidade de diferenciação para diversas linhagens. Em dermatologia, há diversos estudos sobre a eficácia das células-tronco, que apresentam ação antioxidante e efeitos no rejuvenescimento. No entanto, ainda são poucos os relatos sobre os efeitos antienvelhecimento da fração vascular estromal.*
Objetivo*: Avaliar a efetividade da fração vascular estromal no rejuvenescimento facial.*
Métodos*: Estudo prospectivo, comparativo e controlado, com 10 pacientes divididos em dois grupos e submetidos a tratamento do sulco nasogeniano com: Grupo 1: fração vascular estromal e Grupo 2: preenchedor convencional: hidroxiapatita de cálcio. Foram realizadas avaliações clínica, fotográfica e histológica com análise estatística dos dados.*
Resultado*: Ambas as técnicas produziram resultados satisfatórios e semelhantes.*
Conclusões*: A aplicação da fração vascular estromal é técnica relativamente nova que apresenta bons resultados clínicos, sendo opção promissora para o rejuvenescimento.*
Palavras-chave: *células-tronco adultas; envelhecimento da pele; rejuvenescimento*

INTRODUCTION

Adult stem cells have been the subject of many studies due to the absence of both ethical issues that embryonic stem cells may arise and their carcinogenic potential. Among adult stem cells, staminal cells derived from adipose tissue (adipose-derived stem cells - ADSCs) essentially have the same properties of stem cells derived from bone marrow. [1] In addition, they have the advantages of being more accessible and relatively more abundant as compared to other types of adult stem cells. Experiments using ADSCs have been conducted more often in recent years. In dermatology, there are several studies on the effective application of stem cells – for instance on their antioxidant action and rejuvenating effects.[2-4] Among the facts described in the latest publications, the ADSC's effects in the healing of wounds stand out, as well as their role in the photodamaged and aged skin. [5]

The adipose tissue's stromal vascular fraction (SVF) is a source rich in preadipocytes, mesenchymal stem cells, endothelial progenitor cells, T and B cells, monocytes, macrophages and fibroblasts. Due to the fact that it contains a large population of adipose tissue-derived stem cells, it is able to differentiate into diverse lineages. [6,7]

Skin aging involves a series of different degenerative processes as well as a significant decrease in collagen produced by fibroblasts. Several cytokines and growth factors are also involved, stimulating the synthesis of collagen by fibroblasts for rejuvenating the skin. [6] Regenerative medicine, which uses stem cells and growth factors produced by the body, is an alternative therapeutic strategy for repairing damaged tissues. However, there are still few reports on the anti-aging effects provided by the SVF derived from adipose tissue.

In this way, the present study's objective was to evaluate the effects of SVF in stimulating neocollagenesis and compare its effects with those of a common use synthetic cutaneous filler (calcium hydroxyapatite).

METHODS

A prospective, comparative controlled study was carried out at the Dermatology Department of the Universidade de Mogi das Cruzes (São Paulo State, Brazil), including 10 female patients (aged between 30 and 45 years, with Fitzpatrick skin phototypes I to V) who had pronounced nasolabial folds.

The patients agreed to participate in the study and signed a consent form. The institution's Research Ethics Committee approved the study.

The exclusion criteria were: pregnancy and breast feeding, immunosuppression history, immune deficiency disorders or use of immunosuppressive drugs, decompensated comorbidities, keloid or hypertrophic scarring history, skin treatment with laser or other devices in the six months prior to the beginning or during the course of the study, and previous use of botulinum toxin, fat injections or filling substances in the area to be treated.

The sample was divided into two groups: Group 1 (5 patients who underwent SVF application bilaterally in the nasolabial folds region), and Group 2 (5 patients who underwent the application of calcium hydroxyapatite synthetic filler in the same region).

Evaluation methods: included clinical examination and photographic analysis before and after treatment, and histological evaluation with staining usually employed in the analysis of tissues (hematoxylin eosin - HE) and staining specifically used for collagen fibers (picrosirius).

Obtaining the adipose tissue: a mini liposuction was performed on the posterior face of the thigh in order to obtain subcutaneous adipose tissue. The procedure was performed in the operating room with appropriate asepsis and antisepsis measures. Approximately 50ml of fat were aspirated by non traumatic manual technique under low pressure.

Obtaining the SVF: a) washing of the material obtained by mini liposuction with PBS solution (phosphate-buffered saline solution) in order to remove debris, and red cells; b) separation into 3 tubes containing 1g of adipose material, and 1 ml of collagenase (Sigma type); c) immersion of the tubes in water at 37° C with constant agitation for 45 minutes; d) centrifuging for 10 minutes followed by separation of the parts with the removal of the matrix, with only the SVF and the adipocyte remaining. [6]

Injection: asepsis was carried out with a mild and non-abrasive nonalcoholic agent in the treatment areas. The procedure consisted in the injection of 1ml SVF in the deep dermis with a 26 gauge needle, in the nasolabial fold region of Group 1 patients. Group 2 patients were injected with 1ml of synthetic filler (calcium hydroxyapatite) in the deep dermis, with a similar needle, in the same region.

After appropriate asepsis and local anesthesia with lidocaine with epinephrine pretreatment control biopsy was performed with n. 3 punch, in the right retroauricular region. Next, 1 ml SVF and calcium hydroxyapatite were injected in the retroauricular region, aimed at collecting material for the control biopsy procedures, performed after 30 and 90 days.

RESULTS

Two Group 2 patients (calcium hydroxyapatite) abandoned the study and 3 patients remained until the end of the research. The number of patients in Group 1 remained unchanged.

Regarding the histological analysis, evaluations were performed with hematoxylin eosin (HE) and picrosirius, the latter being a specific staining substance for the quantification of collagen in tissues whose collagen fibers are stained in red (Figure 1). The statistical analysis for the quantification of total collagen was initially performed in a generalized manner, without separation of the groups. A baseline mean value of 76% was observed for the collagen in the analyzed tissue, while a value of 84.7% was evidenced after the intervention. Based on the Student t-test, there was absence of statistically significant difference between patients in the pre- and post-treatment experimental timepoints ($p = 0.067$), nevertheless the results revealed a tendency to statistical significance (probably due to the small number of patients).

Regarding the percentage of collagen, the evaluation of individual groups evidenced values of 78% and 85%, corresponding to the before and after the intervention experimental timepoints, respectively, for Group 1 (SVF). Analogously, those values were 71% and 82.9% in Group 2 (calcium hydroxyapatite)

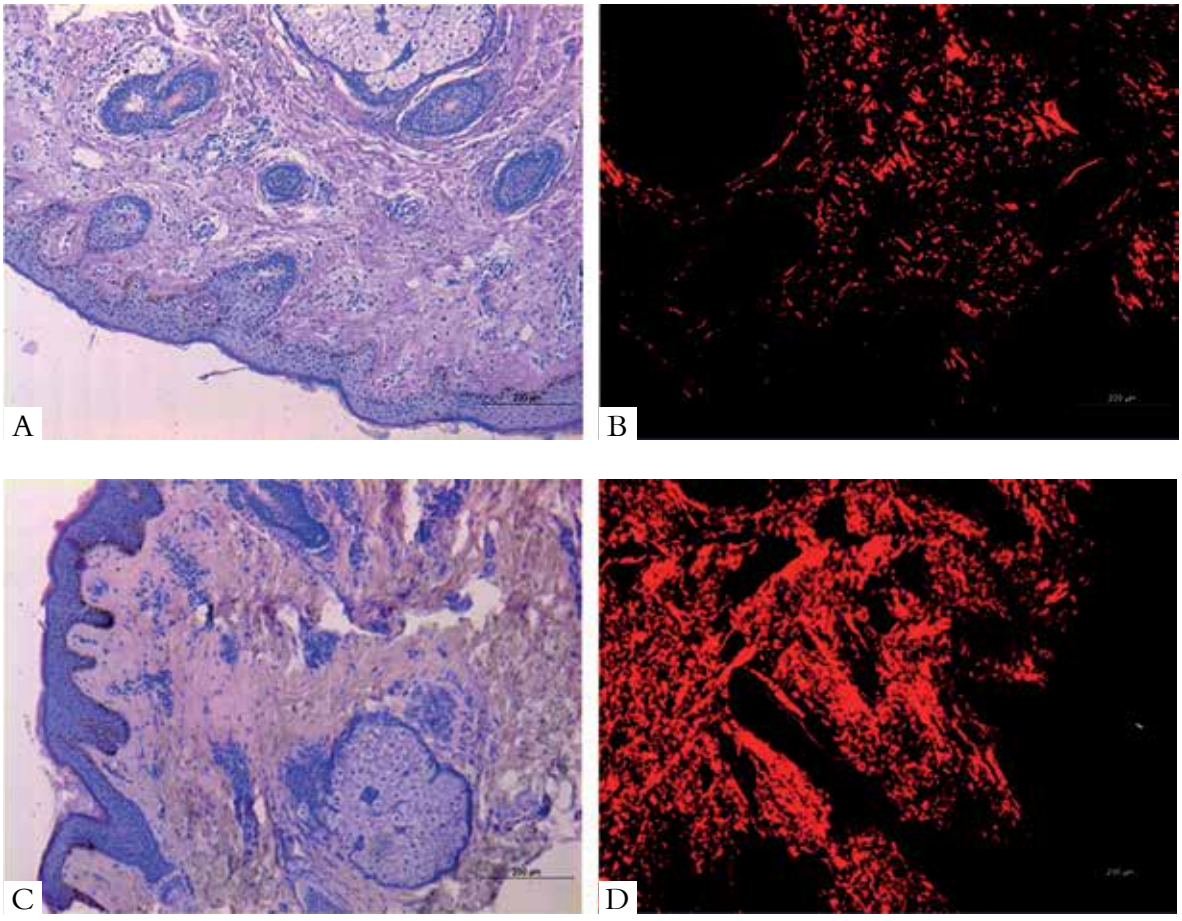


Figure 1: A and B. Biopsy before the procedure (Group 1 – SVF). HE staining 40x, on the left hand side. Picrosirius staining showing the collagen fibers in red. **C and D.** Post-procedural biopsy (Group 1 – SVF). HE staining 40X, on the left hand side. Picrosirius staining showing the collagen fibers in red (greater density of fibers can be observed as compared to the previous image)

(Graph 1). Based on these data, it was possible to observe that a slightly superior improvement was obtained in Group 1 (SVF). On the other hand, the more encompassing (global) and reliable evaluation led to the conclusion that was absence of statistical significance between the two groups.

The analysis of collagen in the pre-intervention period comparing the two groups using the Mann-Whitney test also showed that there was absence of statistical significance ($p = 0.29$). This pre-intervention comparative analysis of collagen shows that the comparison was carried out between similar groups without significant individual differences that could lead to a bias in the final results. Based on this same test, the amount of collagen was evaluated in the post-intervention period by comparing Groups 1 and 2, when absence of statistical significance between them ($p = 0.54$) was evidenced.

As for the dermis' thickness (measured in millimeters - mm), the same analyzes were performed. In the global assessment of patients, the average thickness in the pre-intervention period was 2.22mm, as compared with 1.26mm after the procedure. The Student t test revealed absence of statistically significant difference in the evaluations of the patients' dermis' thickness before and after the procedure ($p = 0.21$).

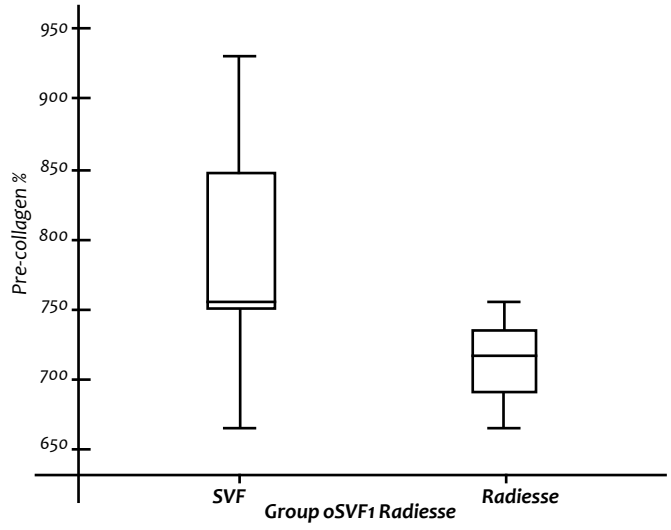
In the individual evaluation, Group 1 obtained a pre-procedure average thickness of 2.44mm as compared to 1.72mm in the post-procedure. In Group 2, the pre-procedure average dermal thickness was 1.86mm, as compared to 1.83mm in the post-procedure. The authors obtained reduced thicknesses after the application of the SVF and the filler, outcomes that are not consistent with the increase in the amount of collagen evidenced by the picrosirius staining. One explanation for this discrepancy in the values of the thicknesses would be the fact that the biopsies were not performed by the same examiner physician in the pre and post periods; the histologic evaluation was also not performed by the same professional.

When comparing the pre-intervention dermis' thickness between Groups 1 and 2, it was possible to observe that there was no statistical difference ($p = 0.549$). The same comparison was carried out after the procedure, also with no observable significant difference between the two groups ($p = 0.64$).

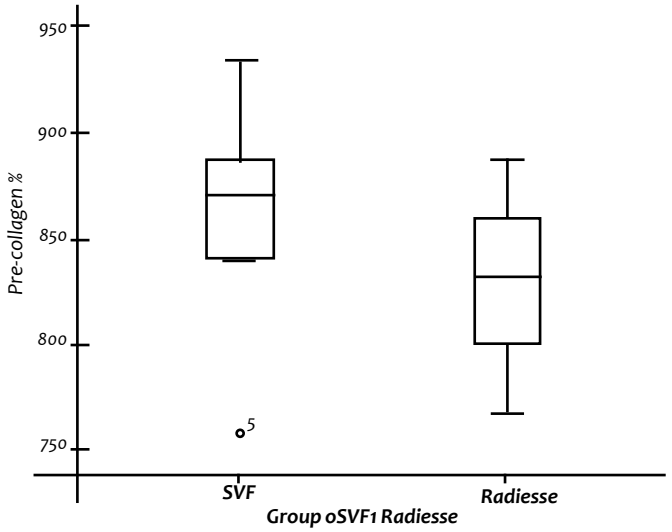
In the clinical and photographic evaluation, conducted with the assistance of a patient questionnaire and the evaluation of an observer physician, it was possible to observe a moderate improvement, which was classified as a satisfactory final outcome by both observers (Figure 2).

DISCUSSION

With the advance of aging, the skin undergoes changes such as uneven pigmentation, thinning and loss of elasticity. The factors that trigger the aging of the skin can be *intrinsic* (or chronological) – which combine into a natural process related



Graph 1A: Evaluation of the pre-procedure percentage of collagen – Group 1 (SVF) versus Group 2 (conventional filler)



Graph 1B: Evaluation of the post-procedure percentage of collagen – Group 1 (SVF) versus Group 2 (conventional filler)

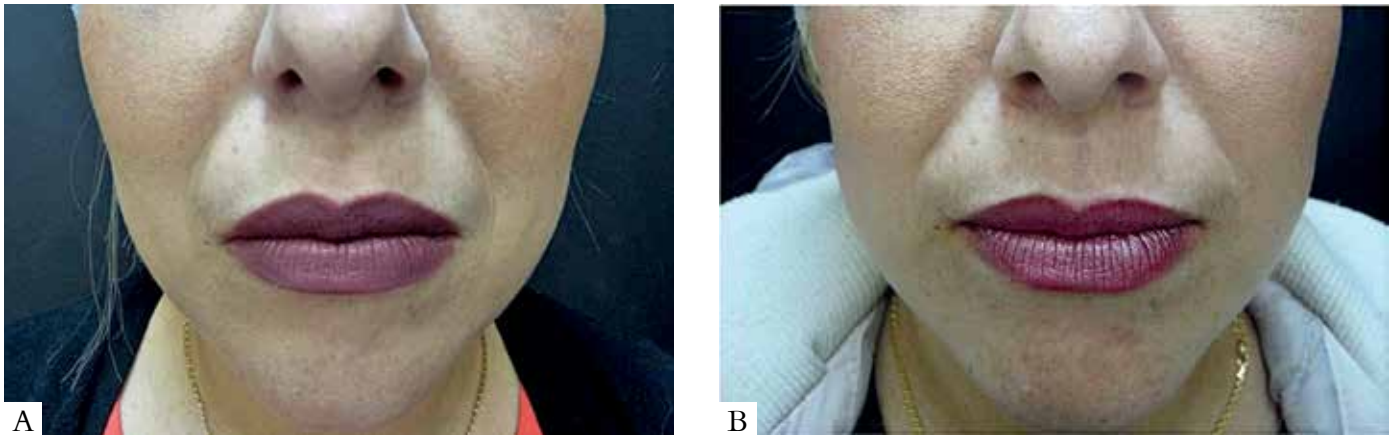


Figure 2: Nasogenian fold before the application of SVF; B - Nasogenian fold after the application of SVF

to genetic factors, the shortening of telomeres, and the action of free radicals; and *extrinsic*, corresponding to photoaging – which is the action of solar radiation on the intrinsic factors.

Regenerative medicine, which uses the body's own stem cells and growth factors, is an alternative therapeutic strategy for repairing damaged tissues that is becoming a predominant cell-based therapy. Stem cells derived from adipose tissue (ADSCs) secrete growth factors such as the vascular endothelial growth factor (VEGF), the insulin-like growth factor (IGF), the hepatocyte growth factor (HGF), and the transforming growth factor beta 1 (TGF-ß1). These proteins control the damage in the neighboring cells. More recently, the production and secretion of growth factors have been identified as an essential ADSCs' function, and many rejuvenating effects on the skin were demonstrated. [8-10] For example, it was demonstrated that ADSCs stimulated the synthesis of collagen and dermal fibroblast migration during wound healing process. [11] Moreover, the factors secreted in ADSCs protect dermal fibroblasts against oxidative stress induced by UVB radiation and chemicals. [11]

Evidence reinforces the critical role of growth factors derived from the ADSCs in wound healing, in the antioxidant effect and in the improvement of the texture and appearance of skin wrinkles, suggesting that they can be good candidates for treating photoaging. [9, 10]

The adipose tissue's SVF is a source rich in preadipocytes, mesenchymal stem cells and endothelial progenitor cells, which have great capacity to differentiate into diverse strains. For this reason, it has been widely studied in aesthetical procedures, scars correction and treatment of rhytids and deep furrows in photoaging.

In other recent studies it was also demonstrated that stem cells derived from adipose tissue associated with fat grafts

showed satisfactory and longer lasting results, with the survival of the adipocyte being one of the main factors that directly interfere with the success of the grafts.

In the present study, the authors aimed at evaluating the effect of SVF in the treatment of deep furrows and found that there was clinical improvement, perceived by the patients and the observer physician, proven by the increase in the percentage of collagen fibers, which was evidenced by the picrosirius staining. As for the thickness of the dermis, contrary to what was expected, there was no significant increase in the comparison with the control in most patients. One explanation for this may be linked to a technical error related to the biopsy, perhaps performed in areas containing the total thickness of the dermis and subcutaneous tissue, and in areas without the presence of all layers of the dermis, thus justifying the maintenance or even a decrease of the thickness after the procedure. This possible flaw could have been avoided by individually measuring the thicknesses of the upper, medium and deep dermis of the control and in the post-procedure.

Regarding the clinical improvement, when comparing the application of SVF with that of the calcium hydroxyapatite based synthetic filler, it was possible to observe that the latter was slightly greater, which was evidenced in the post-procedure by the effect of the local edema and, in the first months, also proven by the increase in collagen fibers. Regarding the thickness, a technical error bias has probably taken place again, with the expected increase in the dermal thickness not being seen after the use of the filler.

In the evaluation and comparison of the two groups it was not possible to observe superiority of one or the other. The authors note that the percentage results were similar, and there was no statistical significance that could benefit one group or another. It is worth to note that the present study was carried out with a small number of patients and that better analyzes are performed in larger groups, with greater reliability predictors.

In the present study, none of the groups experienced serious complications; only local hematoma (Group 1), and hematoma and edema (Group 2) were observed, with resolution within seven days after the procedure. The patients complained of tolerable pain at the time of application in both groups.

In the present project, it is possible to observe that both techniques for treating facial folds, with the application of SVF or calcium hydroxyapatite based filler, led to satisfactory and similar outcomes, and it was not possible to determine the superiority of one over the other.

The application of SVF is a relatively new technique, which leads to good, histologically confirmed clinical outcomes, however there is need for further study aimed at standardizing the harvesting of the material and developing application techniques.

CONCLUSION

The use of SVF is a new treatment option for photoaging, according to the observation of the results obtained in the present study. This procedure has been widely discussed and should be improved, especially due to the possibility of being performed with autologous material. ●

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Original Articles

Clinical epidemiological retrospective study of glomus tumors diagnosed over 16 years in a reference unit

Estudo retrospectivo clinicoepidemiológico dos tumores glômicos diagnosticados ao longo de 16 anos em unidade de referência

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ABSTRACT

Introduction: *Glomus tumor is a benign and rare neoplasm that appears as solitary and painful nodule, mainly subungual. It presents characteristic clinical manifestations such as paroxysmal pain and sensitivity to local pressure and to cold.*

Objective*: To conduct a clinical epidemiological survey of glomus tumors diagnosed in a reference unit in 16 years.*

Methods*: Retrospective study assessing clinical and epidemiological data of 15 patients with glomus tumor confirmed by histopathological report from 2000 to 2016. Data on age, gender, tumor location, associated symptoms, duration of symptoms until diagnosis, clinical presentation, histological type and recurrence after surgery were analysed.*

Results*: Fifteen cases were diagnosed, 11 in women (73.3%) and four in men (26.7%). Mean age was 63 years. The most frequent location was the subungual region. Mean duration of symptoms until diagnosis was 8 years.*

Conclusions*: In this study, the number of cases of glomus tumor fluctuated throughout these 16 years, with a mean of 0.9 cases/year. A higher prevalence in women over 60 years, subungual region location and solid glomus histologic subtype was observed.*

Keywords: *glomus tumor; nail diseases; neoplasms*

RESUMO

Introdução: O tumor glômico é neoplasia benigna e rara que se apresenta como nódulo solitário e doloroso de localização principalmente subungueal. Apresenta manifestações clínicas características como dor paroxística e sensibilidade à pressão local e ao frio.

Objetivo: Realizar levantamento clinicoepidemiológico dos tumores glômicos diagnosticados em unidade de referência em 16 anos.

Métodos: Estudo retrospectivo analisando dados clínicos e epidemiológicos de 15 pacientes com diagnóstico de tumor glômico confirmado pelo laudo histopatológico no período de 2000 a 2016. Foram avaliados dados como idade, sexo, localização do tumor, sintomas associados, duração dos sintomas até o diagnóstico, apresentação clínica, tipo histológico e recidiva após a cirurgia.

Resultados: Foram diagnosticados 15 casos, em 11 mulheres (73,3%) e quatro homens (26,7%). A média de idade foi 63 anos. A localização mais frequente foi a região subungueal. O tempo médio da duração dos sintomas até o diagnóstico foi de oito anos.

Conclusões: Neste estudo, o número de casos de tumor glômico oscilou ao longo desses 16 anos, com média de 0,9 caso/ano. Observou-se maior prevalência em mulheres com mais de 60 anos, na região subungueal e do subtipo histológico glômico sólido.

Palavras-chave: tumor glômico; doenças da unha; neoplasia

INTRODUCTION

The glomus body is a highly specialized arteriovenous anastomosis responsible for thermoregulation.[1] It is located in the reticular dermis throughout the body, and is present in high concentrations in the digital extremities, especially underneath the nail.[2] As a result, the most common location of the tumor is the hands (75% of cases), with preference for the fingertips and subungual space. Other body sites, such as central nervous system, stomach, liver, mediastinum, trachea, lungs, bones, joints and genitals have been mentioned in the literature. Glomus tumor is a benign hamartoma of the glomus body, [1] corresponding to 1 - 4.5% of tumors of the hand.[3, 4], It was first described in 1812 by Wood as a very painful subcutaneous tumor with slow growth and sensitive to temperature variations. [2, 4] It emerges as an intensely sensitive (in special to cold), small, purple or bluish nodule, painful to the touch. [1, 4] Multiple locations are uncommon and mainly occur in children under 16 years old. [2] Solitary tumors are usually found in adults with usually between 30 and 50 years of age, with subungual location, predominantly in females.[1-4] Solitary or multiple tumors have been described in association with neurofibromatosis type 1.[1] Congenital and hereditary forms have autosomal dominant inheritance.[3] The tumor occurs by hyperplasia in one or more normal parts of the glomus body. [2] The pain develops from the contraction of glomus cells.[2] Clinical occurrences are hyperesthesia and/or localized paroxysmal pain, which increase with exposure to cold. [2] Hypersensitivity to cold is observed in 63 to 100% of cases located in the hands, however it is rarely found in extradigital tumors. The combination of magnetic resonance imaging, clinical tests and histopathology allows the diagnosis.[2] There are three main clinical tests for the diagnosis of this tumor. [2, 4] The first is the Love's pin test, when the area where the pain is located is gently pressed with the tip of a pin or clip; in subungual tumors the pressure is directed to the nail plate at different locations until the exact area of the sensitivity is determined.[2, 4] For a positive test, the patient should feel intense pain, sometimes with the jerking of the hand.[2] The Hildreth's test involves placing a tourniquet on the base of the finger where the tumor is located, subsequently applying the Love's test.[2, 4] For a positive result, the patient should not feel pain.[2, 4] The third test is that of the sensitivity to the cold, which is expected to produce increased pain with exposure to cold. [2]

Combined with the clinical tests, high-resolution imaging, such as magnetic resonance, has provided a valuable method for the diagnosis of the glomus tumor. Most of these tumors show high signal intensity on T2 and intense enhancement after gadolinium injection.[2] Plain radiography may evidence bone erosion, suggesting the diagnosis, nevertheless it is a rare finding and takes place in only 22% of cases.[3, 4] Other tests have been described, however with little contribution to the diagnosis. [4]

Histologic analysis of the glomus tumor characterizes it with the presence of small vessels with normal endothelium, circumscribed by compact nests of polygonal cells with round and central nuclei, and eosinophilic cytoplasm. [5] Seven distinct histological forms are described. The glomangioma, which is the most common variant, has a prominent vascular component, with the vessels' lumen being dilated or cavernous. Some cases can have hyalinization of the vessels' walls and thrombi within them. The glomangiomyoma is a rare type, being characterized by muscle cells increased in size and number, surrounding the vascular spaces. The other described types of glomus tumors are: solid, symplastic, glomangiomatosis, infiltrate and malignant. [5] In most cases, surgical treatment leads to the complete resolution of symptoms.[1, 3] Recurrence after surgery occurs in 4 to 15% of cases, depending on the series.[1] Malignant transformation is rare (less than 1% of cases of glomus tumors) and occurs most commonly in non-acral locations. [6]

The objective of the present study was to perform a clinical epidemiological survey of glomus tumors diagnosed at a reference unit during a period of 16 years.

METHODS

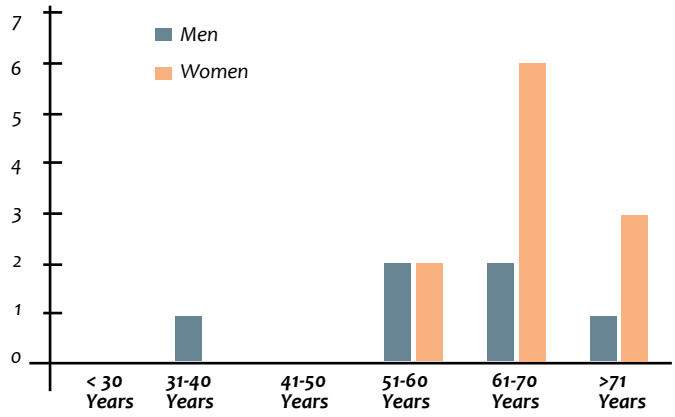
A retrospective review of medical records of patients diagnosed with glomus tumor was carried out at the Dermatology Division of the Instituto Lauro de Sousa Lima, in the city of Bauru (São Paulo, Brazil), covering a 16-year period (from 01/01/2000 to 01/01/2016). The following variables were analyzed: age, gender, tumor location, associated symptoms, duration of symptoms up until diagnosis, clinical appearance, histological type and recurrence after surgery.

RESULTS

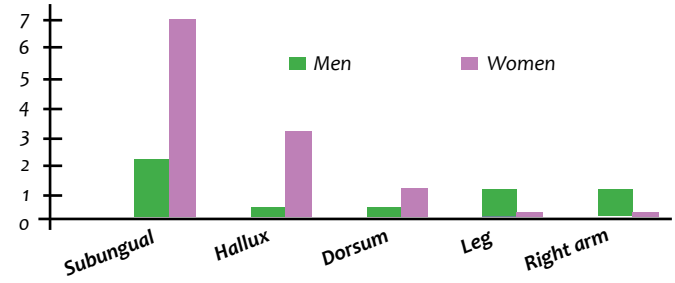
Between the years of 2000 and 2016, 15 cases of glomus tumor were diagnosed (11 women = 73.3% and 4 men = 26.7%, all Caucasian) (Graph 1). The average age at diagnosis was 63 years (min = 36, max = 85), with a predominance of the 61 to 70 years old age group (40%). The average age of women was slightly higher than that of men (66 and 54, respectively). Regarding the location of the lesion, the most common topography was the subungual in the fingers (60%), followed by the hallux (20%), dorsum (6.8%), lower limbs (6.7%) and arms (6.7 %). In both genders the glomus tumor occurred preferably in the subungual region (men = 50%, women = 73%) (Graph 2). The average time of onset of symptoms at diagnosis was 8 years (min = 1, max = 30) (Graph 3). Clinical abnormalities most frequently found were: erythematous-violet dotted area visualized through the nail plate (40%); onychodystrophy (26.7%); medial fissure in the nail plate (20%); and painful bluish nodule in the skin (13.3%) (Graph 4). Pain was present in 100% of patients. The most common histological type was the solid glomus tumor (86.7%), followed by glomangiomas (13.3%). Regarding the treatment, all patients underwent surgical excision, with 13.3% presenting recurrence.

DISCUSSION

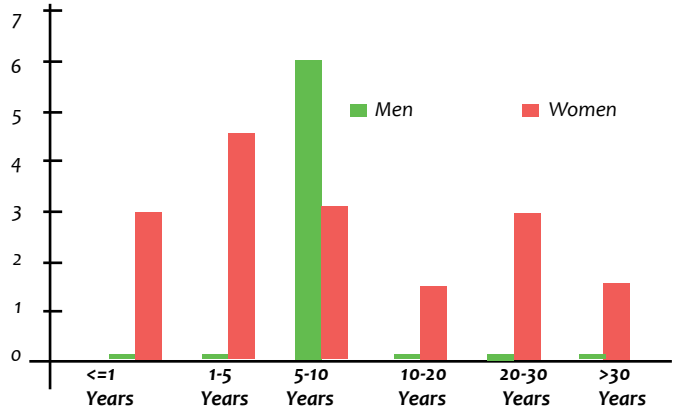
In the present study, the number of diagnosed cases of glomus tumor fluctuated throughout the study period, with a mean value of 0.9 case/year. Regarding the topography, the most common site was the subungual region of the upper limbs



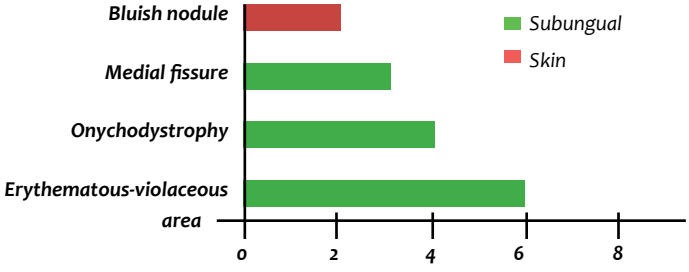
Graph 1: Number of glomus tumor cases distributed by gender and age



Graph 2: Location of glomus tumor by gender



Graph 3: Time of onset of symptoms at diagnosis of the glomus tumor by gender.



Graph 4: Clinical manifestations of the glomus tumor by location

(60%), followed by the hallux (20%), dorsum (6.8%), legs (6.7%) and arms (6.7%). The average time to diagnosis was 8 years. Unlike the present study, a review performed by the Mayo Clinic with 56 extradigital cases evidenced prevalence in the forearms (20%) and knees (18%). [7]

A higher prevalence of glomus tumor was observed in women over 60 years of age and in the subungual region of the upper limbs. These data are in line with the literature, nonetheless differing in age, with the present study evidencing cases at an older age group. [3, 4]

The most frequently found histological subtype was the solid glomus tumor (86.7%), a fact that did not corroborate findings of previous studies, which suggest the glomangioma as the most frequent. [5] The most often observed clinical appearance of the subungual glomus tumor was an erythematous-violaceous area (40%). The clinical tests, useful due to their easy implementation and cost effectiveness, have been performed only in 2 of the 15 cases (13.3%), yielding positive results in both.

Imaging studies were performed in 6 cases (40%), with plain radiography being performed in 4 of them. In only 1 case focal osteolysis was observed in the distal phalanx (25%). Magnetic resonance imaging was performed in 1 case, evidencing the tumor and its topography, leaving no doubt as to the diagnosis. Ultrasonography was requested in 1 case, however it did not evidence injury.

The found recurrence rate was 13.3%, coinciding with that in the literature. [3, 4]

CONCLUSIONS

The present study has demonstrated that the glomus tumor is associated to a delay in its diagnosis, leading the patient to live with chronic pain and which most often has excellent response to surgical treatment. Although this entity is more often found in the subungual region, it can emerge in other body sites. In addition, specific clinical tests are excellent, cost-effective tools when there is suspicion of the diagnosis.

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Alternative methodology for the study of infrared-A radiation effects on human skin

Metodologia alternativa para o estudo dos efeitos da radiação infravermelha-A sobre a pele humana

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ABSTRACT

Introduction: Infrared radiation (IR-A) causes structural changes in the skin, similar to those caused by prolonged exposure to ultraviolet radiation. Evaluation of efficacy and safety of cosmetic products concentrates in in vitro tests and clinical trials. A promising alternative is the use of fragments of human skin from elective cosmetic surgery, to evaluate the actual clinical benefits of a product applied topically.

Objective: The objective of this study was to correlate IR-A radiation effects in biopsies and in ex vivo skin fragments and in human fibroblasts culture by quantifying MMP-1, TIMP-1 and GADD45a mediators.

Methods: Collection of biopsies from 15 volunteers after IR-A applications for 5 consecutive days. Exposure to IR-A radiation of human skin fragments from elective cosmetic surgery, and human fibroblasts culture. Measurement of MMP-1, TIMP-1 and GADD45a mediators for further comparison of results.

Results: In the three models used, the IR-A radiation induced an increase in MMP-1, inhibited the synthesis of GADD45a, and did not changed TIMP-1 values.

Conclusion: Due to the positive correlation of the models studied, it may be suggested the use of ex vivo skin as plausible and sustainable tool to overcome differences between knowledge generated from in vitro and clinical experiments.

Keywords: skin aging; matrix metalloproteinase 1; solar radiation; in vitro techniques

RESUMO

Introdução: *A radiação infravermelha A (IV-A) causa alterações estruturais na pele, similares àquelas provocadas pela exposição prolongada à radiação ultravioleta. A avaliação de eficácia e segurança para produtos cosméticos concentra-se em ensaios in vitro e clínicos. Uma alternativa promissora é a utilização de fragmentos de pele humana provenientes de cirurgias plasticas eletivas, para avaliar os reais beneficios os reais benefícios clínicos de um produto aplicado topicamente.*

Objetivo*: O objetivo desta investigação foi correlacionar os efeitos da radiação IV-A, em biópsias e em fragmentos de pele ex vivo e cultura de fibroblastos humanos, pela quantificação dos mediadores MMP-1, TIMP-1 e GADD45a.*

Métodos*: Coleta de biópsias de 15 voluntárias após aplicações de IV-A durante cinco dias consecutivos. Exposição à radiação IV-A de fragmentos de pele humana provenientes de cirurgia plástica eletiva e cultura de fibroblastos humanos. Mensuração dos mediadores MMP-1, TIMP-1 e GADD45a para posterior comparação dos resultados.*

Resultados*: Nos três modelos utilizados a radiação IV-A induziu aumento de MMP-1, inibiu a síntese de GADD45a e não alterou os valores de TIMP-1.*

Conclusão*: Devido à correlação positiva dos modelos estudados, pode-se sugerir o uso de pele ex vivo como ferramenta plausível e sustentável para suprir diferenças entre conhecimentos gerados a partir de experimentos in vitro e clínico.*

Palavras-chave: *fotoenvelhecimento da pele; metaloproteinase 1 da matriz; radiação solar; técnicas in vitro*

Original Articles

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INTRODUCTION

The electromagnetic spectrum emitted by solar radiation is composed of a wide range of wavelengths. Nevertheless, only a few fractions of these lengths reach the Earth's surface, including ultraviolet radiation (UV 280-400nm), the visible light (VL 400-760nm) and infrared radiation (IR 760nm-1mm). [1]

For many years, photoaging and cutaneous damage were attributed almost exclusively to UV radiation, which represents only 6.8% of solar radiation as compared with the infrared and visible radiations, which correspond 54.3% and 38.9% of incident solar energy, respectively. [1] Currently, however, it is known that IR radiation also induces histological alterations similar to those induced by chronic exposure to UV. [2]

Infrared radiation (IRR) is classified into IR-A (760 – 1,400nm), IR-B (1,400-3,000nm) and IR-C (3,000nm-1mm), according to the wavelength and its penetration into the skin layers. [1-3] Infrared radiation has two effects: thermal (which can be beneficial or harmful, depending on the dose) and oxidative damage (which arises from the range close to IR-A, 760 - 1,500nm). Infrared radiation-A reaches deeper layers of the skin, with 35% of the radiation being dispersed in the epidermis, 48% in the dermis and 17% in the subcutaneous tissue.[2, 4] Although not yet completely understood, the mechanism by which IR-A radiation causes harmful effects involves disturbances in the transportation of mitochondrial electrons, leading to a decrease in energy production and an increase in the formation of reactive oxygen species. [5-7] With the loss of mitochondrial homeostasis, there is oxidative stress and changes in gene expression and dermal metabolism translated into increased expression of metalloproteinase 1 (MMP-1), decreased collagen synthesis, development of solar elastosis and skin hyperpigmentation. [8-11]

In addition, DNA damage, cytotoxicity induction and generation of oxidative stress, with a decrease in antioxidant activity have been reported after acute exposure to IR-A radiation.[2, 9, 12-15] Excessive and repeated exposures to IR-A has also been shown to cause chronic damage as erythema *ab igne* and squamous cell carcinoma,[5, 16] probably as a result of the reduction in the DNA repair process.[17-18]

With the advent of the 3R policy (Replace, Refine and Reduce), which supports the use of alternative tests to replace, refine and reduce the use of animals in research, safety and efficacy assessment of cosmetics became restricted to *in vitro* and clinical tests. *In vitro* trials predict possible toxic effects and determine probable biological mechanisms of action responsible for the clinical benefit of the cosmetic product, complementing the *in vivo* results. Nonetheless, direct inference from the results requires caution due to the fact that not always the mechanisms observed in cell cultures or equivalent skin models can be extrapolated to the real condition of use. Likewise, although clinical results offer an undeniable contribution to the assessment of safety and efficacy of cosmetic products, they do not provide data regarding the mechanisms of action such as those obtained by *in vitro* techniques.

The evaluation of the biological mechanisms of action using skin biopsies obtained from healthy human volunteers as test-systems[19-21] constitutes a model for understanding the real damage that an aggressor agent can trigger, as well as for the genuine clinical benefits generated by a cosmetic or dermatological treatment. However, although frequently reported in the literature, this procedure can be considered invasive when used as an everyday research tool.

Thus, a plausible and sustainable alternative to bridge this gap between the *in vitro* and the clinical is the use of skin fragments obtained from elective plastic surgery (*ex vivo* study), which is characterized as the most suitable model for approximating the actual effect responsible for the clinical benefits of a product applied topically.

The objective of the present study was to correlate the effects of IR-A radiation, both in biopsies and in *ex vivo* skin fragments and cultured human fibroblasts, through the quantification of MMP-1 mediators (matrix metalloproteinases), TIMP-1 (tissue inhibitor of metalloproteinase 1) and GADD45a (growth interruption protein and DNA damage).

METHODS

Human Fibroblasts HFF-1 (BCRJ, Rio de Janeiro, Brazil) were seeded in 75cm^2 bottles (Nunc, Denmark), cultured and expanded in an incubator at 37°C in the presence of 5% CO_2, using specific culture medium. On reaching confluency, cells were seeded in 24-well plates (Nunc, Denmark).

The skin fragments used in the present study were obtained from a 54-year old healthy, skin phototype III [22] individual who had undergone elective plastic surgery in the abdominal region (abdominoplasty). After the surgical procedure, the skin fragments were fractionated into pieces of approximately 1.5cm^2, weighed and kept in 24-well plates.

The cultures of HFF-1 and skin fragments underwent a 360 J/cm^2 dose of IR-A radiation using the Hydrosun 750 and HBM1 devices (Hydrosun Medizintechnik GmbH, Müllheim, Germany). After radiation, the test-systems were incubated in fresh culture medium and maintained for 24 hours for collection of the supernatant, cell lysate and homogenized tissue.

The clinical trial for efficacy evaluation was characterized as open, single-center and prospective, involving 15 volunteers aged between 35 and 45 years, with skin phototypes II and III. Two areas were demarcated in the paravertebral region of all participants included in the study – one area served as a control and did not undergo application of IR-A radiation, while the other was exposed to IR-A radiation. The application of IR-A radiation in the study participants was performed with the 750T Hydrosun IRA device. A dose of 360 J/cm^2 was applied daily for five consecutive days. This radiation dose is physiologically relevant given that the human skin is exposed to significant amounts of solar radiation type IR-A, with an average dose of 108 J/cm^2/hr (summer, Campinas, SP, Brazil).

The study involving the participation of human volunteers and the use of human skin fragments obtained in elective surgeries was conducted after the approval of the Research Ethics Committee of the Universidade São Franciso - SP, Brazil.

The concentrations of MMP-1, TIMP-1 and GADD45a were measured by an immunoenzymatic trial, using commercially available kits (R&D Systems, Minneapolis, MN, USA; Uscn Life Science Inc., Houston, TX, USA). The absorbance reading was performed on monochromator Multiskan GO (Thermo Fisher Scientific Oy, Vantaa, Finland). The mediators' levels were calculated based on the reference values obtained by the standard curve, which was built with known concentrations of recombinant proteins.

The paired t-test with a 95% confidence interval (GraphPad Prism v6) was used for the statistical evaluation.

RESULTS

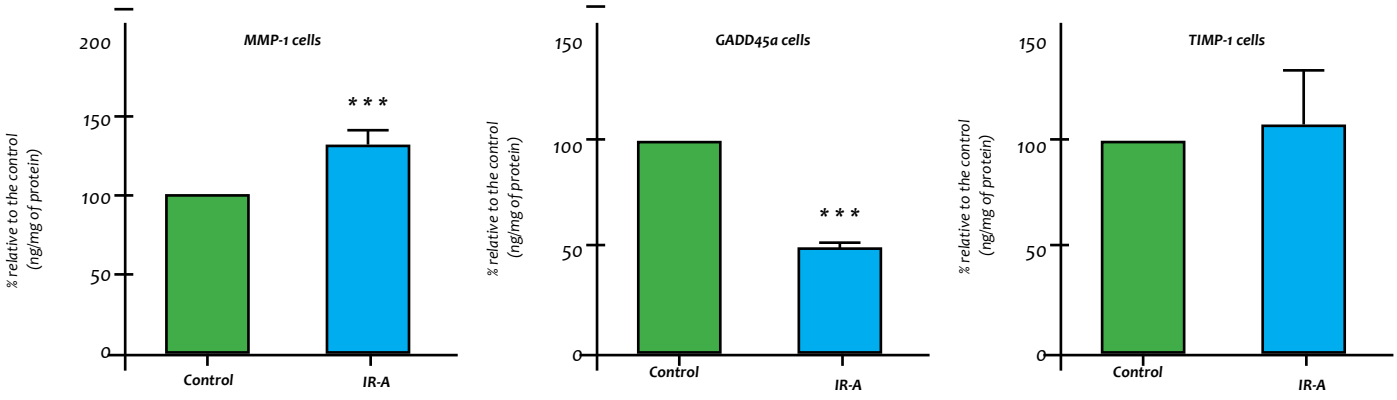
Graph 1 depicts the effects of IR-A radiation on the production of MMP-1, TIMP-1 and GADD45a in cultured human fibroblasts. As can be seen, the IR-A radiation produced a significant increase (31.2%) in the production of MMP-1 as compared to the non-irradiated baseline control. Regarding the GADD45a, the IR-A radiation led to a reduction of 50.5%, however it did not alter the TIMP-1's values.

In Graph 2, it is possible to observe the results obtained after the exposure of human skin fragments to IR-A irradiation, which promoted a statistically significant increase (65.5%) in the production of MMP-1 in addition to a significant reduction in the synthesis of GADD45a (41.6%). TIMP-1 levels did not change compared to the non-irradiated control.

The results obtained in the homogenized tissue of the biopsies harvested after exposure of the volunteers to the IR-A radiation are in Graph 3. The radiation was able to promote a significant increase (33.9%) in the synthesis of MMP-1 and a reduction of 37.9% in the GADD45a protein – however it did not change the levels of TIMP-1.

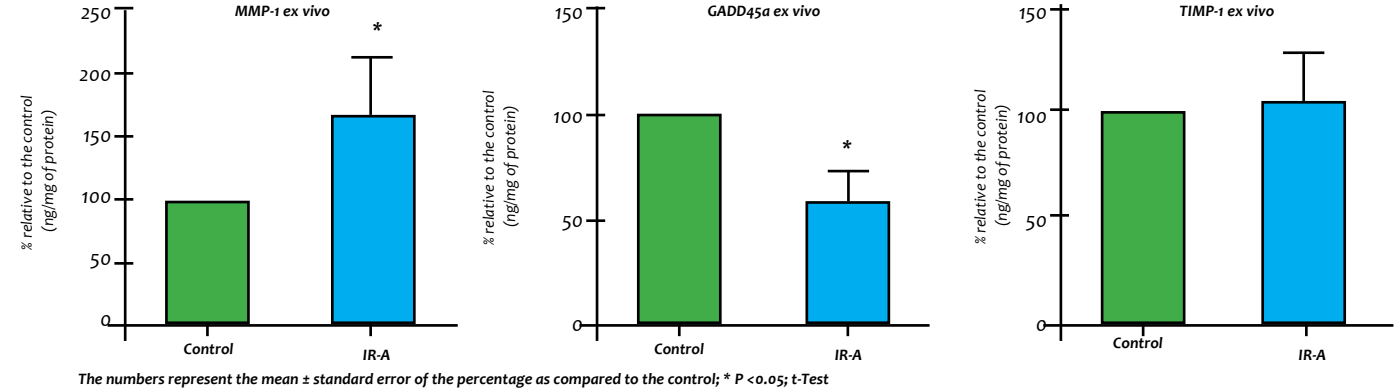
DISCUSSION

A fairly common occurrence after exposure to IR-A radiation is the decrease in the synthesis of the main dermal proteins – collagen and elastin – essential for providing structural support for tissues.[9,23] This change occurs as a result of oxidative stress induced by reactive oxygen species generated upon exposure to radiation and leads to increased proteolytic enzymes, such



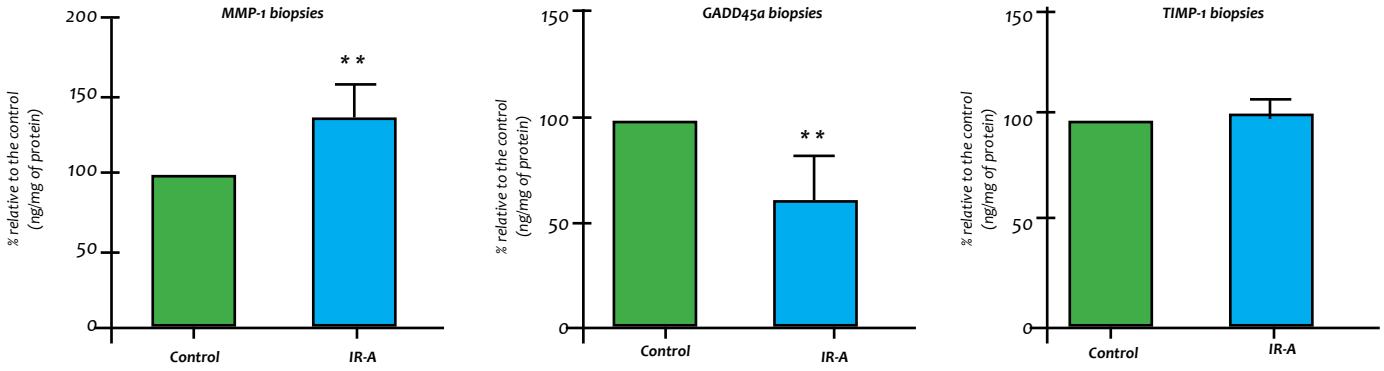
*The numbers represent the mean ± standard error of the percentage as compared to the control; *** P <0.001; t-Test*

Graph 1: Effects of infrared radiation type A (IR-A) on the production of MMP-1, GADD45a and TIMP-1 in cultured human fibroblasts



*The numbers represent the mean ± standard error of the percentage as compared to the control; * P <0.05; t-Test*

Graph 2: Effects of infrared radiation type A (IR-A) on the production of MMP-1, GADD45a and TIMP-1 in cultured human fibroblasts obtained from elective cosmetic surgery



*The numbers represent the mean ± standard error of the percentage as compared to the control; ** P <0.01; t-Test*

Graph 3: Effects of infrared radiation type A (IR-A) on the production of MMP-1, GADD45a and TIMP-1 in skin biopsies obtained from volunteers

as matrix metalloproteinase-1 (MMP-1).[12, 24] This proteinase in turn triggers a collapse in the extracellular matrix and therefore the premature onset of signs of aging skin.[9, 23] The MMPs' activity can be controlled by tissue inhibitors of metalloproteinases (TIMPs), which are synthesized by the fibroblasts located in the dermis and act locally, with the specific function of blocking the activity of MMPs, in this manner preventing the degradation of the matrix extracellular. [25]

Another aspect of the oxidative response induced by IR-A radiation is the damage inflicted to cellular DNA. The ability to promptly repair that type of damage is an important cellular mechanism that protects cells and maintains genomic stability, preventing early oncogenesis.[26-27] Animal cells have a complex defense mechanism to preserve genomic integrity and prevent that damage resulting from the genotoxic stress becomes permanent.[25] Among these mechanisms are the disruption of cell cycle progression or direct activation of apoptosis, depending on the extent of damage and cell type.[26-29] In this context, GADD45a protein plays a crucial role as a cellular stress sensor through the interaction with other proteins, promoting control of cell cycle regulation, DNA repair, epigenetic changes, apoptosis, survival and senescence.[26-29]

In the present study, the authors evaluated markers involved in skin aging using three human test-system models: fibroblast culture, *ex vivo* skin fragments and skin biopsies after exposure to IR-A.

The purpose of this comparative analysis was to validate the use of human skin obtained from elective cosmetic surgery as an alternative tool for assessing the effectiveness of cosmetic ingredients and products, in light of the fact that biological trials in animal models with this product category were practically banned and replaced by *in vitro* and clinical tests.

Despite the innovation of cell culture techniques and the development of increasingly complex three-dimensional skin equivalent models, there is still a gap in the extrapolation of the results for the clinical benefits that a cosmetic is able to promote. Furthermore, considering that the cutaneous tissue interacts structurally and functionally with the entire body and plays a vital role in the maintenance and regulation of the immune, endocrine and nervous systems, [30] biological effects obtained from *in vitro* studies may not precisely convey the observations, results and conclusions that are likely to occur clinically.

The *in vivo* (clinical) evaluation using skin biopsies from volunteers who undergo aesthetic treatments [19-21] constitutes a methodology that allows investigating the pharmacodynamics of molecules or products for, unlike other models, it does not exclude hormonal, nutritional or even immune individual variability. However, due to the fact that it is an invasive procedure, it might in some cases be deemed an aggressive method for proving the effectiveness of cosmetic and dermatological products, being consequently precluded as a day-to-day research tool.

According to a report by the International Society of Aesthetic Plastic Surgery (ISAPS), [31] Brazil ranked first in number of surgical procedures performed in 2013, in special liposuction, breast implants placement and abdominoplasty. The survey also shows that Brazil has nearly doubled the number of cosmetic surgeries performed in the past four years, with a growth of 97.2%.

While fragments of excess skin removed during elective plastic surgery are routinely discarded as infectious waste, its use is a feasible and sustainable experimental alternative that bridges the gap between the *in vitro* and the clinical, leading to almost similar outcomes to those of a product topically applied in a real situation.

The outcomes obtained in the present study confirm the deleterious effects that IR-A radiation is able to promote in the skin tissue, such as accelerated aging and weakening of the mechanisms involved in tissular repair. The production of MMP-1 increased after exposure of the three test-systems – fibroblast culture, *ex vivo* fragments of skin and skin biopsies – to a dose of 360 J/cm^2 of radiation IR-A. Similarly, the IR-A radiation led to a significant reduction in the production of GADD45a when compared to the unirradiated baseline control. One possible explanation for this effect is the increase of consumption and

degradation of this protein as a result of genotoxic stress, which could result in a transient reduction in the levels of GADD45a in the cultures. As already mentioned, the absence of this protein can lead to genomic instability and impairment in the capacity to repair DNA damage.[28-29, 32] Regarding the TIMP-1 levels, there was absence of significant alterations after exposure of the test-systems to IR-A radiation.

The results obtained in the present study clearly show that the *ex vivo* skin model is effective in mimicking the effects of IR radiation on the skin, proving that the use of human skin fragments obtained from elective plastic surgery is currently the safest option and most promising noninvasive option for the study of new active principles and formulations in the cosmetic/dermatological industry.

CONCLUSION

Due to the positive correlation of results among the three assessed models, the authors can suggest that the *ex vivo* trial of skin fragments obtained from elective plastic surgery is an alternative approach to the use of human biopsies, given that it has been proven as a credible and sustainable tool to address differences between the knowledge generated from *in vitro* and clinical experiments.

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Original Articles

Treatment of moderate to severe acne vulgaris with an oral isotretinoin similar to the reference product

Tratamento da acne vulgar moderada a grave com isotretinoína oral similar ao produto referência

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ABSTRACT

Introduction: Acne vulgaris is a chronic inflammatory disease of the pilosebaceous follicles. Treatment should be early and effective to prevent scarring and psychosocial effects, and isotretinoin is the drug of choice for moderate or severe cases.

Objective: To assess efficacy, safety and tolerability of an isotretinoin similar to the reference product.

Methods: A bicentric study, with therapeutic intervention was conducted, including 50 participants aged 13 to 35 years, with moderate to severe acne, using isotretinoin 0.5 mg/kg/day up to 120 mg/kg. Efficacy was assessed through lesions counting, the investigator's global assessment (IGA) scale, patient satisfaction and application of the quality of life questionnaire specific for Acne (Acne Qol). Safety and tolerability were assessed by analysis of adverse events and laboratory tests.

Results: Mean age was 20 years, 70% of participants were men, with a reduction of 99% of lesions after treatment and complete remission of lesions in 91.5% of participants. IGA scale reduced 98% in the score after treatment. Also, 100% of participants declared to be satisfied, with significant improvement in quality of life. Adverse events were similar to those described in the literature.

Conclusion: The assessed isotretinoin was equally effective, safe and well-tolerated when compared with published data of the standard product.

Keywords: acne vulgaris; treatment outcome; isotretinoin

RESUMO

Introdução: *Acne vulgar é doença inflamatória crônica dos folículos pilossebáceos. O tratamento deve ser precoce e efetivo para evitar cicatrizes e repercussões psicossociais, sendo a isotretinoína droga de escolha para casos moderados ou graves.*

Objetivos*: Avaliar eficácia, segurança e tolerabilidade de uma isotretinoína similar ao produto referência.*

Métodos*: Estudo bicêntrico, de intervenção terapêutica, incluindo 50 participantes, de 13 a 35 anos de idade, com acne moderada ou grave, usando isotretinoína 0,5mg/kg/dia, até 120mg/kg. A eficácia foi avaliada por meio da contagem de lesões, escala de avaliação global do investigador (IGA), satisfação do paciente e aplicação do questionário de qualidade de vida específico para acne (Acne Qol). Segurança e tolerabilidade foram avaliadas pela análise de eventos adversos e por exames laboratoriais.*

Resultados*: A idade média foi 20 anos, sendo 70% homens, com redução de 99% das lesões ao final do tratamento e remissão total das lesões em 91,5% dos participantes. A escala IGA reduziu 98% no escore ao final do tratamento. Todos os pacientes se declararam satisfeitos, com significativa melhora na qualidade de vida. Os eventos adversos foram semelhantes aos descritos na literatura.*

Conclusões*: A isotretinoína avaliada mostrou-se igualmente eficaz, segura e bem tolerada quando comparada aos dados publicados referentes ao produto-padrão.*

Palavras-chave: *acne vulgar; resultado de tratamento; isotretinoína*

INTRODUCTION

Acne vulgaris is a chronic inflammatory dermatosis of the pilosebaceous follicles. It is considerably common and affects a percentage that ranges from 79% to 95% of the adolescent population in Western societies. The condition was also reported in 8% of adults between 25 and 34 years of age and in 3% of those between 35 and 44 years old. [1, 2]

Its pathogenesis is multifactorial and results in the occlusion of the sebaceous follicles due to the excessive amount of sebum produced by the sebaceous glands, which stimulation is mediated by androgens, combined with hyperkeratinization and excessive desquamation of epithelial cells in the follicles' walls. This occlusion leads to formation of a micro comedo, which is considered as the primary lesion of acne, and that can become a comedo or an inflammatory lesion. The proliferation of the *Propionibacterium acnes* bacteria is also one of the factors that contribute to the pathogenesis of acne and is favored by an environment created by the mixture of sebum and follicular cells. In addition, this bacterium is responsible for the release of chemotactic factors, such as cytokines and tumor necrosis factor (TNF), which initially attract neutrophils and mast cells, which in turn lead to inflammation. [3-5] The *P. acnes* modulates the expression of the toll-like receptor 2 (TLR-2), activating several nuclear pathways such as NFKB, with the production of other proinflammatory cytokines and the AP-1 pathway, which determines the production of metalloproteinase enzymes, implicated in the development of acne scars. Qualitative changes in sebum secretion are also involved in the inflammation that has been regarded as the central event in acne – present even before the onset of clinical inflammatory lesions such as papules, pustules and nodules. [6, 7] In addition to these mechanisms, genetic factors, stress among others, influence the development and severity of acne.

It is clinically classified as non-inflammatory or comedonian (presence of open and closed comedones) and inflammatory (characterized by papules, pustules, nodules, cysts and abscesses). Inflammatory acne can be sub-divided into mild, moderate and severe. All lesions can leave scars of various types. [8]

Treating the acne is of utmost importance to reduce its severity, potential for recurrence, scarring and psychosocial impact, contributing to improved quality of life. Topical treatments (retinoids, benzoyl peroxide, antibiotics, azelaic acid) are recommended for comedonian and mild to moderate inflammatory acne. For moderate to severe cases, treatment should be carried out with a combination of topical and/or systemic drugs (antibiotics, hormones), since it is a multifactorial disease. [9–11] Isotretinoin, a retinoid derivative of vitamin A, is widely used to treat acne as a monotherapy, since it is the only substance capable of controlling all etiopathogenic factors. [12] Retinoids act in the growth and differentiation of epidermal cells, and the isotretinoin interferes with the activity of the sebaceous gland, has immunomodulatory and anti-inflammatory properties, modulating the TLR 2's activity. As a result, there are a decrease in the comedogenesis, a reduction in the size of the sebaceous glands greater than 90% due to a decreased basal proliferation of sebocytes, a suppression of sebum production and the inhibition of the differentiation of the terminal sebocyte. Although it does not directly affect *Propionibacterium acnes*, the reduction of sebum alters the follicular microenvironment, reducing the number of bacteria and their ability to cause inflammation. It has already been shown that oral isotretinoin significantly reduces the population of *P. acnes* resistant to three antibiotics: erythromycin, clindamycin and tetracycline. [13, 14]

Oral isotretinoin was synthesized in 1955, however only in 1973 the studies on its clinical use in psoriasis began, giving rise to further evaluation on its use in other keratinization disorders. [15] By 1976, it started to be tested in Europe for the treatment of acne. In 1978, a study showed its excellent effect on nodule-cystic acne, with complete and prolonged remission. [16] In the following year, positive outcomes were reported in 14 patients treated with 2mg/kg/day for four months. [17] In 1980, similar results were obtained with the daily dose of 0.1 to 1mg/kg over four months. [18] Only in 1982, however, the first double-blind, randomized study was published, effectively demonstrating the efficacy of oral isotretinoin with a maximum daily dose of 1.2 mg/kg for four months in 33 patients bearing severe forms of acne. [19]

The approved indications for oral isotretinoin are: nodular-cystic acne and pustular papular acne resistant to other treatments or with frequent improvements and recurrences. [20-22] The daily dose is calculated according to the patient's weight and ranges from 0.5 to 1 mg/kg. [23, 24] In order to prevent recurrences, a total dose of between 120 and 150mg/kg is recommended.

Adverse reactions to isotretinoin can be divided into two types: a) undesirable, predictable and controllable pharmacological effects (cutaneous-mucosal) and b) toxic effects involving organs and systems, when no therapeutic effect is expected, particularly alterations in liver function and in serum lipids. [25-28] It is important to advise the patient on the cutaneous-mucosal effects, to prevent and treat early, with the use of lip lubricant and hydrating the skin and nasal and conjunctival mucosas, and use sunscreen daily aimed at preventing that these adverse events become the unnecessary cause for the interruption of treatment. Similarly, laboratory monitoring is required. Teratogenicity is the most serious risk, and the patient must wait for the menstruation to start the treatment and be guided regarding contraception, with two safe methods, during and up to one month after the end of the treatment. [29-31]

Several pharmaceutical companies manufacture this drug, with a frequent doubt among patients, and even dermatologists, being whether the similar isotretinoin has the same efficacy and safety of the standard product.

In this manner, the objective of the present study was to evaluate the efficacy, safety and tolerability of a similar isotretinoin as compared to the standard isotretinoin.

METHODS

A bicentric, therapeutic intervention, open and uncontrolled study was carried out to evaluate the efficacy, safety and tolerability of oral isotretinoin contained in gel capsules (Acnova®) produced by the pharmaceutical company Germed Pharma

Ltda. (Campinas, SP, Brazil), in patients with moderate to severe acne vulgaris.

With the approval by the Research Ethics Committee (07527912.7.1001.5505), all participants signed the Free and Informed Term of Consent. Observing the inclusion and exclusion criteria, 50 patients were selected: 25 in each center, of both genders, aged between 13 and 35 years, with clinical diagnosis of moderate to severe facial acne, who used the studied drug orally (gel capsules) once or twice a day, with individual dose adjustment (~ 0.5mg/kg body weight/day) up until the total dose of 120mg/kg for up to 12 months.

Patients were followed up in eight visits, with clinical, laboratory and photographic assessments.

The impact of the treatment on the patients' quality of life was evaluated through an acne specific questionnaire (Acne QoL) before and after the treatment. The efficacy was assessed by the lesion counts (total, inflammatory and non-inflammatory), change in the intensity/severity of acne according to the Investigator Global Assessment (IGA) (Chart 1) and the patient's satisfaction. The outcomes were analyzed applying the negative binomial regression method for panel data (longitudinal data) using the Stata/SE 13.1 software's xtnbreg procedure (Stata Corp, CollegeStation, Texas), as well as the comparison of the Acne QoL's scores before and after the treatment, through the linear regression analysis for panel data using the xtreg procedure (Stata Corp). The safety and tolerability were assessed by observation and based on reports of adverse events during the follow-up and laboratory tests, through linear regression analysis for panel data using the xtreg procedure (StataCorp). The results are presented as risk ratios (RR) and oddsratio (OR).

A significance level of 5% ($\alpha = 0.05$) was adopted throughout the analysis, meaning the results were considered significant when the p-value was less than 5% ($p < 0.05$).

RESULTS

The age of the 50 participants ranged from 13 to 35 years old, with a mean of 20 years old. Seventy percent were men.

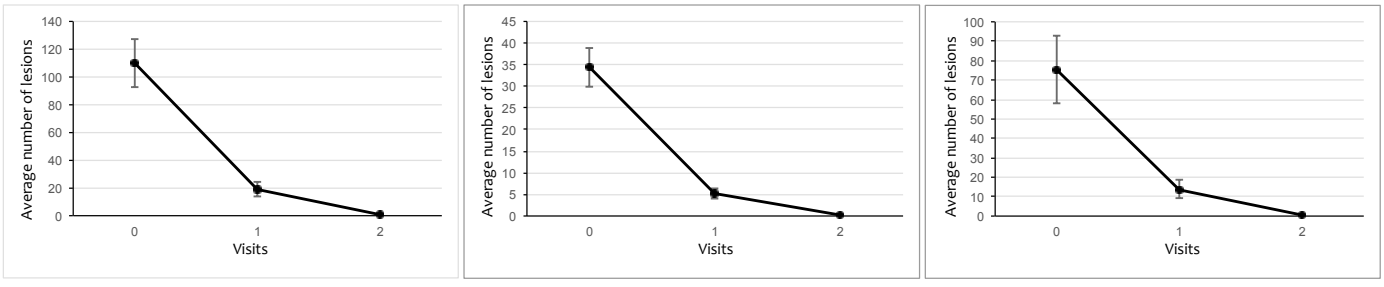
There were 3 premature withdrawals due to personal reasons (not for adverse events), meaning that 47 patients completed the treatment, with 41 (87.2%) becoming very satisfied and 6 (12.8%) satisfied with the outcome.

For purposes of analysis 3 visits considered (initial, intermediate and final). The average time elapsed between the initial and intermediate visits was 118 days or roughly 4 months (standard deviation = 14 days). The average time elapsed between initial and the final visits was 249 days or roughly 8 months (standard deviation = 51 days).

Regarding the number of lesions when compared to the initial visit, the following facts were observed: mean reduction of 83% in the estimated total number of lesions in the intermediate visit, and of 99% at the final visit ($p < 0.001$). For the inflammatory lesions, the reductions were 85% and 99%, and for the non-inflammatory, 82% and 99%, respectively ($p < 0.001$), as depicted in Graph 1.

Chart 1: Investigator Global Assessment Scale for Acne vulgaris (IGA)

0	Cured	Residual hyperpigmentation and erythema may be present
1	Almost cured	Some scattered comedones and a few small papules
2	Mild	Presence of some comedones and some papules and pustules. Absence of nodules
3	Moderate	Many comedones, papules and pustules. A nodule may be present
4	Severe	Covered with comedones, numerous papules and pustules and a few nodules and cysts may be present
5	Very Severe	Highly inflammatory acne covering the face, with presence of nodules and cysts



Graph 1: : Number of lesions estimated by the negative binomial regression model in each of the evaluation timepoints and respective 95% confidence intervals. **A:** Total number of lesions, **B:** Number of inflammatory lesions, **C:** Number of non-inflammatory lesions

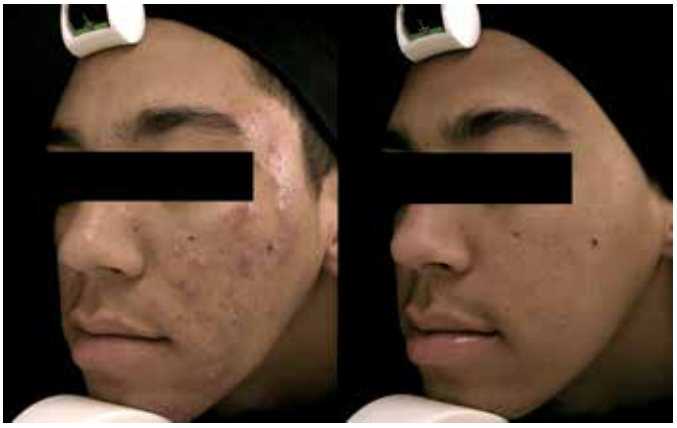


Figure 1: Patient before the treatment 8 months after starting using the medication

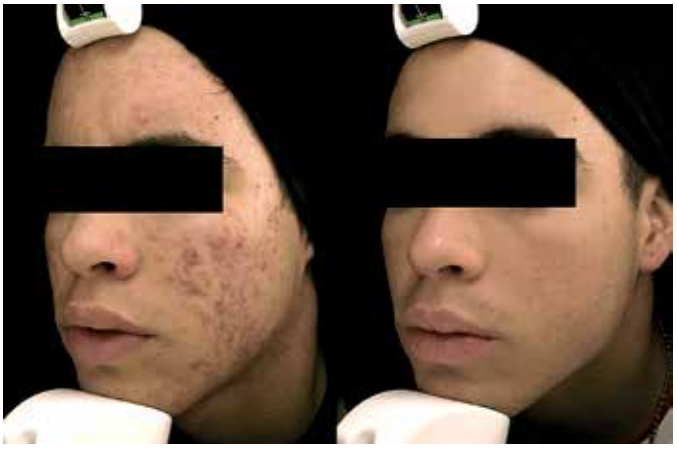


Figure 2: Patient before the treatment 8 months after starting using the medication

Table 1: IGA descriptive analysis according to the visit

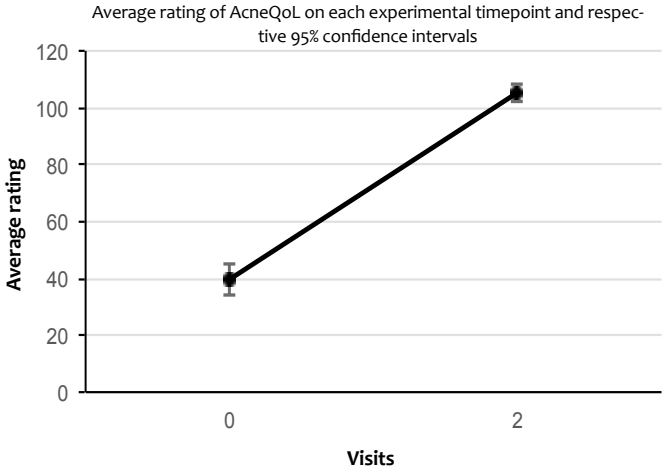
	Initial visit	Intermediate visit	Final visit
IGA			
Median [Q1-Q3]	4 [3 – 4]	2 [1 – 2]	0 [0 – 0]
Minimum - Maximum	3 – 5	1 – 3	0 – 1

Q1 - Q3: first and third quartiles corresponding to the percentiles P25% and P75%, respectively.

The total remission of the lesions was observed in 91.5% of participants, as shown in Figures 1 and 2.

Analyzing the intensity/severity of acne according to the IGA Scale regarding the initial visit, an estimated average reduction of 50% was verified in the intermediate visit (CI 95%: 45%; 56%). The estimated average reduction in the final visit was 98% (CI 95%: 94%; 99%), with p <0.001, as shown in Table 1.

The analysis of the impact of the treatment on the participants' quality of life evidenced that the mean score arising from the Acne QoL questionnaire was 39.5 + 19.4 before the treatment and 105.1 + 10.0 at its end. Using the regression model for panel data it was possible to conclude that this increase was



Graph 2: AcneQoL rating analisys

Table 2: Distribution of erythema, desquamation and dryness according to the intermediate and final visits

	Intermediate visit		Final visit	
	N	%	N	%
Erythema				
Absent	29	58	27	57,4
Mild	19	38	18	38,3
Moderate	2	4	2	4,3
Desquamation				
Absent	17	34	22	46,8
Mild	29	58	16	34
Moderate	4	8	9	19,2
Dryness				
Absent	17	34	24	51,1
Mild	30	60	22	46,8
Moderate	3	6	1	2,1

significant (p <0.001), having been estimated at 65.5 points (CI 95%: 59.5; 71.7), suggesting the presence of a significant improvement in the patients' quality of life (Graph 2).

Safety and tolerability were assessed in the intermediate and final visits by assessing the presence of erythema, desquamation and skin dryness. Table 2 shows the distribution of these occurrences. It is possible to note that in the intermediate visit 42% of patients had erythema, 66% had desquamation, and 66% had dryness. At the final visit, 42.6% had erythema, 53.2% had scaling, and 48.9% had dryness.

Throughout the evaluation, patients were asked about the presence of other adverse events. Table 3 shows the distribution of these adverse events (with at least one occurrence, at any time during the study). No serious adverse event was observed.

Table 4 presents the analysis of laboratory tests.

It was possible to observe that GOT, GPT, gamma GT, total cholesterol, LDL and triglycerides varied along the study period, nevertheless their mean values did not exceeded or fell below reference values. There was no need to discontinue the

treatment due to laboratory abnormalities. Blood count, alkaline phosphatase, glucose and HDL did not change significantly.

DISCUSSION

The efficacy of oral isotretinoin in the treatment of acne vulgaris has been demonstrated in numerous publications since the 80s, with more than 90% of reduction of inflammatory lesions. In the present study, the authors observed a 99% reduction of inflammatory and non-inflammatory lesions, with 100% satisfaction of participants and significant improvement in the quality of life.[31]

The treatment duration (roughly 6 months), is described as sufficient for acne remission in 99% of patients. In the present study, the average duration of treatment was eight months.[32]

As a rule, it is expected a 50% reduction of the pustules within 2 to 4 weeks after the beginning of the treatment. The authors of the present study observed a reduction of 85% in inflammatory lesions in the 4th month of treatment and, in line with the literature, inflammatory lesions improved faster than the comedones. Pustules receded before papules and nodules.[31, 32]

Regarding the alterations found in laboratory tests, there is great variability among studies, depending on the dose used. The most commonly found in the literature are elevated hepatic enzymes (20%), increased triglycerides (20-40%), and increased serum cholesterol with elevated LDL fraction and decreased HDL (10-30%), in line with the present study's observations, even in light of the fact that the mean values remained within the reference levels used in the laboratory. There are reports of hepatotoxic reactions in less than 1% of cases, which was not observed in the present study.[31, 32]

Thus, it is possible to assert that the studied similar isotretinoin led to outcomes similar to those found in the lit-

Table 3: Distribution of adverse events in any of the evaluation visits (at least one report)

ADVERSE EVENTS	%
Cheilitis	100
Dry skin	82
Dryness of the nasal mucosa	70
Epistaxis	52
Ocular dryness	50
Mood changes	30
Epigastric pain	20
Muscle pain	14
Nausea	12
Brittle nails	10
Arthralgia	10
Depression	4
Hair loss	4
Diarrhea	2
Vomit	2
Conjunctivitis	2
Paronychia	-

Table 5: Side effects and incidences: comparison between the present study's findings and the literature (%).

ADVERSE EVENTS	CURRENT STUDY	LITERATURE
Cheilitis	100	96-100
Ocular dryness	50	25
Conjunctivitis	2	43-80
Epistaxis	52	25
Dry nasal mucosa	70	20-50
Dry skin	82	25-50
Brittle nails	10	Unknown
Paronychia	-	Rare
Hair loss	4	10-20
Epigastric pain	20	
Nausea	12	
Vomit	2	
Diarrhea	2	
Muscle pain	14	15-35
Arthralgia	10	15-35
Mood changes	30	
Depression	4	less than 1

Table 4: Descriptive analysis of the laboratory tests according to the visit

	Initial visit	Intermediate visit	Final visit	p
HBV	14,5 ± 1,3	14,5 ± 1,1	14,5 ± 1,4	0,914
WBCV	7183,6 ± 1716,5	6815,8 ± 2873,3	6818,4 ± 1702,5	0,087
PLAT	251380,0 ± 45034,2	264085,1 ± 61876,0	251163,3 ± 70267,9	0,084
GOT	18,4 ± 4,4	23,7 ± 7,7	24,0 ± 9,3	<0,001
GPT	15,3 ± 8,6	17,8 ± 10,4	18,8 ± 10,5	<0,001
FAV	107,1 ± 61,7	99,6 ± 52,4	98,3 ± 50,1	0,371
GGT	19,6 ± 8,3	25,1 ± 14,8	26,0 ± 13,2	<0,001
GLU	85,9 ± 7,8	86,1 ± 7,6	87,2 ± 8,7	0,371
TC	147,5 ± 27,6	168,0 ± 30,0	167,0 ± 32,8	<0,001
LDL	86,2 ± 22,5	105,4 ± 24,5	100,3 ± 28,1	<0,001
HDL	48,4 ± 11,1	45,1 ± 9,8	46,7 ± 14,0	0,098
TRIG	70,3 ± 32,6	91,3 ± 42,0	96,8 ± 60,4	<0,001

erature for the standard isotretinoin regarding its efficacy, safety and tolerability.

The present study is of great practical applicability in the dermatologist's daily life, for the equivalence of similar and standard isotretinoins regarding their safety and effectiveness is often a source of doubt for both patients and even dermatologists.

Limitations of the present study include: the small number of participants and the study design (open, non-controlled or comparative and non randomized).

CONCLUSION

Despite the limitations of the present study, it was possible to conclude that the evaluated similar isotretinoin was equally effective, safe and well tolerated when compared to the literature data on the standard product, a fact that adds great value to the dermatologist's daily routine. ●

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Original Articles

Treatment of rosacea with dual-band wavelength intense pulsed light in a single shot

Tratamento de rosácea com duas faixas de comprimento de onda de luz intensa pulsada num mesmo disparo

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ABSTRACT

Introduction: Rosacea is a chronic disease that usually manifests as flushing, persistent facial erythema, telangiectasia, papules and pustules. Intense Pulsed Light (IPL) is reported for treatment of vascular lesions of facial telangiectasia rosacea.

Objective: To assess clinical and dermoscopy improvement of facial erythema and flushing, and the clearing of vessels to dermoscopic after using IPL.

Methods: Nine patients were selected, with facial telangiectasic rosacea, aged between 36 and 59 years, with skin types I to III, without any treatment in the past six months. The treatment consisted in applications of the Intense Pulsed Light(IPL) with dual-band, 535-680 nm and 860-1200 nm, in one single shot. To favor the target hemoglobin, there is a greater protection for the skin. Three sessions were conducted within the interval of 1 month.

Results: After treatment, 87.5% of patients noticed reduction in flushing and telangiectasia. Adverse events were minimal and transient. To date no treatment was complete for telangiectasia rosacea.

Conclusions: This study demonstrated that treatment with IPL technology using "dual-band" is effective in obtaining a large (>75%) clinical improvement in 50% of patients and moderate improvement (51% to 75%) in 28.6% of patients.

Keywords: *rosaceae; intense pulsed light therapy; telangiectasia, erythema*

RESUMO

Introdução: *A rosácea é doença crônica que geralmente se manifesta como flushing, eritema facial persistente, telangiectasias, pápulas e pústulas. A luz intensa pulsada é usada para tratamento de lesões vasculares de rosácea telangiectásica facial.*

Objetivos*: Avaliar a melhora clínica e dermatoscópica do eritema facial e rubor, e o clareamento dos vasos à dermatoscopia após o uso de luz intensa pulsada.*

Métodos*: Foram selecionados nove pacientes, com rosácea telangiectásica facial, com idade entre 36 e 59 anos, e fototipo I a III, sem qualquer tipo de tratamento nos últimos seis meses. O tratamento consiste em aplicações da luz intensa pulsada com dual-band, 535-680nm e 860-1200nm, no mesmo disparo. Por favorecer o alvo da hemoglobina, há maior proteção para a epiderme. Foram realizadas três sessões a intervalos de um mês.*

Resultados*: Após o tratamento, 87,5% dos pacientes notaram redução de flushing e telangiectasias, e os médicos avaliadores, grande (> 75%) melhora clínica em 50% dos pacientes e melhora moderada (51%-75%) em 28,6%. Os efeitos adversos foram mínimos e transitórios.*

Conclusões*: Até o momento nenhum tratamento mostrou-se completo para a rosácea telangiectásica. Este estudo demonstrou que o tratamento com luz intensa pulsada utilizando a tecnologia dual band é eficaz no tratamento da rosácea.*

Palavras-chave: *rosácea; terapia de luz pulsada intensa; telangiectasia; eritema*

INTRODUCTION

Rosacea is a chronic disease that usually manifests as flushing, persistent facial erythema, telangiectasia, papules and pustules. Intense Pulsed Light (IPL) is described for the treatment of vascular lesions of facial telangiectasic rosacea. [1]

Intense Pulsed Light is a polychromatic, non-coherent light of broad electromagnetic spectrum, capable of emitting wavelengths between 390nm and 1,200nm.[2]

Its principle is based on the absorption of photons by endogenous or exogenous chromophores within the skin. This energy transfer to these target-chromophores generates heat and subsequent destruction of specific structures of the skin through a process called selective photothermolysis. The wavelength should be selected depending on the target-chromophore's peak absorption and the pulse's duration, which should be shorter than the thermal relaxation time. This limits the diffusion of heat and minimizes the damage to the surrounding structures. [3]

The possibility of using different combinations of wavelength, pulse duration, time lapse between shots and fluences allows the use of IPL devices to treat various dermatological conditions, including rosacea.[2]

Rosacea is a chronic dermatosis of unknown etiology characterized by erythema, telangiectasia, papules and pustules.[4,5]

In the present study, the authors used the Omnimax® platform (Sharp Light, Israel), which contains the IPL tip with double absorption band for hemoglobin (535-680 and 860-1,200nm).

METHODS

Nine volunteers were selected (8 women and 1 man, aged between 36 and 59 years, with Fitzpatrick skin phototypes I-III). The following inclusion criteria were established: patients with telangiectasic rosacea (erythema, flushing, telangiectasias) without ambulatorial dermatological treatment for the previous six months. Exclusion criteria were: immunosuppression, neurological or immunological diseases, pregnancy, any local sign of infection or inflammatory skin disease, previous formation of hypertrophic scars or keloids, current use of aspirin or nonsteroidal anti-inflammatory, exposure to UV radiation in the previous four weeks and facial rejuvenation procedures (such as peels, acids, lasers or surgery) in the previous six months. The patients were recruited at the Dermatologic Clinic of the Faculdade de Medicina do ABC, with all having signed the free and informed term of consent. The study was approved by the Institution's Ethics Committee.

Photographs were taken at the beginning of each session and 30 days after the end of treatment, using a digital camera Nikon/Coolpix L320 equipped with ring flash attached to the lens (Lens-shift VR/16.1 megapixels). All photographs were taken in raw format under the same conditions and camera settings. Standardized points of view were used (facial at 90°, and right and left oblique at 45°).

Dermoscopic images were obtained before each session, without using flash, with special dermoscopic lenses (DermLite Hybrid, California, USA) attached to the Sony Cyber-Shot 14.1 megapixels Carl Zeiss lens, with the left medium pupillary line set at standardized 4cm below the lower eyelid, zoom at 3.3 and half of the intensity of the polarized dermoscope's light.

The used device was the Omnimax® (SharpLight, Israel), set on IPL, with two cut filters in the same shot (535-680nm and 860-1,200nm). The wave spectrum between 535 and 680nm primarily affects vascular lesions, and is well absorbed by melanin, meaning that it is also effective in the treatment of pigmented lesions. In turn, the spectrum between 860 and 1,200nm comprises intermediate levels of absorption by the melanin and hemoglobin, thus increasing its heating. Given that longer wavelengths penetrate deeper, this range is more effective for treating larger and deeper lesions. In the 680-860nm wavelength range, the laser shot does not act, increasing the epidermal protection due to the fact that the absorption of oxyhemoglobin and deoxyhemoglobin in this spectrum is relatively weak, even though melanin absorption is significant.

All patients were informed on the need for conducting three sessions with an interval of 30 days. Intense pulsed light was performed with fluences varying from 10 to 20 J/cm2, with pulse duration of between 12 and 25 ms, in one or two passes, depending on the severity of the clinical picture and the tolerance of each patient.

Prior topical anesthesia was not used in order to avoid constriction of the vessels. Patients were instructed to use sunscreen SPF 60 and oily lotion topically for protecting the skin between sessions of IPL.

Potential adverse effects, such as erythema, hypo and hyperpigmentation, blisters, purpura and scars were evaluated in each session using a scale to indicate the intensity of the alteration (none, mild, moderate or severe).

At the end of the study, a questionnaire was used to assess the treatment's efficacy using a scale based on the guidelines of the National Rosacea Society Expert Committee. [6] The symptoms evaluated were flushing, persistent erythema, telangiectasia, burning sensation and overall improvement of the skin. The ratings attributed ranged from 0 to 3 (0 - unchanged, 1 - mild, 2 - moderate, 3 - intense).

The before and after the treatment dermoscopic images were analyzed by two physicians, who observed the general development of the patients' clinical picture according to the following scale: <25%, 25-50%, 51-75% and above 75% improvement of the signs.

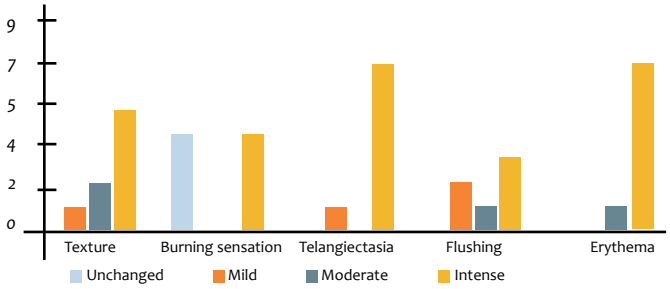
RESULTS

The study patients answered the questionnaire using a scale based on the guidelines of the National Rosacea Society Expert Committee, [6] in which a comparative assessment of the treatment's efficacy was carried out for the following variables: *texture*, *burning sensation*, *telangiectasia*, *flushing* and *erythema*.

The symptoms with most obvious improvements were *erythema* and *telangiectasia*, for which seven of the patients reported significant improvement. Opinions about the skin's *texture* and *flushing* were mostly positive, indicating there had been mild,

moderate or intense improvement of the picture. *Burning sensation* was reported by 50% of patients (Graph 1).

Two physicians also individually evaluated the results through before and after the treatment photographs. The following scale was used: <25%, 25 to 50%, 51 to 75% and >75% improvement. In this analysis, the results were evaluated considering the general appearance of the patient, without differentiating the signals.



Graph 1: Patient's opinion by symptom

Of the analyzed cases, 50% were classified as having had more than 75% of improvement in the overall clinical picture, followed by the second highest improvement rating (51-75%), which has been achieved by 28.6% of patients who underwent treatment with IPL. Only 3 of the 14 analyzed photographs received ratings lower than 50% of clinical improvement (Figures 1 to 4) (Graph 2).

The results of only 8 patients were analyzed, as there was one desistance after the initial selection, due to pain and discomfort during the procedure.

DISCUSSION

A proven effective and safe treatment option for rosacea is the use of light-based technology. [1] The present study was based on the use of phototherapy with IPL operated within two light band ranges for facial rosacea in one single shot.

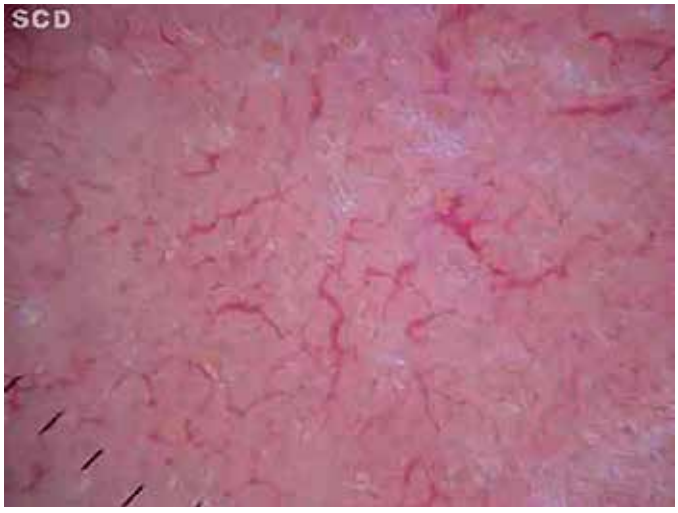


Figure 1: Dermoscopy with telangiectasia before the treatment

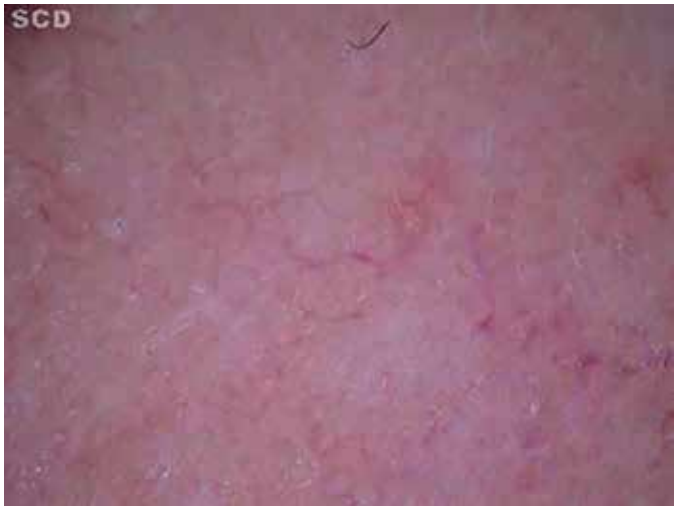
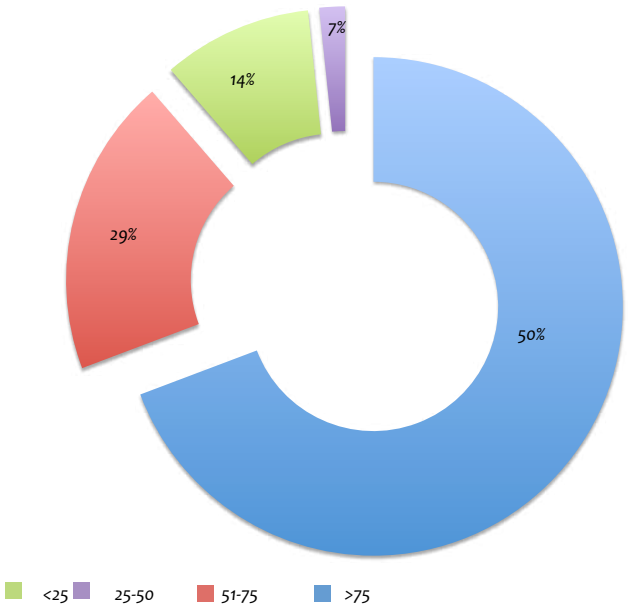


Figure 2: Evident improvement in telangiectasia to dermoscopy after IPL sessions

Figure 3: Patient with telangiectasia rosacea before the treatment

Figure 4: Patient with clinical improvement of the facial telangiectasic rosacea picture after the treatment with dual band IPL



Graph 2: Improvement according to the physicians' assessment

Intense pulsed light technology was designed to treat vascular and pigmented lesions, however it has other applications, such as hair removal and photorejuvenation. The fact that it can generate single or multiple synchronized pulses, coupled with the possibility of varying the duration of these shots, makes it a very versatile tool. [5]

In the literature, Mark et al. [7] demonstrated reductions of 29% in telangiectasia and 21% in erythema after 5 sessions of IPL using a 515nm filter and single pulses with duration of 3ms. Similarly to what was done in the present study, Taub et al. performed a trial with approximately 500 patients, who underwent sessions of IPL or laser associated with bipolar radiofrequency. Based on medical evaluations, one month after the third sessions the patients had their *erythema* reduced to 1.21 from 2.38, and *telangiectasia* to 0.86 from 1.64 (maximum rating = 3). Moreover, they obtained an evident improvement in the skin's *texture*. [8] As compared to that trial, the present study yielded similar outcomes, with a significant improvement in symptoms of *erythema*, *telangiectasia* and in the skin's *texture* after the sessions.

With a smaller sample (34 patients), another article has demonstrated the efficacy of IPL. After 4 sessions, the *erythema* and *severity* scores, as well as the photographic evaluation improved significantly, with the results being maintained in a reassessment carried out six months after, with minimal and transient side effects. [5]

In another study, the analysis of 60 patients bearers of telangiectasia associated with rosacea who underwent treatment with IPL using a wide wavelength spectrum (ranging from 515 to 1,200nm) and different filters (515, 550, 570 and 590nm) during a period of approximately 2 years, it was possible to observe improvement in 77.8% of the lesions. [9]

CONCLUSIONS

The present evaluation showed that the IPL treatment was effective in obtaining intense improvement (>75%) in the clinical aspect of 50% of patients, and moderate improvement (51-75%) in 28.6% of patients, with minimal and transient side effects.

Treatment with IPL increases the amount of superficial collagen and elastic fibers in the dermis. This is due to the selective absorption of light by the water contents in the tissues, increasing the conduction of heat around the collagen, therefore increasing its production. Furthermore, there is increased production of fibroblasts by the photothermal effect. This mechanism explains the better results reported by patients younger than 40, as evidenced by Lim et al. [1]

By using this laser type, it is possible to destroy abnormal blood vessels, reduce the inflammation and the number of active sebaceous glands, in addition to block the altered keratinization process. All these effects contribute to the overall improvement of the rosacea's clinical picture. [8]

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Original Articles

Cosmetics consumption behaviour among men and women and the importance in products indication and treatment adherence

Comportamento de homens e mulheres quanto ao consumo de cosméticos e a importância na indicação de produtos e adesão ao tratamento

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ABSTRACT

Introduction: Cosmetics stands outs in commerce, not only in Brazil but also worldwide. There is great need for knowledge on buying motivations of consumers for the development of better-targeted products and improved adhesion to dermatological treatments.

Objective: To know the cosmetic consumption habits and provide a link from the pharmaceutical with the medical area.

Methods: An analytical observational study, cross-sectional, was conducted by questionnaire.

Results: Main change in male skin is oiliness; in women, besides oiliness, there is concern with blemishes. The consumption of hygiene products is unanimous in both sexes. Women are more concerned with the treatment and prevention of sun damage. The vast majority of women use anti-acne products and makeup. Hair products have the same sales trend for both men and women, but this is not observed among products for skin.

Conclusions: Men and women have different motivations when buying cosmetics. The way consumers relate with products has changed dramatically and they are seeking to express their individuality in society. This reflects a need for medical knowledge of such motivations in order to improve patients' adherence to treatment.

Keywords: cosmetics; habits; questionnaires; data collection; behavior

RESUMO

Introdução: *Os cosméticos apresentam-se em destaque no comércio não só no Brasil, mas mundialmente. Há grande necessidade do conhecimento das motivações de compra dos consumidores para o desenvolvimento de produtos mais bem direcionados e melhora na adesão de tratamentos dermatológicos.*

Objetivo: *Conhecer os hábitos de consumo cosmético e fornecer um link da área farmacêutica com a área médica.*

Métodos: *Estudo observacional analítico do tipo transversal, realizado por meio de questionário.*

Resultados: *A principal alteração na pele masculina é a oleosidade, nas mulheres além dessa há a preocupação com manchas. O consumo de produtos de higiene é unânime em ambos os sexos. As mulheres se mostram mais preocupadas com o tratamento e prevenção de danos solares. A maioria das mulheres utiliza produtos antiacne e maquiagens. Produtos para cabelo apresentam a mesma tendência de vendas tanto para homens quanto para mulheres, não sendo o mesmo observado entre os produtos para pele.*

Conclusões: *Homens e mulheres apresentam diferentes motivações no momento de adquirir produtos cosméticos. A forma de relacionamento do consumidor com os produtos tem mudado expressivamente, e ele vem buscando expressar sua individualidade perante a sociedade. Isso reflete a necessidade do conhecimento médico de tais motivações a fim de melhorar a adesão dos pacientes ao tratamento.*

Palavras-chave: *cosméticos; hábitos; questionários; coleta de dados; comportamento*

INTRODUCTION

The study of consumer behavior focuses on understanding the habits underpinning their actions in different situations involving purchases and consumption. Nevertheless, analyzing their behavior isolatedly is not enough, and understanding why people act in a certain way becomes crucial. Consumers of different products have different characteristics, meaning that it is critical to understand the desires and needs of consumers in different market segments in light of the relevant product.[1]

Currently, cosmetic products stand out in the market place not only in Brazil, but also worldwide. This is due to the more active and steady participation of these products' consumers, who began to use them more often. Due to the high exposure – both in the media and in homes – this type of product became the subject of academic and market research within several areas of study, in special in marketing.[2]

The cosmetics industry is composed of three major segments: cosmetics (linked to the concept of products for improving the appearance), personal care and fragrance products.[1]

The Brazilian cosmetic industry has grown considerably, having surpassed France and Japan, and becoming the world's second largest market for cosmetic products in 2009. In light of this fact, it became important to understand whether the consumers' motivation is strictly related to improving their appearance and beauty or it is also associated with the improvement in their quality of life and skin's health.

There is a big conjuncture change in the way people relate with their personal image and there has been a steady growth of this consumer sector in the cosmetic industry. In addition, the increased access of male consumers to the cosmetic market reflects a possible improvement in their quality of life, since many health problems directly related to the skin are ignored by that consumer segment due to their resistance to treatment with cosmeceutical products.

When seeking to understand consumer behavior, it is necessary to bear in mind what is underpinning that behavior, who is involved and which is the socioeconomic context. Behavior is closely related to stimuli from different sources, and the consumer's response is processed according to the context. For Martins,[3] the factors that motivate consumers to buy can be distributed into five different groups: anthropological or cultural, environmental, organic, psychological, and socioeconomic.

In the 80's, a reconstruction of the male and female models took place through the symbology involving their clothing, gestures, attitudes and the relationship with one's own body and sexuality; there was a change in the pattern of behavior linked to gender. In the face of the women's achievements, men ended up losing their maximum function of being the family provider – inherited from a patriarchal society – and began to engage in a process of transformation of their social *persona* and intimacy, becoming more participating at home and capable of progressively sharing responsibilities with women.[4]

Furthermore, men currently believe that being apparently cleaner, neater and well dressed implies better job opportunities, in addition deriving satisfaction from the perception that they are building their own image. While men are concerned with their appearance, they can acknowledge their weaknesses, their susceptibilities and show that they need care – something rarely seen among men up until the mid-80's. Their concern for health and beauty is such that the cosmetics industry saw a large increase in the demand for products and started to develop lines specific for the male segment.[5]

METHODS

Aiming at understanding the consumption habits regarding the cosmetic products market, an analytical observational cross-sectional study was carried out. After receiving the approval by the Research Ethics Committee CEP/FCFRP n.303, a mixed questionnaire was prepared with 15 closed-ended questions and 1 open-ended question. The questionnaire was applied to the studied individuals, with questions about their social status, cosmetic consumption culture and some health habits, such as use of sunscreen.

The study population consisted of male and female consumers of cosmetics. Individuals who did not reside in Brazil were excluded. The sampling method used was the stratified random group sampling of male and female individuals. All participants answered all questions in the questionnaire. The obtained answers were validated, having their consistency and integrity confirmed.

RESULTS

The questionnaire comparing the purchasing motivations, as well as the way through which consumers interact with cosmetic products was applied to the population study, which consisted of 101 people (49 men and 52 women). The participants' ages concentrated in the range of 18 to 35 years, characterizing the population as young.

As for the participants' income distribution, it was possible to notice a strong concentration in the group earning up to six times the minimum wage (R$ 788,00 in 2015), which may be related to the fact that respondents were mainly young people and adults up to 35 years old (Table 1).

Respondents were asked about physical characteristics regarding their skin and hair. It was possible to observe a greater number of male respondents with oily skin and normal, short and brown hair. As for women, it was possible to note that most of them classified their skin as oily, and their hair as mixed, brown and long. Overall, it was possible to notice that the respondents have mainly oily or mixed hair and skin, a very

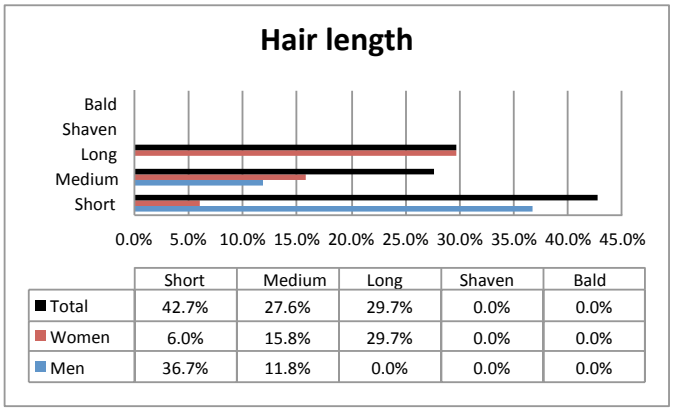
Table 1: Interviewees' distribution by income group

Income	Men	Women	Total
Less than 3 minimum wages	15,8%	26,7%	42,6%
From 3 to 6 minimum wages	16,8%	11,9%	28,7%
From 6 to 10 minimum wages	9,7%	8,8%	18,8%
More than 10 minimum wages	5,8%	3,9%	9,9%

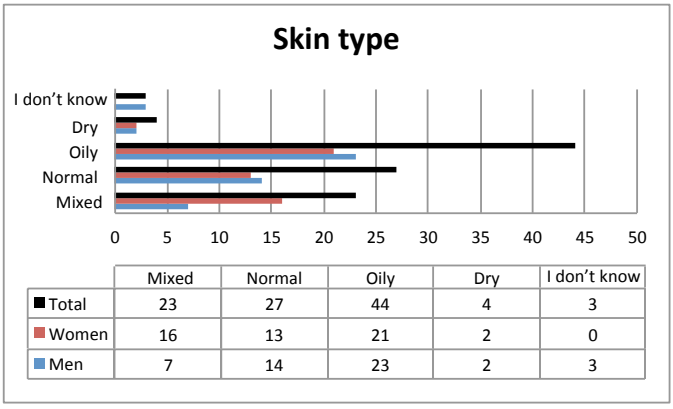
frequently present characteristic among Brazilians. The data on the skin and hair are in Graph 1.

This type of information is important for the dermatologist, in conjunction with a pharmacist, to decide on the best treatment for the individual. This becomes even more relevant in light of the fact that different skin or hair types have different physical and chemical characteristics and composition, which will even influence the form of absorption of the active principles. Thus, dermatological prescriptions can be made more personalized and efficient.

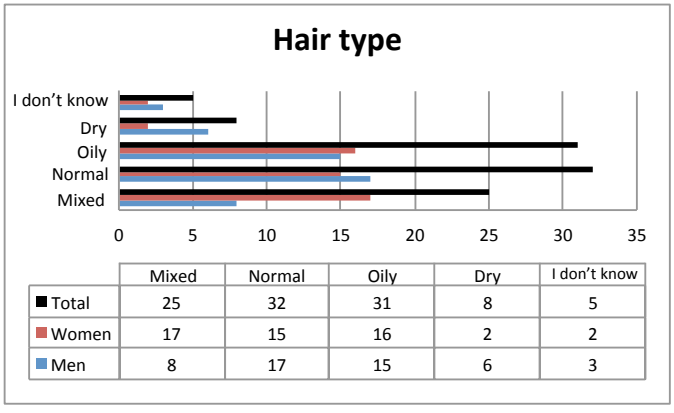
In order to understand the differences in the motivations for purchasing cosmetic products, two questions were asked in the questionnaire: "What are you searching for when you buy a cosmetic product?" and "What do you take into consideration when choosing a cosmetic product?" Although the questions seem very similar, they are important to analyze what consumers conceptually expect from a cosmetic product versus what makes consumers to look for a specific, already commercially avaiable product. The data collected are present in Graphs 2 and 3.



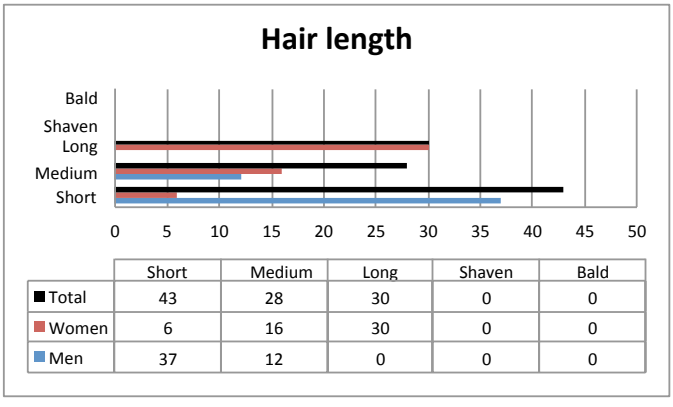
	Short	Medium	Long	Shaven	Bald
Total	42.7%	27.6%	29.7%	0.0%	0.0%
Women	6.0%	15.8%	29.7%	0.0%	0.0%
Men	36.7%	11.8%	0.0%	0.0%	0.0%



	Mixed	Normal	Oily	Dry	I don't know
Total	23	27	44	4	3
Women	16	13	21	2	0
Men	7	14	23	2	3



	Mixed	Normal	Oily	Dry	I don't know
Total	25	32	31	8	5
Women	17	15	16	2	2
Men	8	17	15	6	3

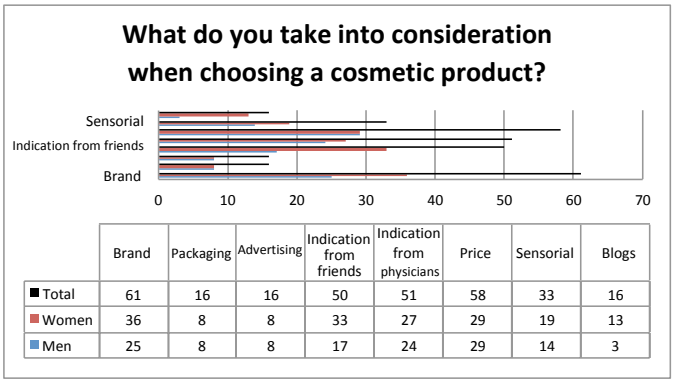


	Short	Medium	Long	Shaven	Bald
Total	43	28	30	0	0
Women	6	16	30	0	0
Men	37	12	0	0	0

Graph 1: Distribution of the interviewees' skin and hair characteristics

	Well-being	An improvement in the appearance	Prevention	Hygiene	Treatment
Total	26	28	6	11	30
Women	14	13	5	1	19
Men	12	15	1	10	11

Graph 2: Consumers' motivations when buying cosmetic products



	Brand	Packaging	Advertising	Indication from friends	Indication from physicians	Price	Sensorial	Blogs
Total	61	16	16	50	51	58	33	16
Women	36	8	8	33	27	29	19	13
Men	25	8	8	17	24	29	14	3

Graph 3: What influences consumers in their choice of cosmetic products

When questioning about what makes consumers to look for a specific cosmetic product, the following picture was obtained: women are more influenced by brands, followed by indication from friends and price, while men are mainly influenced by price, brand and medical indication (Graph 3).

Regarding customer loyalty, the majority of women were little loyal to brands, enjoying varying manufacturers. On the other hand, among men this trend was balanced, according to the data presented in Graph 4.

As part of the questionnaire, respondents should mention up to three brands of cosmetic products that they could recall at the moment. Roughly 60 brands were referred, with 43 arising only once or twice in the sample space. Brands that were mentioned three or more times are shown in Graph 5.

The L'Oreal group stands out as the leader in number of citations, as well as its various cosmeceutical product lines, such as Vichy and La Roche-Posay. Brazilian brands were poorly recalled; with only Natura and O Boticário groups being cited.

The main facial alteration that bothered male respondents was oiliness. Women described cases of oiliness, however problems with spots are also among the main complaints of the interviewees, despite being young. The data is depicted in Graph 6.

Respondents mentioned all cosmetic products that were in use at the time of the study or had been previously used at any stage of their lives. For a better analysis of the data, products for hair, skin and personal care were segregated. Respondents could choose any number of products (it is important to note that there is a greater variety of cosmetic products used by women). The data obtained are in Graphs 7, 8 and 9.

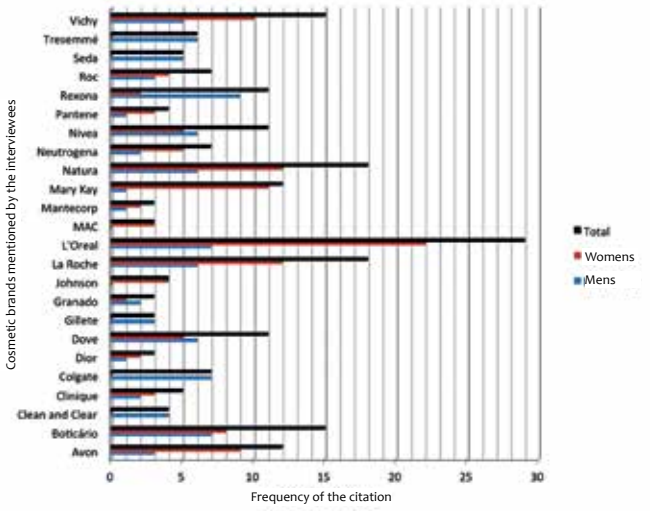
The presence of personal care products is very significant in both genders. Regarding products for the hair, it was possible to notice that men use a wide range of products. A result that has drawn attention is the intense use of hair conditioners by the male public – even in light of the fact that most have short hair. Men more commonly use hair styling creams and gels.

Women use hair moisturizing masks and fixing sprays in greater quantities. The use of lotions for hair loss by men is sporadic, mainly due to the fact that the studied public corresponded to young men, who do not usually seek treatment at the first signs of baldness. These individuals usually seek improvements in their appearance and while the actual problem does not fully arise, male consumers do not seek treatment.

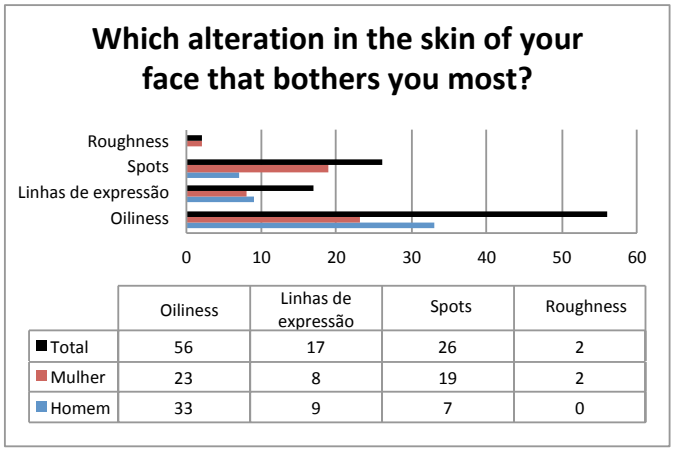
Graph 8 shows that the consumption trend is similar in both genders, nonetheless with different proportions, meaning

	Men	Women	Total
Various brands	24	38	62
The same brand	25	14	39

Graph 4: Consumers' loyalty to cosmetic brands

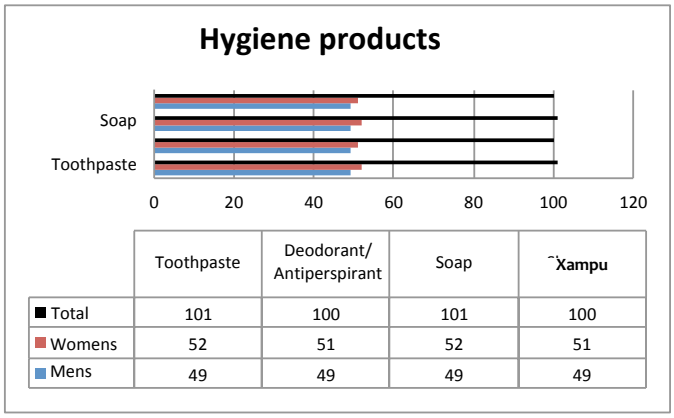


Graph 5: : Cosmetic brands mentioned more than twice by interviewees



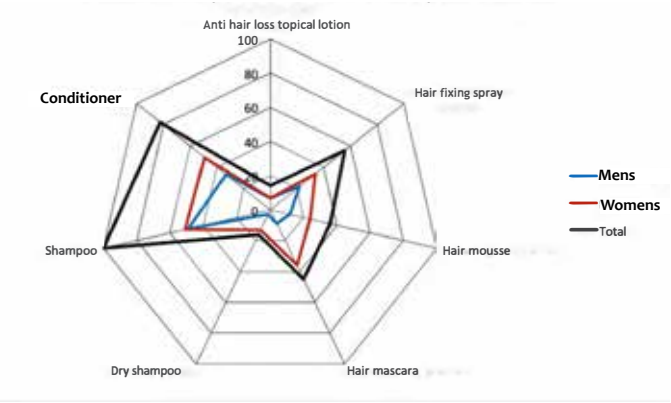
	Oiliness	Linhas de expressão	Spots	Roughness
Total	56	17	26	2
Mulher	23	8	19	2
Homem	33	9	7	0

Graph 6: Alterations in the interviewee's skin

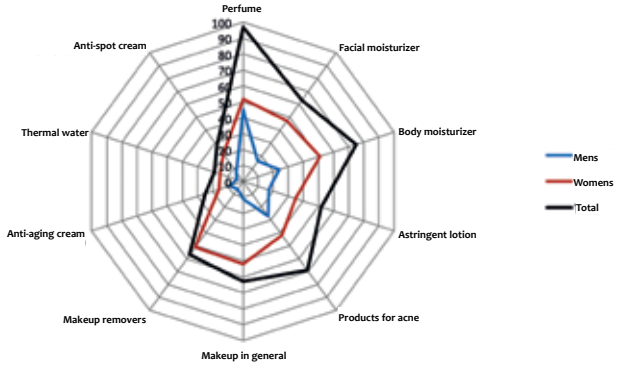


	Toothpaste	Deodorant/ Antiperspirant	Soap	¯Xampu
Total	101	100	101	100
Womens	52	51	52	51
Mens	49	49	49	49

Graph 7: Consumption of personal hygiene products in absolute values



Graph 8: consumption of cosmetic products for the hair



Graph 9: Consumption of cosmetic products for the skin

that men and women tend to purchase the same type of product for the hair, proportionally in greater or more modest quantities. The behavior observed regarding products for the hair is not the same in products for the skin. As shown in Graph 9, there were differences in consumption trends. Women, for instance, tend to consume much greater quantities of makeup, removers and facial moisturizers than men. There is a strong presence of perfumery in this type of consumption, with almost unanimous answers. The fact that more than 20% of men claimed to have already used some sort of makeup such as eyeshadows, correctives or bases is also noteworthy.

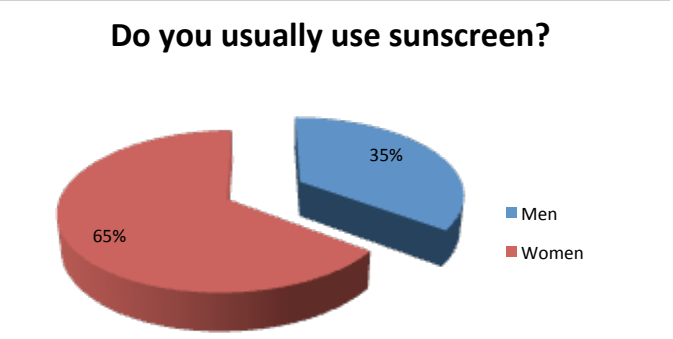
Another interesting finding relates to the use of products for shaving by men: 80% of respondents claimed to use shaving cream while only 49% claimed to use after shave lotions. In line with this, the development of product lines for shaving should focus on the production of shaving creams and / or increase the investment in improving the quality of after shave lotions in order to improve the acceptance of the latter by consumers.

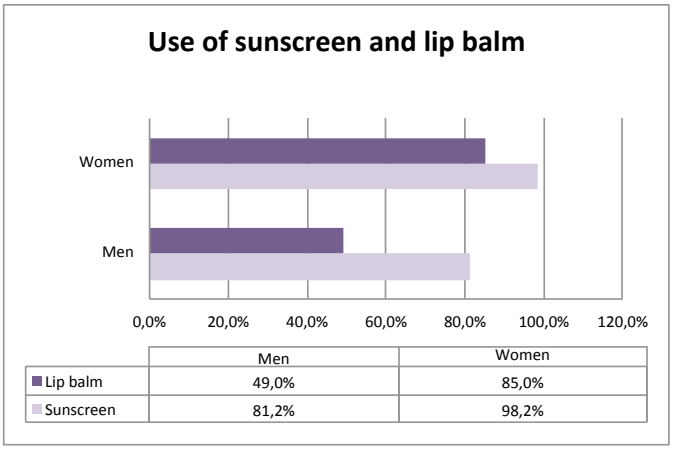
Regarding sunscreens, the questionnaire provides the following picture: women are more concerned, making more use of the products than men, as can be seen in Graph 10. A surprising finding is that roughly 20% of men claim they have never used sunscreens.

DISCUSSION

Based on the results obtained and described in the present study, it was possible to observe that in general men are concerned with improving their appearance, improving their well-being and receiving treatment, in this order of priority. On the other hand, women have receiving treatment as their main motivation, followed by improving their well-being and improving their appearance. These results confirm what is observed in the macro society, since the search for improved masculine appearance is mainly related with men's lack of self confidence towards how to present themselves regarding a new job, their social status or partner. The questions related to the motivation for purchasing are crucial to understand consumer behavior, however they become even more important as tools for the dermatologist to understand how their patients behave. For example, it is possible to observe that the brand, price and medical indications are the three main considerations at the moment of obtaining a cosmetic product. Thus, these are three important points relevant to the dermatologist at the moment of the prescription.

Moreover, treatment, well-being and improvement of the appearance are the most popular factors when consumers are purchasing cosmetics. The understanding of the consumer's profile by dermatologists, combined with the knowledge of the trends in the cosmetic market, is extremely important for the prescription to be more precise, according to the patient's profile.





	Men	Women
Lip balm	49,0%	85,0%
Sunscreen	81,2%	98,2%

Graph 10: Interviewees' sun protection habits.

Men seek to build a receptive self-image that is capable of assisting them to achieve their goals. In addition, lifestyle has been disconnected from sexual orientation, increasingly becoming an expression of their individuality.[5] In turn, women are concerned with the future impacts that a certain alteration in their skin can cause, seeking cosmetic products that are not only associated with an improvement in the appearance, but also with the correction and / or prevention of specific changes, such as formulations that reduce the skin's oiliness, for example.

Although women complain about spots, they do not make substantial use of creams for treating them, usually making more use of products for acne beforehand, despite the fact that this type of alteration is more common in men. This consumption is driven by their vanity, suggesting that women pay more attention to changes in their skin, noticing them as soon as they arise.[6] This information is relevant to the medical public for women often do not have knowledge about possible treatments for the spots about which they complain. Moreover, these cutaneous alterations may have different origins and only an effective dermatologic examination can lead to an effective treatment.

The cosmetic product brand appeal became evident with the findings about the purchase motivation. This is in line with studies indicating that advertising is one of the main factors influencing the purchase of cosmetic products[7] combined with the perception of body image. However, the influence of price, coupled with the fact that women take into account indication from friends or blogs at the time of purchase, show that they may no longer maintain their loyalty to the brand in case they find a better product offered by a competing manufacturer.

A more loyal and conservative behavior is observed among men, meaning that from the moment they find the product they were looking for, they halt the search process. This confirms the notion that men are always practical, even when taking care of their appearance, while women prefer to prolong the time leading to the moment of choice.[8] This shows that, despite the fact that men are approaching an area that has been traditionally considered exclusive of women, gender differences still linger.

It is important to note that brands that are more present in supermarkets and drugstores, such as Nivea, Dove and Rexona, are more remembered by men than by women, with the same being observed regarding personal care products. Tres-Semmé is an essentially feminine brand and advertising focusing on this public, however it was mentioned only by men. Brands found in supermarkets are the most remembered by the male audience. This is in line with previous studies showing that men often buy their cosmetic products in supermarkets, pharmacies and drugstores.[9]

Women seem much more likely to spend more on cosmetic products, and prefer to follow suggestions from friends rather than medical indications, with the opposite being observed among men. These behaviors are very present in today's society, nonetheless it is possible to notice a growing number of blogs, magazines and Internet sites responsible for spreading the use of cosmetic products among the male audience. This is a trend already established in Europe and that will not take long to reach the conceited Brazilian masculine market.[10]

It is important to note that knowledge of this trend is critical to dermatologists, with a view to a possible dissemination channel for dermatological knowledge. Physicians should be alert to possible Internet websites that can assist with correct dermatologic information.

Although Brazil is considered the second largest cosmetic products consumer market and the world leader in growth in this sector, few national companies were recalled. These companies should explore strategies and specificities in the composition of the skin and hair of Brazilians, providing specialized products.[11] Notably, products developed abroad cannot fully be adapted to the skin of Brazilian consumers due to the particularities of the population.

Understanding which brands the consumer market prefers helps to prescribe cosmeceutic products, and increases patients' adherence to the treatment. Some brands, such those of the L'Oreal group, make use of clinical efficacy studies, which may partly explain their intense presence among the cited brands *vis a vis* their relatively high cost. Knowing how the product is manufactured and the company's integrity, combined with the preferences of the consumer market, can assist towards a more effective adherence to the treatment.

Correlating data from the present study with previous ones[12], it was possible to observe that the Brazilian cosmetic industry needs to invest in strengthening its identity through marketing strategies, pricing policies that are aligned with what consumers attribute to the products, in addition to market knowledge. In this manner, the Brazilian companies will be able to reach more consumers and supply cosmetic products consistent with the local population.

Personal care products have almost unanimous use among the population. This cosmetic market segment is very lucrative and affects the population in an almost homogenous way. The industry as a whole, and in special research and development teams, should be aware of this fact, leveraging opportunities within this sector.

Men reported the use of products that are traditionally considered feminine, such as makeup for instance. This finding demonstrates a disconnecting trend in gender constructions. Men are more concerned with their overall presentation than with the premeditated judgment of their spending habits.

Additionally, when examining cosmetic products, the solar protection and impact it causes on the quality of life and long-term physical appearance cannot be left aside.[13] The use of sunscreen is the main prevention against more severe consequences, such as wrinkles or loss of the natural elasticity of the skin, in addition to skin cancer, which affects an important percentage of the Brazilian population, given that Brazil is a tropical country with high rates of sunlight incidence.

There are studies suggesting that the Brazilian population is aware of the risks associated with the exposure to the sun and the importance of photoprotection. Nevertheless, individuals struggle to create long-term habits of using sunscreen.[14] A fifth

of the male population stated to have never used sunscreen. This data is consistent with previous studies showing that men use sunscreen less frequently than women.[15] This kind of behavior reveals a challenge to be addressed: photoprotection awareness campaigns should target the male audience more efficiently and stimulate the habit of applying sunscreen.

Knowledge of such behavior is of significant importance to the dermatologist regarding skin cancer prevention campaigns, for instance. In addition, it helps the physician when prescribing sunscreens, for the approach to male audiences must be more concise and robust.

CONCLUSIONS

Men and women have different motivations when buying cosmetics. While the first are more concerned with the improvement in the appearance, along with a good cost/benefit ratio, the latter are more concerned with products associated with treatments and seek indications of new brands and products from friends. The way consumers relate to products has been changing dramatically, while people are seeking more authentic ways to express their individuality in society, regardless of pre-established standards.

It is possible to realize a pattern of behavior in which people increasingly become protagonists of their own wills – and not necessarily seek to appropriate ideals typical of certain social classes. Caused by a less polarized, hyper-connected and more democratic world, this behavior opens the possibility that people not only have access to common references regardless of their origin, class, gender or age, but also find ways to authentically voice their individuality.

Having the understanding of such data may seem exclusive to marketing activities, nevertheless it reveals a range of important information, enabling dermatologists to perform more modern and effective therapeutic approaches. Having knowledge of the patients' behavior means to understand which impacts a treatment can have in their quality of life. Moreover, this knowledge helps the physician to understand the more modern and humane therapeutic approaches.

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Original Articles

Laser toning e *drug delivery*: estudo-piloto utilizando laser *Q-switched* Nd:YAG 1064nm

Laser toning and drug delivery: a pilot study using laser Q-switched laser 1064nm

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ABSTRACT

Introduction: Laser toning technique is performed with the Q-switched Nd:YAG laser 1064 nm, aiming at stimulating neocollagenesis. The technique can also be associated with the application of suitable medicines for drug delivery, increasing its potential for skin permeation.

Objective: To evaluate the results of laser toning Q-switched Nd:YAG laser 1064 nm associated with drug delivery through a pilot study.

Methods: Four patients underwent four laser sessions with application of a formula for drug delivery or placebo, fortnightly.

Results: According to the photographic assessment, laser toning promoted improvement of acne, pores, wrinkles and sensitivity. When associated with the drug delivery, there was superiority in results. In clinical evaluation differences were observed only in the pores analysis (+11%). 75% of patients had acneiform eruption.

Conclusion: Results of this pilot study show that laser toning can be enhanced when combined with drug delivery.

Keywords: lasers; administration, cutaneous; collagen; hydroxyproline; hyaluronic acid; ascorbic acid

RESUMO

Introdução: *A técnica de laser toning é realizada com a modalidade Q-switched Nd:YAG 1064nm, com o objetivo de estimular a neocolagênese. A técnica também pode ser associada à aplicação de medicamentos apropriados para drug delivery, aumentando seu potencial de permeação cutânea.*

Objetivo: *Avaliar os resultados da técnica de laser toning Q-switched Nd:YAG 1064nm associada ao drug delivery por meio de estudo-piloto.*

Métodos: *Quatro pacientes realizaram quatro sessões do laser com aplicação de uma fórmula para drug delivery ou placebo, em intervalos quinzenais.*

Resultados: *Segundo a avaliação fotográfica, o laser toning promoveu melhora da acne, poros, rugas e sensibilidade. Quando associado ao drug delivery, houve superioridade nos resultados. Na avaliação clínica observaram-se diferenças apenas na análise de poros (+11%). 75% dos pacientes apresentaram erupção acneiforme.*

Conclusão: *Os resultados deste estudo-piloto demonstram que o laser toning pode ser potencializado quando associado ao drug delivery.*

Palavras-chave: *lasers; administração cutânea; colágeno; hidroxiprolina; ácido hialurônico; ácido ascórbico*

INTRODUCTION

The transportation of drugs through the skin surface has been receiving increasing attention within various medical specialties, as it is a non-invasive, safe, effective and easy to access method. This administration route avoids first-pass metabolism in the liver and degradation of the drug in the gastrointestinal tract, which is crucial for many medications.[1]

In dermatology, the topical route for delivery of drugs is very important. However, the bioavailability of most drugs varies from 1% to 5%, and many do not reach the depth necessary to act on the target tissue. [2] For this reason, drug delivery techniques via transepidermal route – for instance, facilitated by lasers – are being continuously studied and improved.

The 1,064nm Q-switched Nd:YAG laser was one of the first non-ablative lasers used for rejuvenation and facial resurfacing with clinically and histologically proven results.[3] It can also be used in the treatment of hyperpigmentation, rejuvenation, tattoo removal, hair reduction and in the treatment of scars.[4] The laser toning technique is performed with Q-switched laser, with wave pulses in the magnitude of nanoseconds, aimed at stimulating dermal fibroblasts to engage in neocollagenesis. Multiple passes are performed at a low fluence.[5] The technique provides improved tone and texture of the skin, reducing pores, sebum secretion, rhytids and dyschromias, in addition to promoting drug delivery. [6]

The laser toning technique employing the 1,064nm quality (Q)-switched Neodymium:Yttrium-Aluminum-Garnet (Nd:YAG) laser associated with the application of medications suitable for drug delivery immediately after the procedure, was assessed in the present pilot study.

METHODS

Four female patients aged between 39 to 54 years, with Glogau aging grades from II to III and Fitzpatrick phototypes II to IV were selected. All ethical principles were observed in the research protocol and all patients signed a free and informed term of consent, agreeing to participate in the study.

In order to evaluate the outcomes of using the laser toning technique as a vector for drug delivery, four sessions were performed at fortnightly intervals, with the application of a specific dispensed formulation immediately after the laser, in two patients. The dispensed formulation contained: 5% Hyaxel®, 4% Hidroxiprolisilane C®, 5% DMAE Pidolato®, 6% Nano Vit C®, 4% Matrixyl 3000® in anhydrous fluid serum. In the other two patients, only the vehicle was applied as a placebo. The patients continued using the formulations (test or placebo) at home, throughout the duration of the study.

The laser toning technique was performed with the 1,064nm Q-switched Nd:YAG (neodymium-doped yttrium-aluminum-garnet), Etherea® platform (Vydence Medical, São Carlos, São Paulo, Brazil) with the 7mm tip, 5Hz frequency, two passes across the face. The energy used in the first session was 600mJ, being increased to 900mJ in the second, and to 1,200mJ the third and fourth sessions. Roughly 2,500 laser passes were performed in each session.

The following evaluations were carried out: clinical analysis of photographs before and after 15 days of the last session by a blinded dermatologist physician; objective comparison using the Focco® device (Focco Fotografias, Fabinject, Taubaté, São Paulo, Brazil) for the parameters *wrinkles*, *pores*, *acne lesions*, *UV index* (photographs with UV lighting, coupled to the device for the analysis of hyperchromia, even when imperceptible to visible light), *sensitivity*, *spots,* and *vessels*; subjective evaluation using a patient satisfaction questionnaire. The device allows the progressive comparison of the patient's photographs during the experimental time, including graphs and separate analyzes of all the parameters described above.

RESULTS

According to the objective evaluation performed with the Focco® device, the laser toning procedure associated with the placebo formulation, led to the improvement of acne, pores, wrinkles and sensitivity, as shown in Graph 1. The parameters spots and UV index worsened (16.78% and 68.8% respectively). These results remained for 120 days after the last laser session. The photographs of the patients who underwent the placebo treatment are shown in Figure 1.

When the *laser toning technique + placebo* is compared with the *laser toning technique + drug delivery*, there was superiority of the combined technique in the parameters acne, stains, pores, texture and UV index, according to Graph 2. When comparing the laser toning technique in isolation with associated drug delivery, both showed similar results in the improvement of wrinkles and sensitivity. Photographs of patients who underwent treatment with drug delivery are shown in Figure 2.

The clinical evaluation evidenced improvement in all aspects, in all patients. Nevertheless, the difference between the test-group and placebo-group was observed only in the analysis of pores (+11%).

All patients reported improvement with the procedure in all assessed aspects. There was absence of complaints about the pain caused by the procedure, which was classified as painless for most patients (75%). However, 75% of them – in both groups – showed acneiform eruption, most probably related to the vehicle.

DISCUSSION

Several chemical and physical methods, such as lasers and microneedling, have been studied aiming at increasing the skin's permeability. [5] Lasers promote the permeation of drugs through three mechanisms: direct ablation; optical breakdown by photomechanical waves that transiently permeabilize the stratum corneum without removing it; and photothermal effect.[7, 8] The photomechanical waves promote the expansion of the lacunar spaces in the stratum corneum's lipids, creating pores for the permeation of molecules and also causing changes in cell membranes, thereby facilitating the transcellular route.[7, 9]

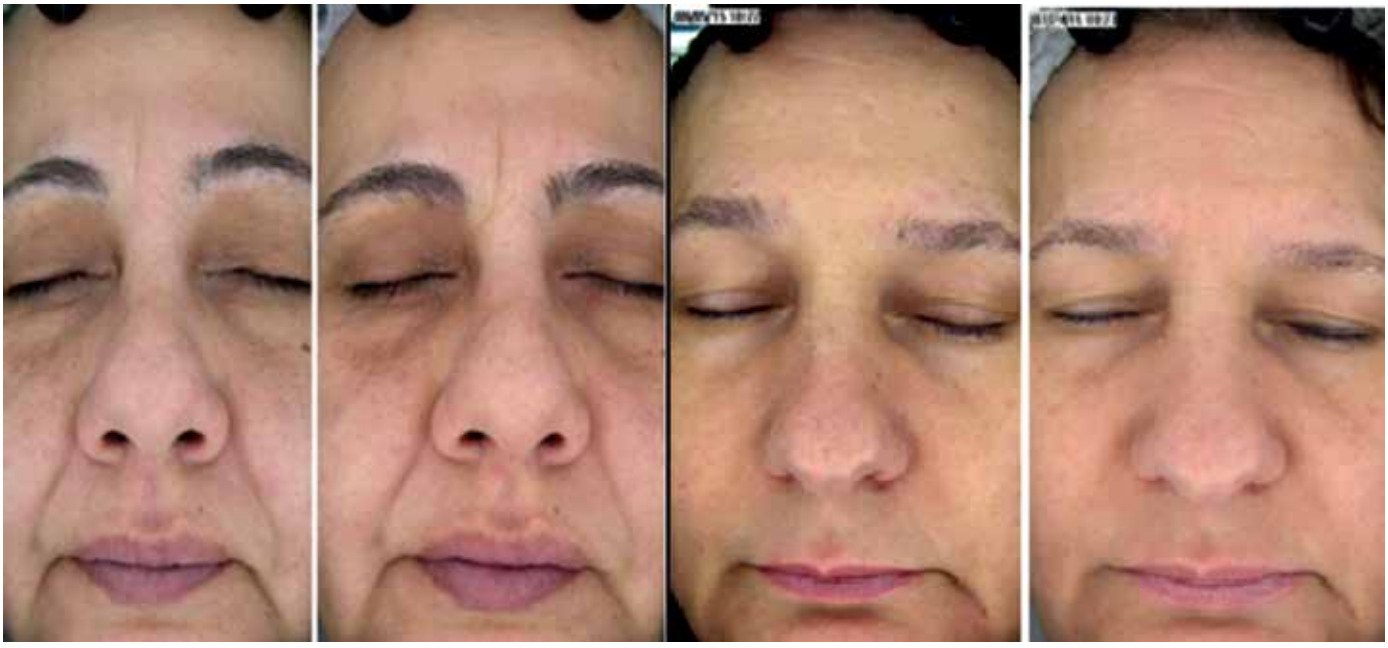
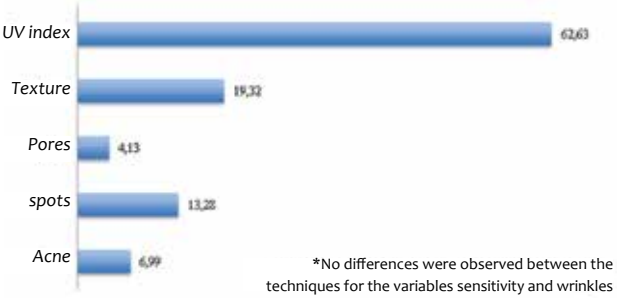


Figure 1: Before (left) and after (right) photographs of the two patients in the placebo group (before and 15 days after the last laser session)

Figure 2: Before (left) and after (right) photographs of the two patients in the drug delivery group (before and 15 days after the last laser session)

Graph 1: Mean value of the improvement in each variable with laser toning + placebo comparing the baseline to 15 days after the end of the treatment



Graph 2: Number of times when the combination laser toning + drug delivery led to better results as compared to the isolated laser toning technique for each variable

Furthermore, there is a possibility of modulating the degree of permeation according to the fluence and number of pulses applied. [7] In general, the fluence required to promote transepidermal delivery is lower than that used for other therapeutic purposes, for once the stratum corneum – which is the main barrier for the drug delivery – is ruptured, there is no additional benefit. [2] Another advantage associated with the use of lasers for the delivery of drugs is the fact that it is a physical method, which reduces the risk of irritating cutaneous reactions and interference with the permeated drug, which can occur when chemical methods are used for drug delivery. [9]

The first lasers studied in connection with the promotion of drug delivery were the fractional and non-fractional ablative. The potential use of non-ablative lasers were analyzed later on.[10] The benefits of the use of non-ablative lasers arise from the shorter recovery time needed, lower risk of adverse effects, preservation of the epidermal integrity, and the potential to achieve many of the results obtained with ablative lasers. [11, 12] In 2014, Lim et al described the use of the fractional non-ablative 1,550nm Erbium:glass laser for drug delivery of aminolevulinic acid (ALA). The results, analyzed by porphyrin fluorescence, showed greater penetration of ALA in the areas treated with the laser and confirmed the drug delivery-promoting effect of the 1,550nm Erbium:glass laser. [11]

The non-ablative 1,064nm Q-switched Nd:YAG laser emits ultra-short waves with duration of nanoseconds and high energy peaks that completely disrupt the keratin and corneocytes, forming micropores in the stratum corneum with minimal increase of the temperature.[7, 8] These changes allow increased cutaneous permeation of up 12 times relative to that of the intact skin, that may last for up to one week after the application of the laser.[2, 8] In addition, there is promotion of dermal remodeling without ablation by the laser toning technique, carried out with lasers of the Q-switched type. The neocollagenesis results from the thermal injury caused by the laser in the dermis, and occurs to a lesser degree than that produced by ablative lasers.[12, 13]

The laser toning technique comprises the use of Q-switched lasers in multiple passes with low fluence, and has been used for many years in Asian countries for facial rejuvenation and for treatment of melasma. [14]

In 1997, Goldberg performed a pioneering pilot study describing the use of the 1,064nm Q-switched Nd:YAG laser for the treatment of facial rhytids as compared to the treatment using the 10,600nm CO2 laser.[15] In 1999, Goldberg and Metzler continued studying the 1,064nm Q-switched Nd:YAG laser, observing improvement in the skin's texture and elasticity, and facial rhytids after three monthly treatments.[16] In 2001, the same author carried out a study evaluating histological changes in six patients treated with one session of Q-switched Nd:YAG laser: there was an improvement of the solar elastosis and in the organization of collagen fibers, and an increase in thickness of the papillary dermis observed by histological analysis, three months after treatment.[13] Also in 2001, Trelles described the use of the 1,320nm Q-switched Nd:YAG laser in four sessions for facial rejuvenation with an increase in the epidermal thickness and density of collagen fibers in all patients. [17] Another study by Berlin et al. in 2008, evaluated ten patients who underwent six fortnightly sessions of 1,064nm Q-switched Nd:YAG laser, with the histological analysis confirming Goldberg's findings.[3] All these studies confirm the effectiveness of the laser toning technique for dermal remodeling and improvement of the cutaneous firmness in facial treatments.

The use of 1,064nm Q-switched Nd:YAG laser for the treatment of periorbital rhytids in six fortnightly sessions in eight patients was described by Karabudak et al.. Fifty percent of them had clinical improvement while all treated patients showed an increase in the average density of collagen fibers ($p < 0.05$), demonstrating the effectiveness and safety of Q-switched lasers also in the treatment of the periorbital area.[5]

The combination of laser toning technique and drug delivery was described for the treatment of melasma in a split-face study. The 1,064nm Q-switched Nd:YAG laser was applied across the face associated with the ultrasonic application of vitamin C in a single hemiface, in four monthly sessions. The evaluation three months after the last session showed superiority of results in the hemiface treated with laser toning associated with drug delivery. [4] Other drugs described in the literature that have had their permeation increased through Q-switched lasers are: ALA and 5-fluorouracil.[18, 19]

The results of the present study demonstrate that the laser toning technique can be enhanced when associated with drug delivery and selected active principles. Each of the formulation components had a specific function. As Hyaxel® (an hyaluronic acid of low molecular weight, whose vector is the organic silicon) and Hidroxiprolisilane C® (a source of hydroxyproline) have an effect on neocollagenesis, the authors suggest that the improvement in the skin's texture can be linked to the presence of these two components as well as DMAE Pidolado®, which acts as a surface tensor. Additionally, the Nano Vitamin C® (a nanocoated vitamin C that acts as an antioxidant, whitener, sebum production reducer and neocollagenesis stimulator agent, enabled the improvement in the parameters *acne, texture, stains, and UV index* when observed using the Focco® device. Finally, Matrixyl 3000® (an extracellular matrix re-densifier that stimulates the synthesis of macromolecules which promote increased skin elasticity), being capable of improving texture parameters and reducing pores.[20]

CONCLUSION

The present pilot study showed promising results arising from the combination of the laser toning technique using Q-switched laser with a drug delivery-specific formulation.

The drug delivery technique deserves attention due to its capacity to optimize the laser toning results, discussing the benefit of the combination of procedures that guarantee more promising results due to increased permeability of the stratum corneum. Due to the fact it is an innovative technology, with a short recovery time, and which does not preclude patients from carrying out their daily activities, in addition to the fact that it can be performed in higher phototypes with minimal risk of

side effects as compared to other laser types, the method evaluated deserves further scrutiny aimed at confirming the findings reported in the present paper.

Studies exploring the use of Q-switched laser for drug delivery are fewer than those related to the use of ablative lasers, either fractional or not. Therefore, further studies are needed to clarify the doubts that persist on the subject matter. ●

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Review article

Hyaluronic acid in the rejuvenation of the upper third of the face: review and update - Part 1

Ácido hialurônico no rejuvenescimento do terço superior da face: revisão e atualização - Parte 1

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ABSTRACT

In recent years there has been a breakthrough in non-invasive techniques of facial rejuvenation. The greater understanding of the anatomical changes involved in the aging process was accompanied by rapid evolution in how to address these changes and the expansion of substances and technologies used in this approach. Of the arsenal of substances used for rejuvenation, the upper third of the face was before an almost exclusive territory of neuromodulators. Currently, fillers have stood out, especially those based onhyaluronic acid (HA), because they are safe and produce immediate and lasting – but reversible – results. The objective of this first article is to provide a brief literature review and update on the use of HA fillers in the rejuvenation of the upper third of the face, focusing on the forehead and glabella areas.

Keywords: dermal fillers; forehead; hyaluronic acid

RESUMO

Nos últimos anos houve grande avanço nas técnicas não invasivas de rejuvenescimento facial. O maior entendimento das alterações anatômicas envolvidas no processo do envelhecimento foi acompanhado por rápida evolução na forma de abordar essas alterações e pela expansão de substâncias e tecnologias usadas nessa abordagem.

Com relação ao arsenal de substâncias usadas para rejuvenescimento, o terço superior da face, era antes território quase exclusivo dos neuromoduladores. Atualmente, os preenchedores vêm ocupando lugar de destaque, especialmente aqueles à base de acido hialurônico (AH), porque são seguros e produzem resultados imediatos e duradouros, porém reversíveis.

O objetivo deste primeiro artigo é oferecer breve revisão da literatura e atualização sobre o uso de preenchedores de AH no rejuvenescimento do terço superior da face, enfocando as regiões da fronte e da glabela.

Palavras-chave: *preenchedores dérmicos; fronte; ácido hialurônico*

INTRODUCTION

The upper third of the face comprises the area covering the hair line or the frontal muscle extension in bald patients (upper limit), eyebrows and the nasal dorsum (lower limit) and temples (lateral limits).[1-3]

ANATOMY

Recent studies in fresh cadavers without fixation suggest that the facial subcutaneous fat is divided into compartments separated by fibrous septa, where the vessels irrigating the skin lie. In the frontal region, there are three fat compartments: one central and two lateral (Figure 1).[1-5]

The skin in this region is thick and inelastic and in the frontal region consists of five layers: skin; subcutaneous cellular tissue; galea aponeurotica (epicranial aponeurosis, which involves the frontal muscle); loose areolar tissue and periosteum[2,6]– also identified by the mnemonic SCALP (Skin, Connective tissue, Aponeurosis, Loose areolar connective tissue, Pericranium). The vascular structures and nerves are mainly located in the fibrous septa connecting the subcutaneous cellular tissue with galea aponeurotica (extension of SMAS – Superficial Aponeurotic Muscle System). The loose areolar tissue is also referred to as "glide plane", as it does not provide resistance to fillers, and it is safe because does not contain vessels and nerves (Figure 2).

The main neurovascular bundles in this region are the supratrochlear and the supraorbital. The former is located 17-22mm away from the facial midline,[7] and the latter emerges from the supraorbital foramen located in the mid-pupillary line (Figure 3).

AGING OF THE FOREHEAD AND GLABELLA

The physical changes caused by aging are complex and not only occur in the skin – with atrophy, loss of elasticity and emergence of spots and wrinkles, but also in the soft tissues and bones, in which reabsorption and/or displacement help complete the typical characteristics of the aging process.

In the forehead and glabella aging, we can notice two main processes. Firstly, there is the emergence of lines and thin wrinkles secondary to skin thinning and repetitive muscle movements (frontal muscle and glabellar complex). Then, volume reduction takes place due to bone reabsorption, and loss or thinning of fat compartments,[8] altering the youthful convexity of the forehead, which begins to show concavities in the mid third and sides. Such changes deepen the frontal wrinkles and contribute to the poor positioning of eyebrows and eyelids, which, not having the appropriate height and projection anymore, lend a tiring or aged appearance to individuals.[3,9] Cosmetic dermatology specialists know that the isolated use of botulinum toxin in these cases might accentuate the eyebrow ptosis, as a result of the weakening of the frontal muscle. Volume replacement then becomes necessary for rejuvenation of the upper third of the face, recovering the natural projection and repositioning eyebrows.[9]

FUNDAMENTALS OF THE USE OF HYALURONIC ACID

In the volume replacement of the upper third of the face, hyaluronic acid (HA) stands out as a preferred product because it is malleable and safe; produces immediate, long-lasting, although impermanent results and is reversible with the use of hyaluronidase.

Apart from volume replacement, HA has been used as a cutaneous remodeler, due to the observation of the persistence of the filling effect for much longer than the filler's bioavailability. Studies have shown that HA may induce an increase of

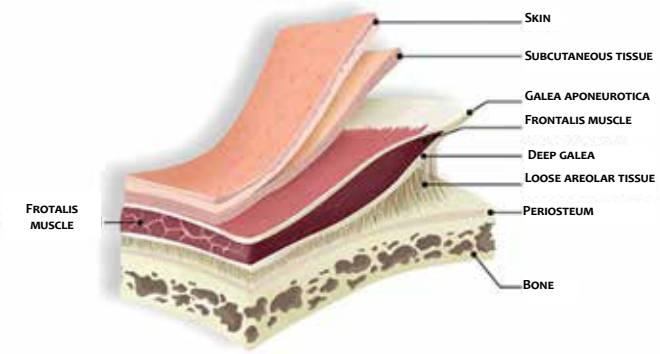

Figure 2: Tissue layers of the forehead - skin, subcutaneous, galea aponeurotica or epicranial aponeurosis – which comprises the frontal muscle, loose areolar tissue and periosteum. Reproduced from Trindade de Almeida[4]

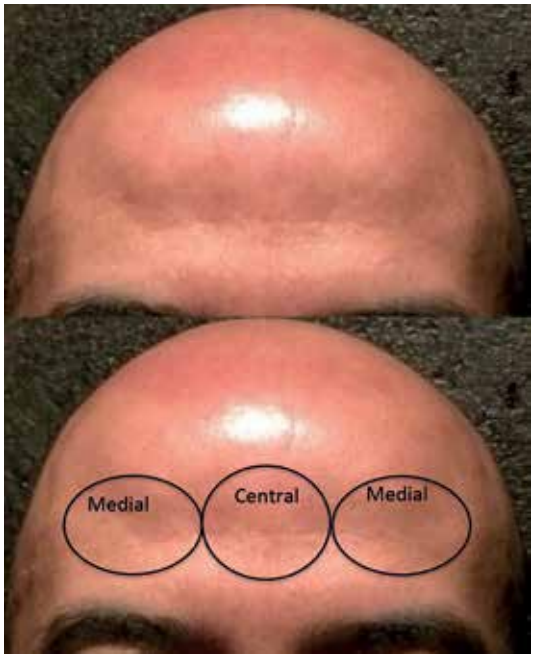

Figure 1: Fat compartments in the forehead

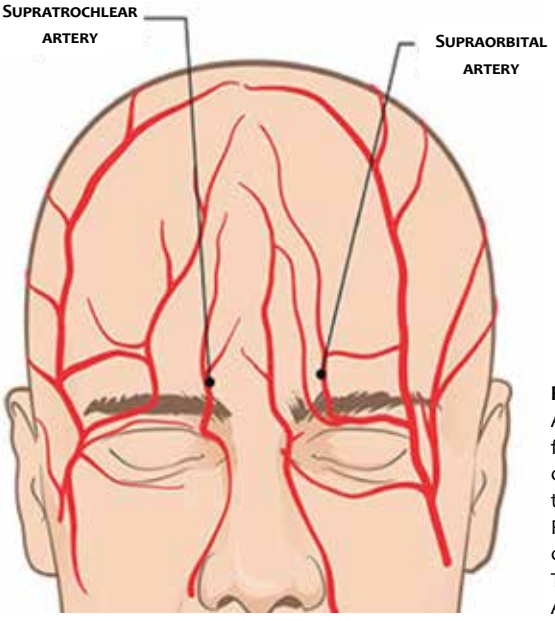

Figure 3: Areas of risk for vascular occlusion in the glabella Reproduced from Trindade de Almeida[4]

collagen and elastic fiber production, restoring the extracellular matrix through direct stimulus and/or mechanic stretching of fibroblasts.[10,11]

There are a number of preparations of HA fillers with different levels of cohesiveness and viscosity. This ensures high versatility, allowing the use in both superficial and deep lines for volume replacement. Several preparations already have anesthetics added to the products, which makes the procedure easier because it becomes less painful and, therefore, more comfortable.[3]

In addition, although this practice is not a consensus as some authors fear to alter the filler composition, the products can be diluted right before use. Lidocaine (2%), lidocaine plus epinephrine (1:100,000) or 0.9% saline solution can be added to the HA at ratios of 20-50% (0.2-05ml of diluent for each 1ml of HA), using1-ml Luer-Lock syringes, connected by a two-output transfer device. This addition provides the product with some benefits: variation of HA concentration depending on the need (superficial lines or volume replacement) and injection plan (superficial or deep), easiness of injection due to lower extrusion force and higher malleability and dispersion into tissues, thereby avoiding irregularities. It is even believed that there may be edema reduction and lower chance of ecchymosis due to the action of the vasoconstrictor.[2,9] The authors of this article use 30% dilutions, when needed.

FOREHEAD REJUVENATION

Volume replacement:

To allow for higher comfort to patients, the authors apply topic formulations of anesthetic (Dermomax, Pliaglis, etc.) during 30 minutes prior to the procedure. Immediately before, and once asepsis with 4% alcoholic chlorhexidine has been performed.

For volume replacement, a number of techniques are described. One of them is the injection of small volumes (0.2ml) into the subgaleal space (above the periosteum), where there is lower resistance to distension and absence of vessels. By using a 27G needle, we proceed with previous aspiration and deposition in perpendicular bolus in a consecutive disposition. The objective is for these deposits to work as "support towers" anteriorly projecting the forehead.[2] For such, the authors prefer products with higher cohesiveness and mid viscosity that allow higher elevation of structures, lower diffusion and good tissue integration (Chart 1).

For injections into more superficial layers, the selection of a cannula, either 25G or 27G, seems to be more appropriate. The injection can be anterograde or retrograde of small volumes (0,2-0.5 ml) in both the central compartment (above the glabella) and the lateral portions (above the eyebrow), and the products may have lower viscosity and cohesiveness (Figure 4).

Massage following injection ensures better distribution of the product, elimination of irregularities and shadows, smooth recovery of the contour and forehead projection, mitigation of horizontal lines and eyebrow elevation.The required total volume ranges from 1-3ml, injected in one or more sessions and the durability of the procedure varies from 10-18 months (Figure 5).[12]

Another technique, known as *3D forehead reflation* was described by Carruthers & Carruthers in 2015. It consists of the anterograde injection of 2-ml HA 50-100%, diluted in saline solution (total, 4ml), with cannula or needle. The total volume is divided into 1.3-ml bolus and injected into three "portals" in the forehead: 1 at each outer corner of the eyebrows (next to the temporal fusion line) and 1 central, in the glabella (between the supratrochlear vessels). The higher malleability of hyperdiluted HA safely makes the massage easier and the product distribution even, with no need of multiple needle punctures or cannula movements.

SUPERFICIAL FILLING OF FRONTAL LINES:

In this technique, the injection is performed with a 27G or 30G needle at a 45°angle against the skin, into the superficial dermis, in small volumes (lower than 0.02 ml). In this plan, the chances of intravascular injection decrease. Because the major arteries in this region (supratrochlear, supraorbital and superficial temporal) send small branches that radially enter the deep dermis, the superficial filling should be above this layer.The best choice is products containing less reticulated, more fluid HA (Chart 1). The mean durability is 6-9 months, especially when associated with botulinum toxin (Figure 6).

Chart 1: Hyaluronic acid options according to cohesiveness, viscosity and indication:

Volumizing forehead and glabella	Superficial filling of frontal and glabellar lines
Juvederm Voluma	Juvederm Refine, Juvederm Ultra, Vollift or Volbella
Restylane Perlane	Restylane
Fortelis Extra or Modelis (Intense or Volume Belotero)	Basic or Soft Esthelis (Soft or Advanced Belotero)
Emervel Volume or Classic	Deep Emervel
Perfectha Deep or Subskin	Perfectha Derm
Teosyal Ultra Deep or Ultimate	Teosyal First Lines, Deep Lines or Global Action

Figure 4: Increase of the lateral compartment volume of the forehead, with cannula.

Figure 5: Volume replacement in the forehead. Before and after 1ml HA

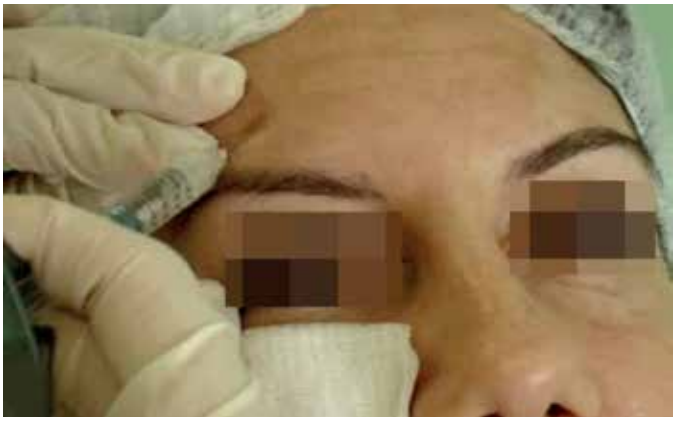

Figure 6: Filling technique for frontal lines –the injection is performed using a 27G or 30G needle, at a 45° angle against the skin, into the superficial dermis, in small volumes (lower than 0.02ml)

Whatever filling method is used, side effects may occur, such as pain, edema and ecchymosis. Asymmetries will be corrected with massage, new HA application or hyaluronidase injections after 1 or 2 weeks, when needed.[13,14]

GLABELLA REJUVENATION

Volume replacement:

The glabella, just like other facial regions, also loses volume. This causes concavity and local wrinkle accentuation in mild cases and ptosis in more severe cases, even to the point of "collapse" of the medial eyebrow region.

When volume replacement is the goal, the filler should be deeply deposited into the midline, into the subgaleal plane. For such, with the non-dominant hand, the skin above the procerus muscle should be clamped, forming a cutaneous fold, and the 27G needle introduced up to the supraperiosteal plane. This maneuver prevents dispersion of the filler to the sides of the nose. Aspirate before injecting. The injection is anterograde, slow, upward and then slightly lateral (*radial fanning*). When properly used, this technique is safe and atraumatic, as the supratrochlear arcades are 17-22mm apart from the midline at each side and angular vessels are lateral and inferior to this point. In this plane, the filler is easily spread by digital pressure toward the head, thereby preventing the formation of nodules and the need for new punctures to lessen medial frontal lines (Figures 7 and 8).

Another technique uses 25G or 27G cannulas positioned through the medial frontal compartment, craniocaudally directed or through the lateral frontal compartment up to the medial portion of the eyebrow, bypassing the orbital rim. In this step, the authors prefer products with higher cohesiveness and mid viscosity, as they allow for higher elevation of structures, lower diffusion and good tissue integration (Chart 1). The total volume used varies from 0.4-0.6ml HA, approximately, and the durability is 10-18 months.

SUPERFICIAL FILLING OF GLABELLAR LINES:

In this procedure, the injection is performed with the use of 27G needles at a 45° angle against the skin into the superficial dermis. The application is retrograde linear or provoking whitening of the skin, known as blanching technique, with approximate total volume of 0.1ml.[15] The preference is for products containing less reticulated, more fluid HA, and the mean durability is 6-9 months (when associated with botulinum toxin). Asymmetries can be corrected with massage, additional HA or hyaluronidase injections, 1 or 2 weeks later (Chart 1).

COMPLICATIONS

Complications that are inherent to the filling techniques have been reported, such as sporadic bleeding, ecchymosis, excessive product, superficial accumulation, formation of nodules and, more rarely, intravascular injections. Knowing the local anatomy, using careful techniques, adequate to the type of material used, with slow and resistance-free injection, in the appropriate plane may avoid such complications.

The upper third of the face is considered an area of risk, especially the glabella, due to the possibility of major vascular impairment, thereby leading to serious side effects, such as tissue necrosis and even blindness. The vascular supratrochlear and supraorbital bundles (branches of the internal carotid artery) irrigate the glabella, nasal wall, and central-inferior portion of the forehead. Tissue necrosis in these territories may occur by intravascular injection, compression by large volumes of HA and/or vascular injury, diminishing local blood supply.

Venous congestion may occur if excessive quantities are deposited in small spaces, causing persistent, disproportionate pain, as well as areas of violaceous discoloration, which might be underestimated as discomfort inherent to the procedure. The distal arterial embolization causes an immediate effect: sudden

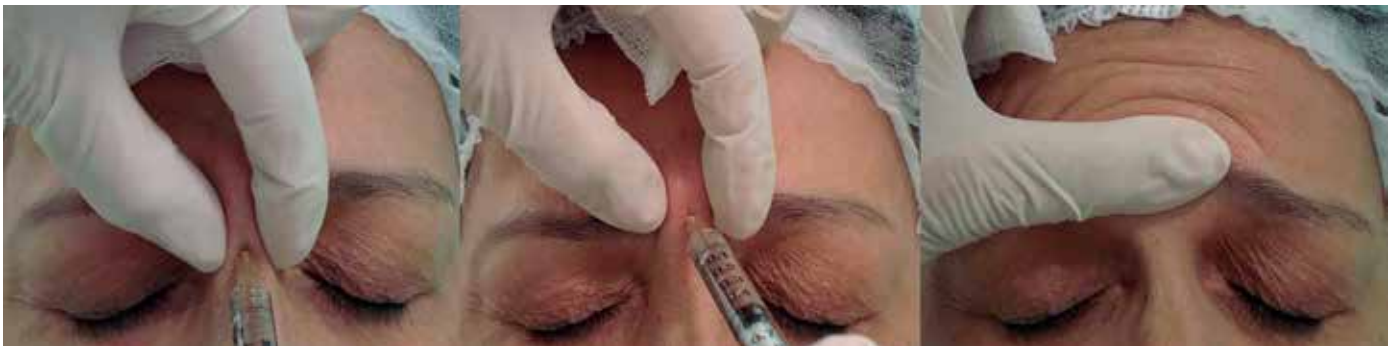

Figure 7: Glabella filling technique

Figure 8: Before and immediately after the filling of the glabella with 0.2 ml HA

blanching of the skin with variable pain (minimum to severe), possibly followed by rectiform cutaneous darkening, formation of ulceration and eschar.

In such cases, we should immediately interrupt the procedure, massage the site and stimulate local vasodilation by applying warm compresses or nitroglycerin ointment. The use of heparin with the goal of impeding thrombotic processes or embolization has been reported in the acute phase, as well as the use of vasodilators (e.g., pentoxifylline, sildenafil, acetaminophen), antiplatelet aggregation agents, systemic corticosteroid therapy (topical and systemic) and antibiotic therapy. The abundant injection of hyaluronidase into the affected area and neighboring regions in order to reverse the process is a consensus in theliterature.[16,17]

Cases of blindness and amaurosis, particularly in the glabella have been reported, probably due to the retrograde diffusion of the injected material to the ophthalmic artery and its irrigation branches of the retina: central retinal artery and short posterior ciliary artery – both with documented reports in the literature.[18] However, there are other hypotheses for the embolization pathway leading to blindness from (medial and lateral) forehead fillings: variation of the ophthalmic artery as a middle meningeal artery branch (branch of the external carotid), and anastomose of superficial temporal artery branches with supratrochlear or supraorbital artery. There are reports of brain ischemia due to diffusion of the injected material to the territory of the internal carotid (middle cerebral artery).

Virtually, vascular occlusions may occur at any anatomic location of the face.[17] To prevent or minimize complications, the main recommendations are: deep knowledge of the local anatomy, adequate training on techniques and filling materials, attention to color variations at the treated site and complaints of pain by patients and the availability of products and drugs for immediate use, such as hyaluronidase and vasodilators.

CONCLUSION

Volume replacement allows the recovery of the natural convexity and projection of the upper third of the face, eliminating innate or acquired with aging depressions and repositioning eyebrows. Procedures are quick, on an outpatient basis, without need for tests or having to stop daily life activities. Results are effective, natural and long lasting; however, they not are risk-free and major side effects may occur. An adequate training should be recommended before any procedure. ❑

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New Techniques

Use of cyanoacrylate accelerator in the fixation of flexible plastic blade for the treatment of transverse hypercurvature of the nail

Uso do acelerador de cianoacrilato na fixação de lâmina plástica flexível para o tratamento da hipercurvatura transversa da unha

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ABSTRACT

Transverse hypercurvature is a deformity of the nail plate, unaesthetic and painful, causing discomfort to the patient. Treatment can be conservative or surgical. Related to the conservative treatments, placing the flexible plastic blade on the nail plate using cyanoacrylate glue, promotes rapid improvement of pain and its widening from three to six months. The use of cyanoacrylate accelerator facilitates the procedure, making it faster.

Keywords: nails, malformed; nails, ingrown; nail diseases; ambulatory surgical procedures

RESUMO

A hipercurvatura transversa é deformidade da placa ungueal, inestética e dolorosa, provocando desconforto ao paciente. O tratamento pode ser conservador ou cirúrgico. Dos conservadores a colocação da lâmina plástica de memória sobre a placa ungueal, utilizando cola de cianocrilato, promove rápida melhora da dor e seu alargamento entre três e seis meses. O uso de acelerador de cianoacrilato facilita o procedimento tornando-o mais rápido.

Palavras-chave: *unhas malformadas; unhas encravadas; doenças da unha; procedimentos cirúrgicos ambulatorios*

INTRODUCTION

Transverse hypercurvature of the nail is a deformity is characterized by an increase in the curvature of the nail plate.[1–3] It can be classified into three types: pincer nail, tile nail and folded nail. In the pincer nail, there is a longitudinal increase in the curvature, which intensifies in more distal portions of the nail's longitudinal axis. In the tile nail, the curvature remains unchanged along the longitudinal axis; while in the folded nail there is an abrupt angle in one or both lateral margins.[1, 2] The hypercurvature of the nail can be hereditary or acquired. The hereditary form is symmetrical and occurs in many family members. In addition to the halluces, other fingers can be affected. It is linked to the misalignment of the phalanges, in a way that the halluces are deflected laterally, while the other fingers are deflected medially.[1, 2] The acquired form tends to be limited to

the halluces and is generally not symmetric, relating to various conditions, such as foot deformity caused by poorly adapted footwear; degeneration of the distal interphalangeal joint (more common in older women); trauma, such as repeated ungual exeresis; tumors of the nail apparatus (exostosis, epidermal cyst, myxoid pseudocyst) and inflammatory onychopathies such as psoriasis.[1-3]

Some articles relate the hypercurvature etiology with the selective widening of the phalanx's base caused by juxta articular osteophytes that are closely linked to the nail matrix by collagen fiber ligaments. [1,3]

It is a painful and uncomfortable condition that interferes with the patient's quality of life.[1-3] Treatment can be either surgical or conservative. Examples of conservative techniques are: taping of the lateral folds, nail abrasion, use of plastic tubes and metal or plastic braces fixed on the nail plate. Plastic ortheses (clip system) relieve pain in a few weeks and widen the nail, reducing the hypercurvature within six months, and are mostly indicated in cases of pincer nails. Despite being considered an easy to perform technique, the fixation of plastic devices onto the nail plate can be difficult, especially in cases where the hypercurvature is more pronounced. The authors suggest the use of the cyanoacrylate accelerator in order to facilitate the procedure, reducing the time of implementation.

TECHNIQUE

The authors use the clip system (LUGA®, Spain) consisting of an elliptical semi-rigid, flexible shape-memory polyurethane sheet, available in sizes from 16 to 26mm.

The nail plate is initially sanded on its surface and degreased with acetone in order to increase the plastic sheet's adherence.

The sheet is then molded in its longer axis so that fits transversely on the nail plate, in its medial-distal portion, maintaining a distance of 1mm from the lateral folds. One of its faces is also lightly sanded aiming at increasing adherence to the nail plate.

A thin layer of cyanoacrylate glue is placed on the plastic sheet with the aid of a toothpick (Figure 1). In the described technique, the cyanoacrylate accelerator (ZAP®, PACER TECHNOLOGY, Rancho Cucamonga, USA) (Figure 2)

Figure 1: Application of a thin layer of cyanoacrylate glue on the plastic sheet with the aid of wooden toothpick

Figure 2: ZAP® brand cyanoacrylate accelerator used in the technique

FIGURE 3: The cyanoacrylate accelerator is placed in a plastic container

is poured into a plastic container (Figure 3). The plastic sheet is attached to the nail plate with the aid of the operating physician's fingers, exerting slight pressure. The cyanoacrylate accelerator, soaked in a wooden toothpick, is placed on the sides of the orthesis using the other hand (Figure 4). By capillarity, the accelerator comes into contact with the glue and immediately fixes the orthesis to the nail plate (Figure 5).

The plastic sheet should be replaced every 30 or 60 days.[1]

DISCUSSION

Transverse hypercurvature is a nail deformity that is prevalent in the population. Treatment is indicated for situations where there is aesthetic discomfort or pain. [1-4] The most commonly used conservative treatment is the application of plastic sheets due to its safety, efficacy and low cost.

The orthesis exerts light and constant pressure, flattening the nail plate and reducing its pressure against the lateral folds.

Figure 4: The plastic sheet is attached using the operating physician's fingers, while the accelerator is applied to the sides of the orthesis with the aid of a toothpick

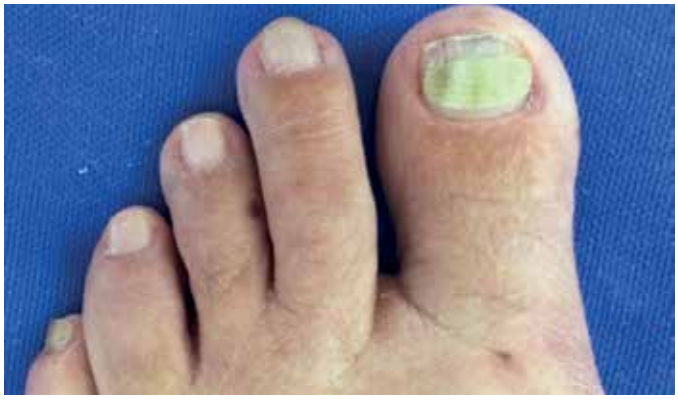

Figura 5: Final result with the plastic sheet fully adhered, especially on the lateral portions, where the hypercurvature is more intense

The plastic sheet is tough and little pliable, making its fixation difficult, especially at the lateral borders, where the hypercurvature is more pronounced.

The use of the cyanoacrylate accelerator facilitates the placement of the orthesis, as it increases the cyanoacrylate glue's bonding speed and filling capacity. [5]

The cyanoacrylate glue has ethyl cyanoacrylate, methyl methacrylate and hydroquinone in its composition, while the accelerator is composed of dimethyl-p-toluidine (DMT), hydrocarbon propellant and VMP naphtha. Although these products are considered sensitizers, the rapid polymerization and immediate adhesion to the nail plate's keratin prevent their penetration in the epidermis and contact with the antigen presenting cells. [6] In this way, the patient's possibility of developing an allergic contact dermatitis (ACD) is unlikely. The physician who performs this procedure is at increased risk of developing ACD, meaning he or she should make use of personal protective equipment.

There are reports of ACD by DMT, which is also present in the orthopedic cement accelerator and dental acrylic cement, where sensitization is greater in workers using industrial adhesives, surgeons and dentists, due to the frequent contact with this substance. [7]

CONCLUSION

The cyanoacrylate glue accelerator is a useful and cost effective tool, allowing a more rapid and effective placement of the orthesis.

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New Techniques

Male androgenetic alopecia treated with microneedling alone or associated with injectable minoxidil by microinfusion of drugs into the skin

Alopecia androgenética masculina tratada com microagulhamento isolado e associado a minoxidil injetável pela técnica de microinfusão de medicamentos pela pele

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ABSTRACT

Androgenetic alopecia is a condition with an important psychological impact. Clinical treatments present variable responses and require care for long periods, a factor that decreases the chances of adhesion. Microneedling with or without minoxidil injection is a new treatment modality. This study reports cases of two male patients, aged 30 and 44 years, with satisfactory partial response to four sessions of microneedling with minoxidil and three sessions of microneedling alone, using a tattoo machine and microinfusion of drugs into the skin technique.

Keywords: alopecia; minoxidil; needles

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ABSTRACT

Androgenetic alopecia is a condition with an important psychological impact. Clinical treatments present variable responses and require care for long periods, a factor that decreases the chances of adhesion. Microneedling with or without minoxidil injection is a new treatment modality. This study reports cases of two male patients, aged 30 and 44 years, with satisfactory partial response to four sessions of microneedling with minoxidil and three sessions of microneedling alone, using a tattoo machine and microinfusion of drugs into the skin technique.

Keywords: *alopecia; minoxidil; needles*

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INTRODUCTION

Androgenetic alopecia is the most common cause of follicular miniaturization, which leads to a pattern of non-cicatricial thinning of the hair.[1] It affects genetically predisposed individuals and can be associated with a major impact on quality of life.[2] As a result, there is great interest in the search for viable therapeutic options to assist in treating these patients.

The classic clinical approach continues to be advocated, associated or not with surgical treatments such as hair transplant. Among the used medications, the most recommended are topical minoxidil and oral finasteride.[3,4]

Recent evidence has shown a possible superiority of injectable minoxidil as compared to topically applied minoxidil, yet without indication whether the optimization would be de-

rived from the injection of the drug at a location that is closer to the follicle or from the micro-trauma inflicted, which may have an important role. [5]

Microneedling was recently included in the androgenetic alopecia's therapeutic armamentarium due to the following facts: it releases platelet-derived and epidermal growth factors, it enables regeneration through wounds, it activates stem cells in the bulb and leads to the overexpression of genes related to hair growth, such as the Wnt3a and Wnt10-b pathways, and the vascular endothelial growth factor in rats. [6]

Microneedling is traditionally carried out with the use of rolling cylinders with needles, which produce 1.5mm deep punctures into the scalp (rollers). [7,8]

The recently described MMP® technique (microinfusion of drugs through the skin) promotes the infusion of medicaments (drug delivery) associated with the microneedling procedure using the device for performing tattoos and appropriate needles that meet adequate principles of equipment sterilization and disposal of piercing and cutting material.[9] Even when the infusion of drugs is not intended by the physician, the orifices inflicted in the skin by the device have a similar effect to that of the rollers.

For the procedures described below the Cheyenne® brand tattoo apparatus was used (Germany, Anvisa: 80281110016). It comprises a device that allows controlling the back and forth movement's speed, and basic *on and off* operation buttons. The apparatus' body is connected to a power source and a tip, in which the needles cartridge (Anvisa: 80281110015) is coupled. In the present cases, the authors used 17 queued microneedles and a cartridge that allows aspiration of the medication that will be released later, during the performance of the procedure (Figure 1).

CLINICAL CASES

Case 1

Patient "JPA": 30 years old man, with clinical and dermoscopic androgenetic alopecia diagnosis, without treatment for over a year. Has used 1mg/day finasteride for 4 years, however suspended the use of the medication 3 years before due to decreased libido and poor therapeutic response. Had previously made use of topical minoxidil for 6 months, also suspended due to the frequent forgetfulness and the poor cosmetic appearance of the medication. Does not want to undergo hair transplant at the moment. Underwent 4 monthly microneedling sessions with the infusion of minoxidil using the following technique:

- Topical anesthesia with 4% lidocaine cream (Dermomax® Laboratorio Aché, São Paulo, Brazil) was carried out 30 minutes before the procedure. After this period, the cream was removed with saline, and the antisepsis of the entire area to be treated subsequently performed with alcoholic chlorhexidine. Once the area had been completely dried, a fenestrated sterile drape was put in place delimiting the area to be treated.

- Removal of the tip from the sterilization envelope, and coupling of its distal end to the Cheyenne® apparatus, and its proximal end to the cartridge with rowed needles (model 17-bp-Magnum) (Figure 1). A small sterile container was opened for the insertion of the medication (0.5% minoxidil, injectable solution, Healthtech dispensing pharmacy, Anvisa 9003878, Rua Teresina 208/210, Vila Bertioga, São Paulo – SP, Brazil).

- The apparatus' speed was set at 90. The medication was aspirated from the sterile container into the cartridge just as it comes in contact with the needles by their rapid back and forth movement, when the device was turned on. The microneedling and drug delivery process was effected through the perpendicular puncturing of the epidermis, with manually adjusted depth at roughly 1.5mm. Renewed aspirations of medication are necessary when the amount in the cartridge is used up. The procedure is completed when a pinpoint bleeding is produced throughout the treated area (Figure 2). The cleansing after the procedure was performed with a gauze moistened in saline. Post-procedural care includes gentle washing with a neutral shampoo 6 hours after the procedure and the use of simple analgesics in case of local pain. Post-procedural photographs were taken 1 month after the 4th session (Figures 3 and 4).

Figure 1: The Cheyenne® device and 17-bp Magnum needle

Case 2

Patient "UQT": 44 years old man, with clinical and dermoscopic diagnosis of androgenetic alopecia. Regular use of minoxidil for 2 years, stable picture, with absence of improvement in the previous year. Did not tolerate the use of finasteride due to decreased libido. Underwent 3 microneedling sessions with equipment and techniques similar to those described above, however without infusion of medications. The procedure was completed when pinpoint bleeding arose (Figure 2). The post-procedural photographs were taken 1 month after the 3rd session (Figures 5 and 6).

DISCUSSION

The demand for new treatment techniques for androgenetic alopecia is growing due to the great number of patients affected and the major impact on the patients' quality of life.

The clinical treatment of the condition leads to varying – and often unsatisfactory – responses.[4]

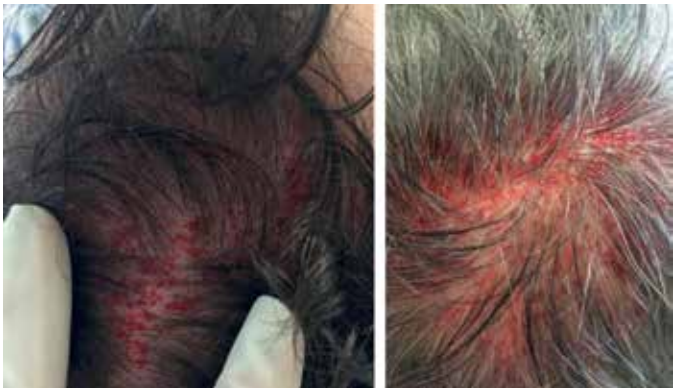

Figure 2: Patients 1 (left) and 2 (right): post-procedural pinpoint bleeding

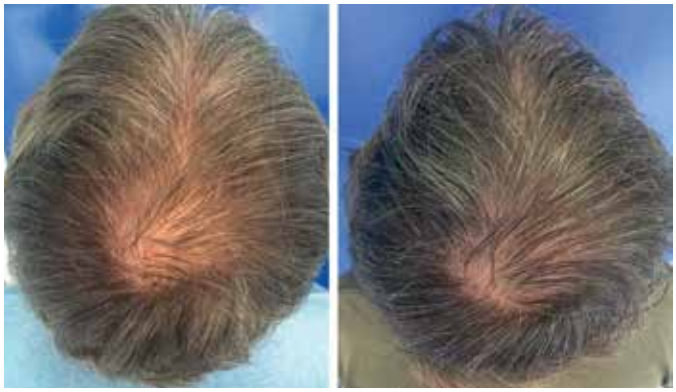

Figure 5: Patient 2 - Pre-treatment (left) and post-treatment (right) appearance, after 3 microneedling sessions with the Cheyenne® device, without injection of medications

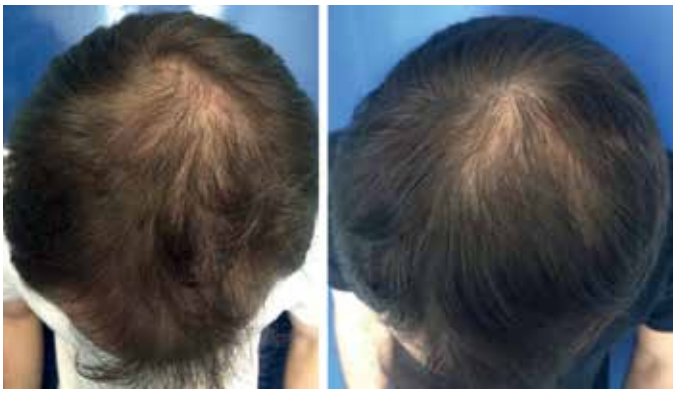

Figure 3: Patient 1 - Pre-treatment (left) and post-treatment (right) appearance, after 4 microneedling sessions with the Cheyenne® device and minoxidil infusion

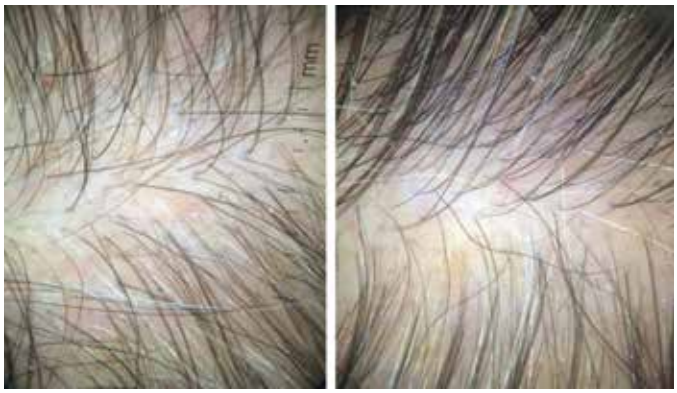

Figure 6: Patient 2: Appearance before (left) and after (right) 3 microneedling sessions

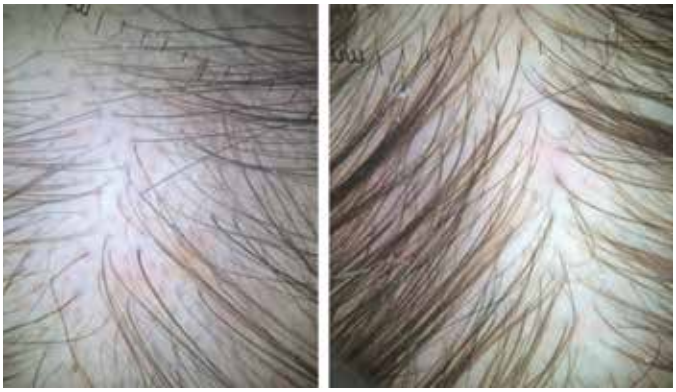

Figure 4: Patient 1- Trichoscopy of the vertex before (left) and after (right) 4 microneedling and minoxidil injection sessions

The adherence to a long-term treatment can be very difficult due to the necessity of performing it daily and the medication's side effects, as in the case of the patients presented in the present study.

Options of low risk adjuvant treatments are attractive and necessary.

Pain is an important undesired side effect of the microneedling technique and MMP® in general. Although it was not significant in the present cases, it can be limiting for many patients. [10] There were no major side effects in the cases described in the present paper or in similar microneedling treatments reported previously. [7,8]

In addition to the studies that have been carried out in animals and, in lesser numbers, in humans, further evidence is necessary to prove the superiority of minoxidil injections associated with microneedling as compared to the simple topical use of the medication, to the isolated use of microneedling and to the effectiveness of the MMP® technique.

Other factors to be clarified include the required number of sessions, interval between them and maintenance.

Despite the lack of more objective evidence of improvement, there were partial and cosmetically satisfactory responses in both patients, who had few treatment options available and appropriate for their lifestyle. It is important to note that there was a considerable improvement in both cases – the one that underwent minoxidil infiltration and the other, which underwent only the microneedling process. Two sessions were necessary so that the initial improvement could be observed, therefore indicating the technique is efficient and of low complexity, with comfortable posology and that can be performed in an outpatient basis.

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Botulinum toxin application in the secondary intention healing

Aplicação de toxina botulínica na cicatrização por segunda intenção

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ABSTRACT

Use of botulinum toxin type A in first intention healing wounds has been widely adopted in order to inhibit the formation of hypertrophic scars. In this report we demonstrate the use of the toxin in a surgical wound left to heal by secondary intention, after the removal of a squamous cell carcinoma in situ by Mohs micrographic surgery in supralabial region, with good cosmetic result. Botulinum toxin acts by inhibiting the proliferation of fibroblasts, by differentiating fibroblasts and by producing type I collagen, which are the main factors responsible for the good quality of the healing process.

Keywords: botulinum toxins, type A; cicatrix; wound healing; carcinoma, squamous cell

RESUMO

O uso da toxina botulínica tipo A em feridas de primeira intenção tem sido bastante adotado com a finalidade de inibir a formação de cicatrizes hipertróficas. Neste relato demonstramos o uso da toxina em uma ferida operatória deixada cicatrizar por segunda intenção, após a remoção de um carcinoma espinocelular in situ por cirurgia micrográfica de Mohs, na região supralabial, com bom resultado estético. A toxina botulínica age inibindo a proliferação de fibroblastos, na diferenciação em miofibroblastos e na produção de colágeno tipo I, que são os principais fatores responsáveis para a boa qualidade do processo de cicatrização.

Palavras-chave: *toxinas botulínicas tipo A; cicatriz; cicatrização; carcinoma de células escamosas*

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INTRODUCTION

Scars are a major concern for patients, especially if located in the face.[1] They are unavoidable consequences of surgical treatments in general.[1] An important factor that can hamper the sound development of the healing process is the presence of tension in the wound's borders. The facial muscles and their connections with the skin promote continuous tension on the surgical wound, impairing the final cosmetic outcome. [2]

Botulinum toxin type A has been shown to be a good option for optimizing the healing process. [3] It is a powerful neurotoxin produced by the bacterium *Clostridium botulinum*, an anaerobic rod cell, which promotes inhibition of acetylcholine release at the neuromuscular junction. In the 1970s, Scott was the first to propose the use of the toxin as a medical therapy for the treatment of strabismus.[2]

After undergoing endocytosis at the nerve terminal, the toxin promotes inhibition of acetylcholine release at the neuromuscular junction, suppressing muscle contraction for a period of two to six months. [3, 4] When applied to cutaneous wounds, it reduces tension in the wound's borders, providing aesthetic gain.[5]

There are many reports of toxin use for primary sutures, but few records of its use in healing process by secondary intention. In the present report, the authors describe the case of intraoperative application of botulinum toxin followed by secondary intention healing, with excellent aesthetic results.

CASE REPORT

A 36 year-old male patient had had an erythematous infiltrated plaque in the central supralabial region for two years. The lesion's biopsy diagnosed Bowen's disease. He had undergone photodynamic therapy with methyl aminolevulinate (two sessions with an interval of one week), without resolution of the picture. The patient was then referred for Mohs micrographic surgery.

At the time of surgery, the lesion measured 1.5 x 0.9cm (Figure 1). Five stages were necessary for the total removal of the tumor, with histology compatible with Bowen's disease. The final defect measured 3.0 x 1.6cm (Figure 2). Eight units of botulinum toxin type A were then applied in the surgical wound, leaving to heal by secondary intention.

Eighteen days after the surgery there was complete healing of the wound, with the formation of a slightly erythematous cicatricial tissue in the upper lip and a discreet extension into the supralabial region (Figure 3). The resulting appearance remained in the late 3-month postoperative period, with excellent aesthetic and functional outcomes (Figure 4 A and B).

DISCUSSION

Botulinum toxin has been used to encourage the development of healing due to its immobilizer effect.[6]

In their study, Hei Sun et al. presented data in which the proliferation of fibroblasts – and consequently of type I collagen, the main component of the extracellular matrix – was significantly reduced after treatment with botulinum toxin type A due to its inhibitory action on the first. [3]

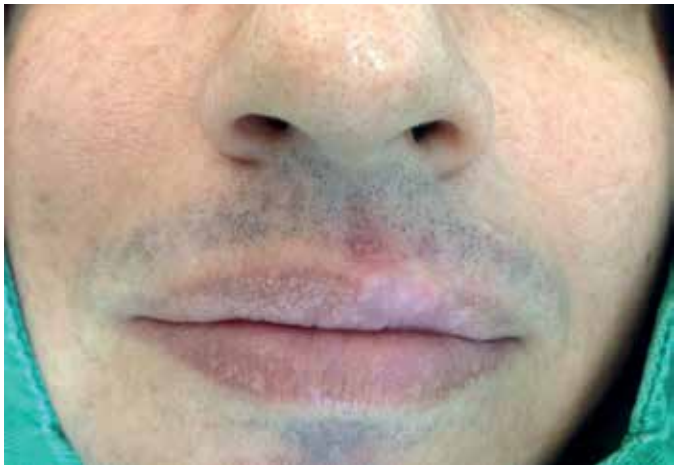

Figure 1: Preoperative erythematous, slightly flaky, poorly defined plaque in the supralabial region

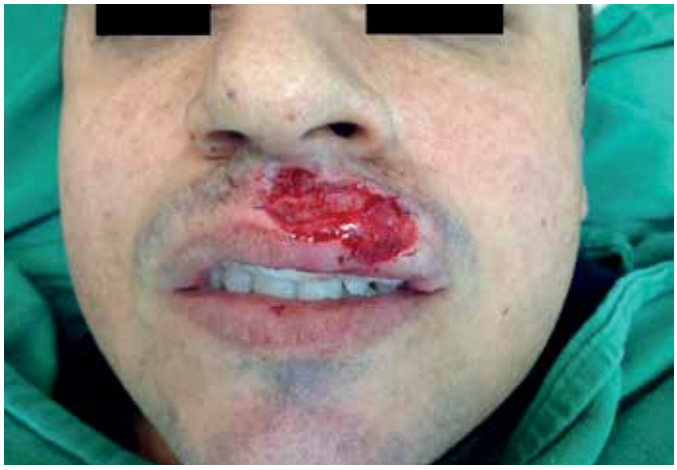

Figure 2: Immediate postoperative, 3.5 x 1.9cm surgical defect

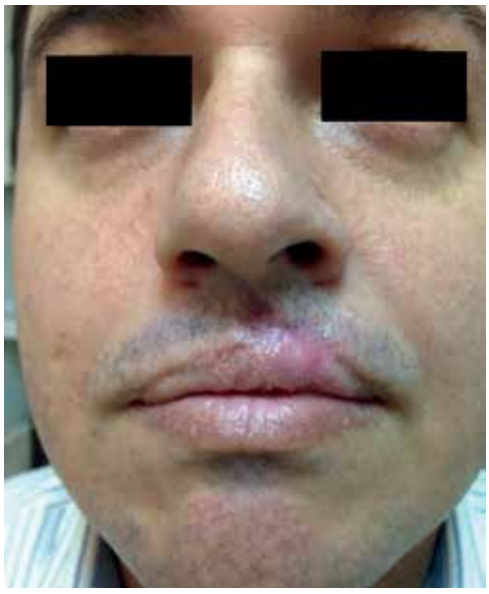

Figure 3: Eighteenth postoperative day, cicatricial plaque with a slight retraction

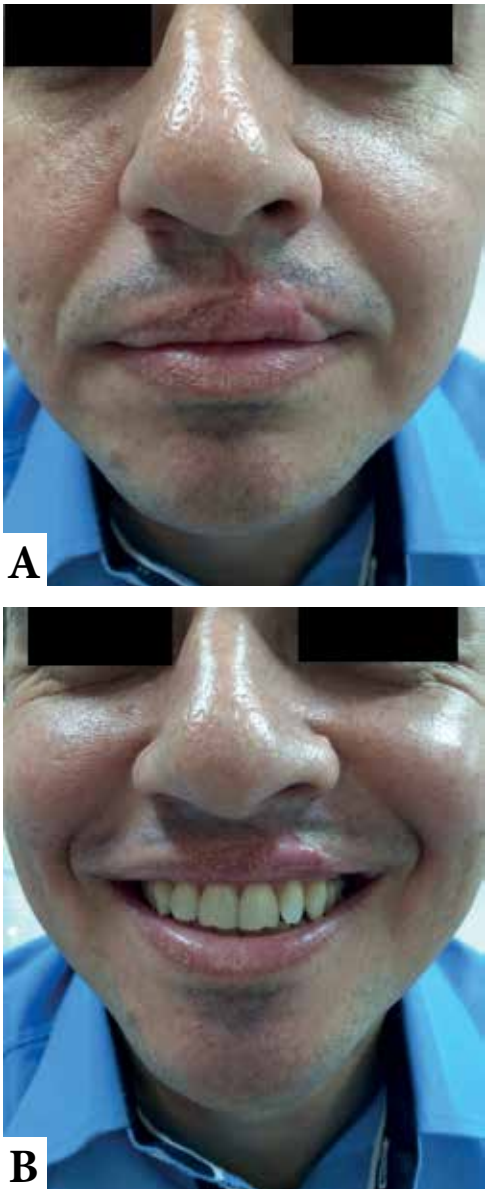

Figure 4: A and B - Three-month postoperative, cicatricial plaque with slight retraction, good aesthetic appearance and with functional motion

Another finding presented in same study was the suppression of the differentiation of fibroblasts into myofibroblasts, which are responsible for the acceleration of the wound contraction process, by inhibiting the expression of TGF-β1. Myofibroblasts express the smooth muscle's alpha actin that is present in hypertrophic scars. [3] TGF-β1 expression is increased during abnormal scarring. By suppressing its expression, a reduction in the formation of pathological scarring is expected. [3]

Analyses of reverse transcription reaction in polymerase chain demonstrated decreased levels of smooth muscle alpha-actin's mRNA in cells treated with TGF-β1 associated with botulinum toxin type A, when compared to cells treated only with TGF-β1. [3]

Another study containing histological analysis noted that the weakening of the contraction effect might occur in the healing process when there is reduction of alpha-actin expression and myosin II in smooth muscles. The results also showed that the higher the concentration of botulinum toxin type A, the more obvious the inhibition effect, thereby partially explaining the molecular mechanism for the toxin-based treatment. Thus, inhibiting fibroblast proliferation and reducing the expression of alpha-actin in smooth muscles and myosin II can determine the degree of fibrosis in a scar. [4]

The botulinum toxin type A's molecular properties of suggest that their action is better at the beginning of healing, when the fibroblasts are still in the proliferative phase and intense apoptotic activity. [1] For this reason, many questions arise about the possible benefits of injection of botulinum toxin in surgical wounds, especially if applied intraoperatively, as was done with the patient treated in the present study.

Despite evidence of the significant contribution of botulinum toxin in promoting proper healing, possible benefits in the healing process by secondary intention were not yet evaluated. The successful outcome of the present case establishes a precedent for further studies on chronic ulcers, in addition to serving as a new alternative for reconstruction of surgical wounds.

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Combined treatment for rhinophyma

Tratamento combinado para o rinofima

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ABSTRACT

Rhinophyma tends to determine important nasal changes, with aesthetic and functional impairment, especially in more advanced cases. Despite the various techniques already described, the search for the ideal treatment persists. Two patients with rhinophyma underwent tangential excision associated with electrocoagulation, with subsequent intensive cosmetic treatment. The described technique is effective, safe, with excellent aesthetic results and no recurrences during the study period. This proposed combined treatment appears as a great alternative for the treatment of rhinophyma due to its technical simplicity and its good long-term results.

Keywords: *rhinophyma; electrocoagulation; nose diseases*

RESUMO

O rinofima tende a determinar importantes alterações nasais, com prejuízos estéticos e funcionais, especialmente nos casos mais avançados. Apesar das diversas técnicas já descritas, a busca do tratamento ideal persiste. Dois pacientes com rinofima foram submetidos à excisão tangencial associada à eletrocoagulação, com posterior tratamento cosmético intenso. A técnica descrita se mostrou eficaz, segura, com excelente resultado estético e sem recidivas ao longo do período avaliado. Essa proposta de tratamento combinado configura-se como excelente alternativa para o tratamento do rinofima, devido a sua simplicidade técnica e seus bons resultados em longo prazo.

Palavras-chave: *rinofima; eletrocoagulação; doenças nasais*

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INTRODUCTION

Rhinophyma is a benign cutaneous lesion of slow growth and potentially disfiguring that affects the nose. It leads to hyperemia and telangiectasia, causing dilated pilosebaceous pores, increased volume and nodule formation in the region. These changes may lead to the complete deformation of the nose, entailing functional, aesthetic and psychological consequences to patients.[1] It is histologically characterized by hyperplasia of sebaceous glands and fibrovascular proliferation of the nasal dermis.[1,2] Its etiology has not yet been fully elucidated.[1, 2] Some authors believe that rhinophyma is correlated to centrofacial rosacea stage IV, being considered an uncommon subtype (3.7%) by them.[1,3] Others believe that the condition is an entity on its own for, unlike rosacea, it predominates in men and can manifest in the absence of the typical acneiform picture. Some risk factors for its development are described in the literature: exposure to sunlight, age (men over 40 years of age), alcoholism and stress.[1] Surgery for

rhinophyma resection dates back to the 19th century, when Von Langerbeck performed a complete resection of the skin, leaving it to heal by secondary intention.[4] Total skin grafts were also widely used in the recent past. [5] Innovative less aggressive treatments, such as dermabrasion, cryosurgery, CO_2 or argon laser ablation, and trichloroacetic acid have been recommended by most authors.[1, 3, 4, 6] Despite the various techniques already described, there is still no gold standard for the surgical treatment of rhinophyma.[7] The search for the best therapeutic option continues, especially for the most advanced cases, where good aesthetic outcomes are not always achieved with less aggressive treatment options.[7, 8] Although it has been used for many years, tangential resection associated with electrocoagulation is a simple and safe technique that does not require the use of complementary technology. There is abundant literature regarding the variety of proposed postoperative cosmiatric treatments, however there is consensus on the fact that when carried out intensely and in a sustained manner, they can lend superior results in both functional and aesthetic aspects.[4] The objective of the present study is to describe the results obtained in patients with rhinophyma treated with the combination of surgery and postoperative cosmiatric care.

CASE REPORTS

Two patients bearing rhinophyma were treated with the method proposed below, at the author's private clinic in 2009. The tangential excision technique combined with electrocoagulation, with the subsequent cosmetic treatment was performed in a hospital setting, under fentanyl and midazolam-based light sedation, as described below (Figure 1). The author opted for the use of local anesthesia in the nasal area with the injection of roughly 20 ml of solution containing 0.125% lidocaine and 1:200,000 epinephrine. The tangential resection was performed with a number 24 scalpel blade, removing linear segments of varying thickness (1mm to 2mm) from across the affected region, observing the nasal aesthetic units. After the entire surface had been treated in this manner, the vigorous electrocoagulation of the bloody area with traditional electrocautery. At the end of the procedure the wound was covered with collagenase ointment, with the patient being discharged about four hours later. Instructions were given for the application of collagenase ointment 4 times a day during the first 30 days, with weekly visits to the practice for reassessments with the surgeon. A humectant re-epithelizing lotion composed of essential fatty acids; medium chain triglycerides, vitamins A and E began to be applied on the 30th day, associated with the frequent use of a diverse lotion containing a high sun protection factor. On the 60th day after the surgery, a silicone-based gel was introduced, with six applications per day, associated with the overnight coverage of the lesion with a silicone gel sheet. This conduct was maintained up until the 6th postoperative month. After this period, the patients continued to use only the lotion containing sunscreen for another 6 months (Figure 2).

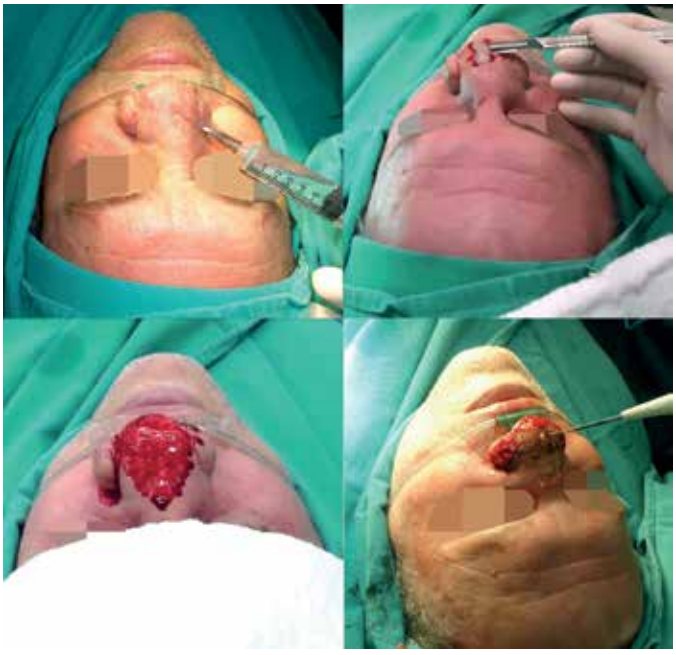

Figure 1: Intraoperative aspects: local anesthesia, nasal tangential resections and electrocoagulation of the bloody area

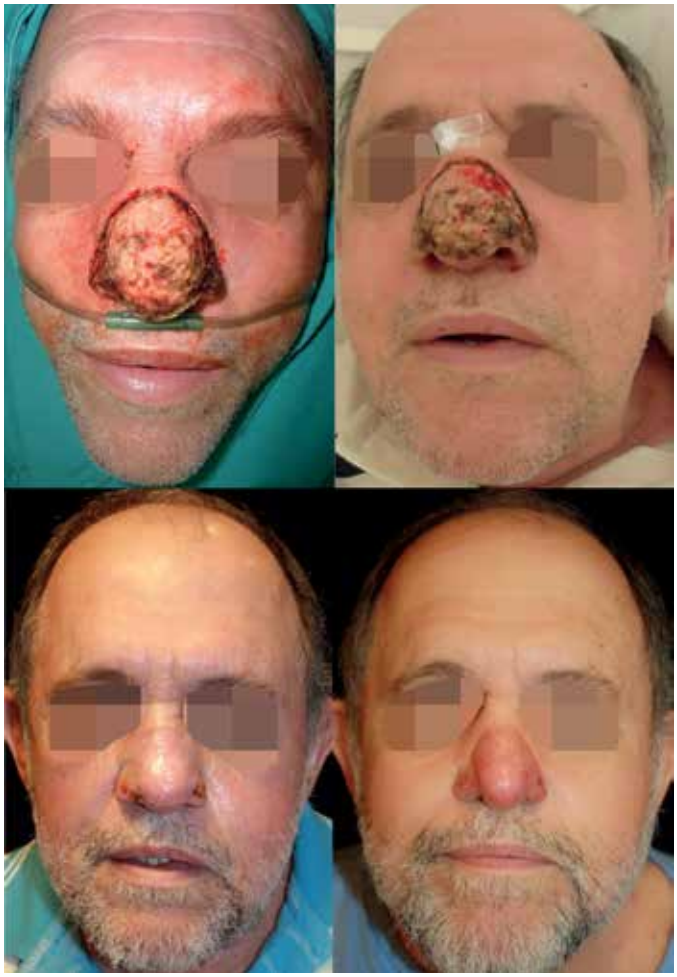

Figure 2: Nasal appearance in the immediate postoperative period after 30 and 60 days

Patient 1: Mr. "JLC", 59 years old, white, diabetic, non-alcoholic, presenting thickening of the nose, nodules, telangiectasia, dilation of pilosebaceous pores for 3 years (Figure 3).

Patient 2: Mr. "LT", 54 years old, white, alcoholic, presenting erythema, telangiectasia, cutaneous thickening and dilation of pilosebaceous pores in the external nasal area, with two years of development (Figure 4).

DISCUSSION

Much remains to be discussed about the treatment of rhinophyma. [2] Several interesting options – surgical or not – are available in the literature. Nevertheless, the need for more effective, less aggressive alternative techniques that lead to better results is reported by various authors for years, especially for more advanced cases of the condition.[2, 9] The use of topical treatments – such as trichloroacetic acid – and ablative techniques – such as CO_2 laser and RF – have emerged in recent years as non-surgical alternatives for the treatment of rhinophyma.[1] The latter use ablation of the lesion associated with cauterization of the wound, promoting adequate hemostasis, technical precision and less tissue destruction.[2, 9] These procedures, however, are more time consuming, rely on technology and/or proper training, which are not always available to all physicians. Moreover, the outcome can be different from that one obtained with the combined technique, especially in severe cases.[4, 9, 10] The results described in the present study demonstrate that an established technique, such as tangential excision, combined with electrocoagulation, can be improved based on the association of simple, cost effective and easy to perform cosmetic treatments. The topical treatment with collagenase (used in the initial postoperative period) ensured the cleansing of the treated areas, enzymatically dissolving necrosis and crusting. In addition, it also promoted the formation of granulation tissue.[11] It is commonly reported that re-epithelialization of the wound after electrocoagulation takes between 10 and 15 days.[7] In the present study, the use of such technique reduced scarring and deformity, and accelerated the re-epithelialization from the remaining sebaceous glands. [8] The association with sunscreen may have prevented the undesirable hyperpigmentation described in the conventional technique.[2] Several authors advocate the prolonged use of sunscreen in cases of rhinophyma, since irritating factors, such as ultraviolet radiation, can contribute to the progression of rosacea.[4] Furthermore,

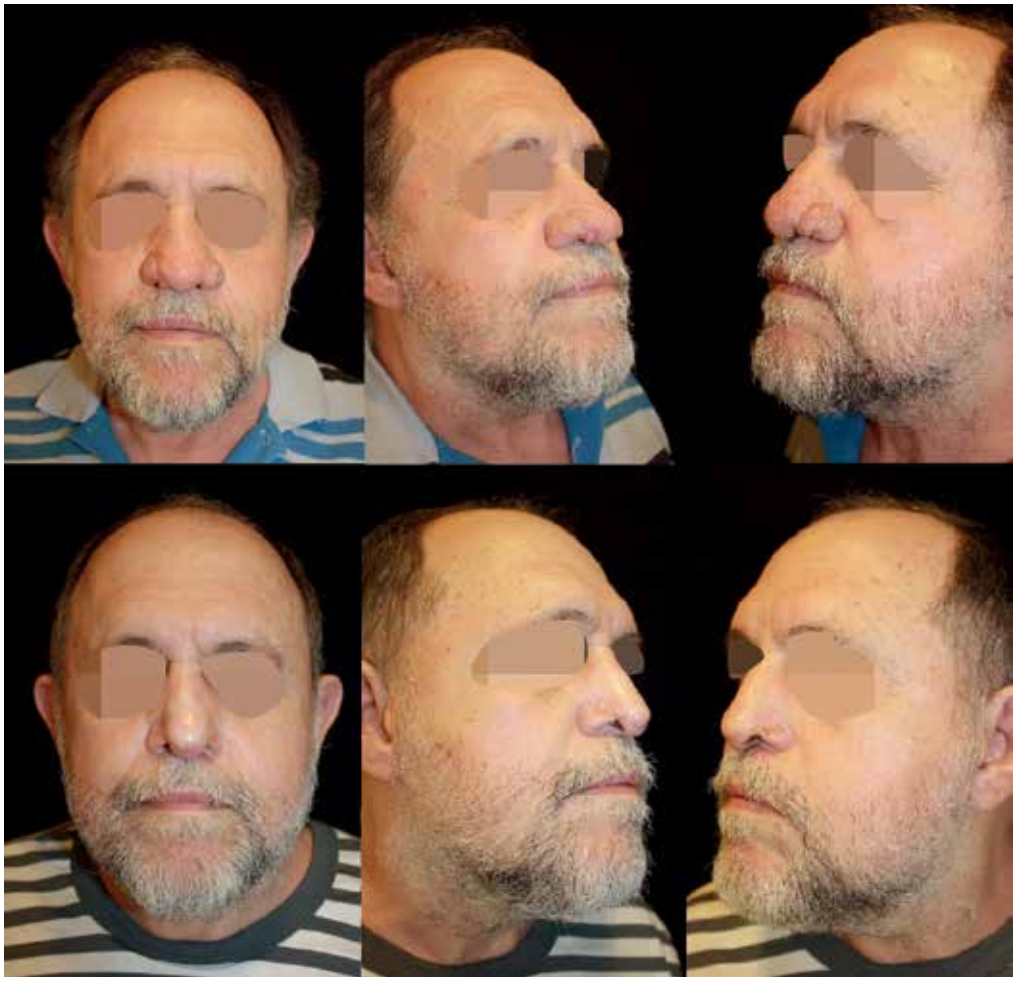

Figure 3:
APreoperative and postoperative (two years after) aspects

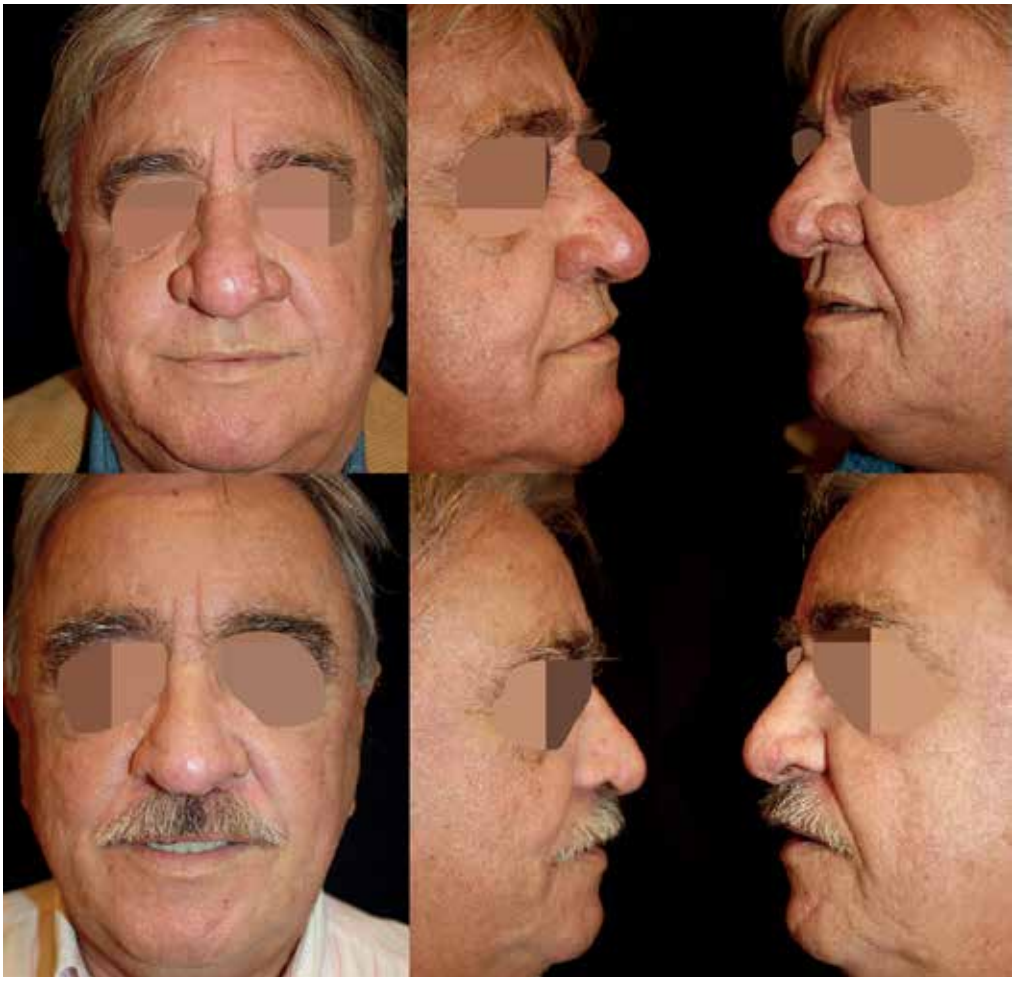

Figure 4:
Preoperative and postoperative (two years after) aspects

exposure to the sunlight can trigger the hyperpigmentation of the lesion due to its intense proinflammatory effect. [12] None of the patients experienced worsening of the lesion or local irritation caused by the use of sunscreen. Among the potential complications of electrocoagulation, which were not observed in the present study, are the formation of unsightly scarring, and asymmetry and perforation of the nasal cartilage.[8] Covering the lesion with the silicone gel plate promoted an increase in the local temperature and strengthened the action of endogenous collagenase, allowing the final resolution of the scar, preventing its hardening and reducing the degree of contraction.[13] The combined use of the ointment and silicone plate improved the final appearance of the wound, minimizing the risk of complications described in the conventional technique.[8] The final results obtained in patients treated with this method have been achieved due to the combination of the beneficial effects provided by the use of various cosmiatric techniques – some already established in the literature, others still requiring further studies. [4] Still, each of them played a key role in the successful treatment and maintenance of the outcomes, which remained stable for a period in excess of 5 years, demonstrating the safety and effectiveness of the method.

CONCLUSION

The combination treatment described in the present study arises as an excellent alternative for the treatment of rhinophyma due to its technical straightforwardness and good long-term results.

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Case Reports

Grafting by epidermal scraping in stable vitiligo: a therapeutic option

Enxerto por raspagem epidérmica no vitiligo estável: uma opção terapêutica

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ABSTRACT

Vitiligo is an acquired depigmentation characterized by partial or total loss of epidermal melanocytes. Many therapeutic modalities have been proposed for its treatment. In cases of stable vitiligo surgical treatments are preferred. Grafting by epidermal scraping is a variant of micrografts by punch technique. It is a new, simple and low cost technique, with high rates of repigmentation. The objective of this report is to demonstrate the authors' experience with this technique and discuss the results in an initial series of two cases (three lesions).

Keywords: phototherapy; vitiligo; pigmentation disorders; dermabrasion; melanocytes

RESUMO

O vitiligo é despigmentação adquirida caracterizada pela perda parcial ou total dos melanócitos da epiderme. Inúmeras modalidades terapêuticas foram propostas para seu tratamento. Nos casos de vitiligo estável os tratamentos cirúrgicos são a preferência. O enxerto por raspagem epidérmica é uma variante da técnica de microenxertos por punch. Constitui técnica nova, simples e de baixo custo, com altas taxas de repigmentação. O objetivo deste relato é demonstrar a experiência dos autores com essa técnica e discutir os resultados obtidos numa série inicial de dois casos (três lesões).

Palavras-chave: *fototerapia; vitiligo; transtornos da pigmentação; dermabrasão; melanócitos*

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INTRODUCTION

Vitiligo is a disorder consisting of acquired depigmentation that is aesthetically disfiguring and characterized by partial or total loss of epidermal melanocytes. It affects from 0.5% to 1% of the world population.[1] It arises as hypo- or achromatic macules, usually bilateral and symmetrical. It can be classified into different clinical forms: vulgaris, acrofacial/acral, focal, mucosal, segmental and universal.[2] Many therapeutic modalities have been proposed for its treatment. In stable cases of vitiligo – defined by the absence of both new lesions (or the progression of existing ones) and the Koebner phenomenon for at least one year, surgical treatments are preferred.[3] Surgical treatments have been described since 1964, and numerous techniques have been developed.[4] The choice of the method depends on the location of the lesions, the extent of the picture, skin phototype of the patient and the experience of the surgeon. Chart 1 describes the main surgical techniques and indications. The epidermal scraping grafting technique is a variant of the punch micrografting technique. It is a new, simple and cost effective technique that leads to high rates of repigmentation. Its outcome is compared to that of the transplantation techniques

Chart 1: Key surgical techniques and their indications

	Donor area	Preparation of the receiving area	Indications	Advantages	Disadvantages	Success rate (%)	Note
Punch grafts	Punch biopsy	Preparation of the receiving area	Segmental, localized, unilateral lesions, lips, fingers, palms and soles	easy to implement, does not require special equipment, cost effective	Cobblestone appearance, dyschromias, scars in the donor area, time consuming	68-82	Test-area advisable
Partial thickness grafts	Shaving biopsy	Punch biopsy	Multiple lesions, lips, eyelids and extremities	Absence of scars	Milia, scars in the donor area, partial loss of the graft, thick margins	78-91	Repigmentation of leucotrichia described
Suction blistering grafts	Liquid nitrogen, syringe, special negative pressure device	Dermabrasion with dermabraser or laser	Limited lesions, segmental, facial lesions, lips, eyelids, bony prominences of the fingers	Easy, safe and without scars	Hyperpigmentation, time consuming	73-88	A new graft between the blisters may be necessary
Cultured epithelial grafts	Shaving biopsy	Abrasion with dermabraser or laser	Extensive lesions	Indicated for extensive areas, absence of scars	Transient hyperpigmentation, long lasting erythema, requires specific device, time consuming	33-54	Immobilization in order to avoid loss of the graft
Keratinocyte - melanocyte suspension grafts	Shaving biopsy	Blistering, or abrasion with dermabraser or laser	Multiple lesions	Indicated for extensive areas, easy and quick to perform, absence of scars	Long lasting erythema, requires specific device, contraindicated for lips and eyelids	66-85	Good fixation required
Melanocyte suspension grafts	shaving biopsy	Dermabrasion with dermabraser or laser	Extensive lesions	Indicated for extensive areas, absence of scars	Time consuming, requires specific device, transient hyper- and hypopigmentation temporary	22-72	Outcomes infrequently reported

Chart 2: Description of the vitiligo cases

Case	Age	Gender	Vitiligo's stability (years)	Classification	Location	Previous treatments
1	F	13	5	Focal	Dorsum of foot	Oral and topical corticosteroids, oral psoralen, topical tacrolimus, oral antioxidants, phototherapy
2-A	F	68	>10	Segmental	Upper dorsum	Topical and intralesional corticosteroids, oral psoralen, oral antioxidants, phototherapy
2-B	F	68	>10	Segmental	Right lateral cervical	Topical and intralesional corticosteroids, oral psoralen, oral antioxidants, phototherapy

with culture of melanocytes.[3] Despite the fact that it is a technique that has been developed more recently, it is already widespread in some countries – in India for example. The objective of the present report is to demonstrate the authors' experience with this technique and discuss the outcomes obtained with an initial series of two cases (three lesions).

CASE REPORTS

1- Description of cases: Epidemiological (gender, age, skin color) and clinical information (duration of stability, classification and location of the vitiligo), and previous treatments of the patients involved in this study are in Chart 2.

2 - Description of the technique:

Donor area (lumbosacral region).

Figure 1: Obtaining the ideal tissue fragment: the blade can be read due the transparency of the tissue. Detail: final consistency of the material obtained after fragmentation

The antisepsis was performed with aqueous chlorhexidine and local anesthesia injection was carried out with 2% lidocaine.

With the skin stretched, thin tissue slices were obtained using sterile razor blade (with firm and smooth upward and downward movements). The tissue obtained should ideally be thin enough to allow that the inscription imprinted on the blade be read through transparency. This tissue was then placed in a sterile container with saline and fragmented with a delicate scissors for about 20 minutes, up until a homogeneous consistency was obtained (Figure 1).

The dressing of the donor area should not be adherent and prepared with petrolatum gauze, with patients being instructed on the local hygiene and the daily change of the dressing.

Receiving area

Antisepsis and local anesthesia were performed similarly to the procedure carried out in the donor area. The receiving area was then manually dermabraded with sandpaper up until it reached the point of pinpoint bleeding. The obtained exudate should not be removed. The material obtained from the donor area was subsequently placed on the abraded area, within the limits of the lesion (Figure 2A).

The area was covered with non-adherent open mesh cotton dressing soaked in paraffin and chlorhexidine, and then finalized with a transparent polyurethane film (Figures 2B and 2C).

Patients should be instructed not to wet the dressing and immobilize the treated area for seven days. After that period, careful local hygiene should be carried out daily.

3 - Development:

Fifteen days after the procedure, phototherapy of the treated area was started with narrow band ultraviolet B (NB-UVB), being performed twice a week.

The follow-up visits took place at weeks 0, 2, 8 and 18, with photographic records being carried out.

From the second week it was already possible to observe uniform epithelialization of the treated area. In both cases the authors obtained good outcomes (uniform pigmentation present in virtually the entire area treated in addition to homogeneous pigment with color similar to the adjacent area), and a high repigmentation rate (Figures 3 to 5).

It was also possible to observe the complete epithelialization of the donor area (Figure 6). Both patients are being followed up at the Dermatologic Clinic, undergoing phototherapy sessions and maintaining the results obtained.

DISCUSSION

The epidermal scraping grafting technique is very simple, easy to perform, does not require expensive materials or equipment and provides high rates of repigmentation. The main advantage of this method as compared to the original punch micrografting technique is that it does not lead to the "cobblestone" aspect in the treated area, dyschromias in the donor and recipient areas, elevation of the grafted area, poor healing of the donor area and, in special, limitation in the extensibility of the donor area.[3,5]

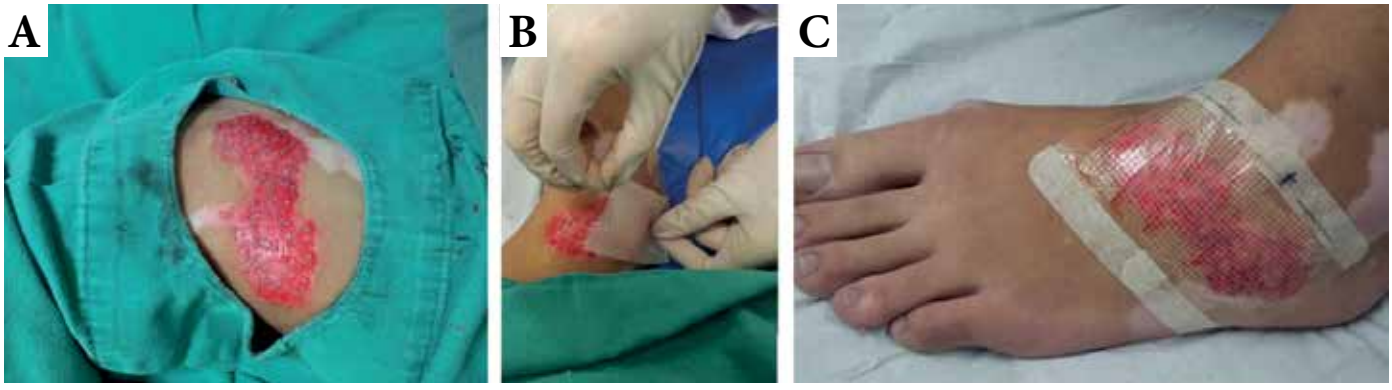

Figure 2: A - Skin fragments positioned on the abraded area; B – Placement of the non-adherent dressing; C - Dressing covered with transparent polyurethane film.

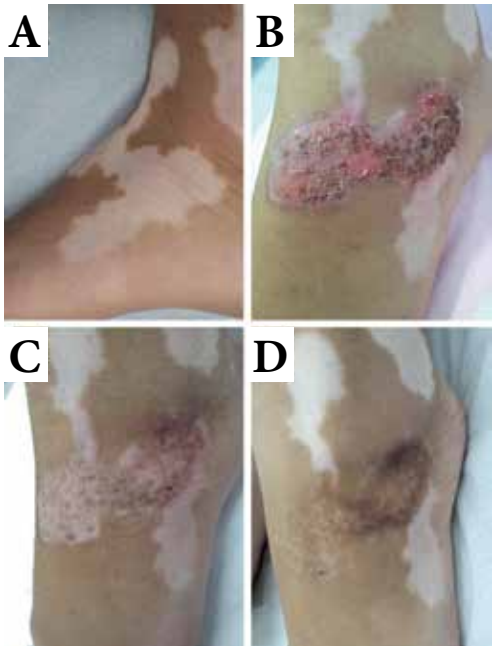

Figure 3: **Case 1**
A - Before the treatment;
B - Two weeks after;
C - Eight weeks after;
D - Eighteen weeks after

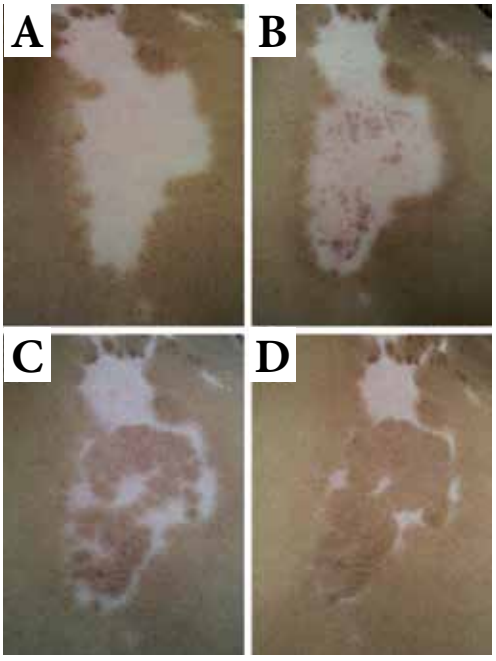

Figure 4: Case 2a
A - Before the treatment;
B - Two weeks after;
C - Eight weeks after;
D - Eighteen weeks after

The epidermal scraping grafting technique can be performed on extensive areas due to the homogeneous consistency of the material laid on the area to be treated. Studies show that the donor area can be up to 1/10 of the receiving area's size. [3]

Regarding the donor area, the most used locations are the thighs, buttocks and lumbosacral region due to the fact that they are photoprotected areas and obtaining tissue from them is straightforward. In general, the donor area has fast and satisfactory epithelialization. Nevertheless, post-inflammatory hyperpigmentation, hypertrophic scars and unsightly scars may occur, depending on the individual healing process and the surgeon's skills.[3]

The receiving area can be prepared using several techniques, such as dermabrasion, laser abrasion, and blistering induction by suction or liquid nitrogen. [5] In the present study, the authors chose to use the manual dermabrasion with sandpaper technique. The acral regions and the areas over the joints should be avoided – especially in very young patients – for it is considerably difficult to implement the techniques in these locations and there is risk of treatment failure. In addition, the receiving area should be dermabraded only until the pinpoint bleeding emerges in order to avoid unsightly scars. Among the complications reported in the receiving area are: dyschromias, infections and local pain.[3]

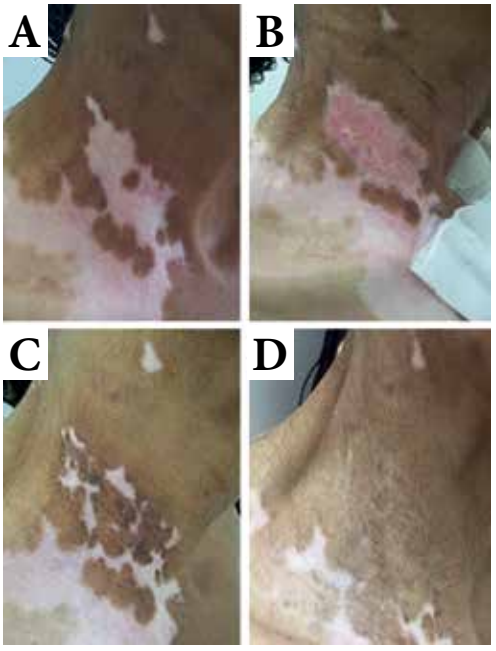

Figure 5: Case 2b
A - Before the treatment;
B - Two weeks after;
C - Eight weeks after;
D - Eighteen weeks after

Figure 6: Final appearance of the donor area.
A - Case 1;
B - Case 2a;
C - Case 2b.bra

There was absence of complications in the present study. Patients should be properly instructed regarding the post-operative care. The treatment area should be kept immobilized and covered with a dry dressing for one week. After this period (when the dressing should be removed), it is important to provide guidance about the expected clinical aspect and instructions on the need for meticulous daily cleansing, aiming at allowing the spontaneous peel off of the crusts. Despite the small number of references on this fact, the high rate of repigmentation obtained with this technique is a consensus in the literature.[1, 3, 6, 7] Studying 26 patients, Krishnan et al.[3] achieved repigmentation rates of 90% five months after the treatment.

Yet, the reason for the success in achieving high pigmentation rates with this technique is still unknown[7] and some authors have questioned whether the obtained pigment is a result of the transfer of melanocytes or of post-inflammatory hyperpigmentation, without diffusion of melanin.[5]

Other studies show that the abraded area would be of crucial importance for the success of the procedure since it produces growth factors, such as the vascular endothelial growth factor, which is important for the epithelialization and repigmentation processes.[3, 8]

It is also believed that melanocytes are not absent in vitiligo; rather, they would be inactive and a stimulus, such as curettage or, as was the case in this study, abrasion, would encourage the transcription of the tyrosinase gene, through the activation of the c-kit receptor by the cytokines induced by the stimulus.[9, 10]

Finally, the combination of the stimulus with the transfer of melanocytes and keratinocytes appears to be more effective than the isolated stimulus. While the difference was not statistically significant, Quezada et al.[6] demonstrated the presence of a faster response and a more uniform pigmentation of the treated area with dermabrasion associated with the transfer of melanocytes and keratinocytes as compared to the isolated abrasion.

CONCLUSION

Vitiligo is a condition with great psychosocial impact and surgical treatments have proved promising for their positive effect in the therapeutic response of recalcitrant cases. The epidermal scraping grafting technique has high repigmentation rates and does not require expensive technology, which has motivated the authors in the present study, corroborating the literature and helping to disseminate this technique.

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Late granulomatous reaction to hyaluronic acid associated with rheumatoid arthritis treated with leflunomide

Reação granulomatosa tardia por ácido hialurônico associada à artrite reumatoide em uso de leflunomide

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ABSTRACT

Hyaluronic acid is the currently most used filler in dermatology due to its low risk of adverse events. The objective of this study is to report a case of granulomatous reaction after filling with two types of hyaluronic acid, in the perioral region and in the nasolabial folds. A female patient with rheumatoid arthritis treated with leflunomide presented onset of symptoms 30 months after filling. Autoimmune diseases may facilitate the occurrence of complications and should be followed carefully before filling with hyaluronic acid. As already reported with the use of interferon and omalizumab, granulomatous reaction to fillers may occur after use of leflunomide.

Keywords: hyaluronic acid; granuloma; rheumatoid arthritis; foreign-body reaction

RESUMO

O ácido hialurônico é o preenchedor atualmente mais utilizado na dermatologia devido ao baixo risco de efeitos colaterais. O objetivo deste trabalho é relatar um caso de reação granulomatosa após preenchimento com dois tipos de ácido hialurônico, na região perioral e no sulco nasogeniano. A paciente, portadora de artrite reumatoide em tratamento com leflunomide, apresentou início dos sintomas 30 meses após o preenchimento. Doenças autoimunes podem facilitar a ocorrência de complicações e devem ser observadas com cuidado antes do preenchimento com ácido hialurônico. Como já relatado com uso de interferon e omalizumab, a reação granulomatosa por preenchedores pode ocorrer após o uso de leflunomide.

Palavras-chave: *ácido hialurônico; granuloma; artrite reumatoide; reação a corpo estranho*

INTRODUCTION

Ideal cutaneous filling substances have low incidence of complications, low potential for allergenicity and inflammatory reactions, lasting effects, absence of migration, are easy to apply and cost effective. Products with profiles that more closely resemble that one are derived from hyaluronic acid (HA). Despite being generally safe, cases of granulomas and other complications have been described following filling procedures with HA. The present paper describes a case of a granulomatous reaction following a filling procedure, associated with the beginning of use of leflunomide.

CASE REPORT

The patient "MRS", a 59 year-old woman, had complaints of perioral wrinkles. She had a history of well-controlled rheumatoid arthritis and Sjögren syndrome. In May 2007, after having signed a Free and Informed Term of Consent, she un-

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derwent a deep dermal filling with a high viscoelastic HA based gel in the nasogenian fold and a superficial dermal filling with a lower viscosity gel in the superior perioral region. The patient was satisfied with the outcome, however a slight overcorrection in a transverse groove to the left of the upper lip was noticed[2] weeks after the procedure. A palpable papule of 0.3cm in diameter proved persistent in the 3-month reevaluation after the procedure. As it was barely noticeable, a decision was made for observing its development. Nevertheless, the papule persisted in the 19-month review consultation of the lesion in the left supralabial region.

Thirty months after the procedure, the patient returned due to the emergence of multiple nodules in the supralabial region bilaterally, with a 2-week development and progressive increase. She denied having undergone other aesthetic procedures in the region since the initial filling. The patient also reported worsening of the rheumatoid arthritis picture 4 months before, with an increase of prednisone to 20mg/day for 2 weeks and the beginning of 20mg/day leflunomide. A biopsy of the nodular lesion suggested the presence of a chronic foreign-body granulomatous dermatitis affecting the superficial and deep dermis. An amorphous material compatible with HA was observed in the center of the reaction (Figure 1). A treatment was proposed with intralesional injection of hyaluronidase, however the patient rejected it. A systemic corticosteroid therapy was then prescribed, with oral prednisone 1 mg/kg for 2 weeks and 0.5 mg/kg for 2 additional weeks, associated with the suspension of leflunomide, with improvement of the picture.

DISCUSSION

Hyaluronic acid is considered the safest dermal filler, with good cosmetic response. It is a natural polysaccharide – an important structural element of the skin, subcutaneous, connective tissue and synovial fluid. It belongs to a group of a few substances that are identical in all living beings. It acts by adding volume to the tissues and restoring contours. Yet, there are some cases of side effects caused by the product. [1]

Interferon and new immunomodulators can produce granulomatous reaction in patients with dermal fillers, both with HA and calcium hydroxyapatite. Although this complication is rarely reported and the filler used is often difficult to identify, this seems to be the first case described with leflunomide, with the fact that the patient had been followed up since the initial procedure simplifying the diagnosis.

Leflunomide interferes with the hyaluronic acid synthase, suppressing the production of HA in the fibroblast-like synoviocytes in a dose-dependent effect, aiding in the treatment of rheumatoid arthritis. Little is known about its interference in the skin's HA. The use of leflunomide – as well as of methotrexate – in patients with rheumatoid arthritis favors the development of a granulomatous response with increased frequency of rheumatoid nodules. [2]

In the present case, it was not possible to exclude the hypothesis that the frequent use of systemic corticosteroids may have masked a preexisting granuloma, nevertheless the rapid progress after the start of leflunomide and the improvement after its suspension suggest the involvement of this drug in the process. A deviation of the T helper 2 immunity (Th2) to Th1 can

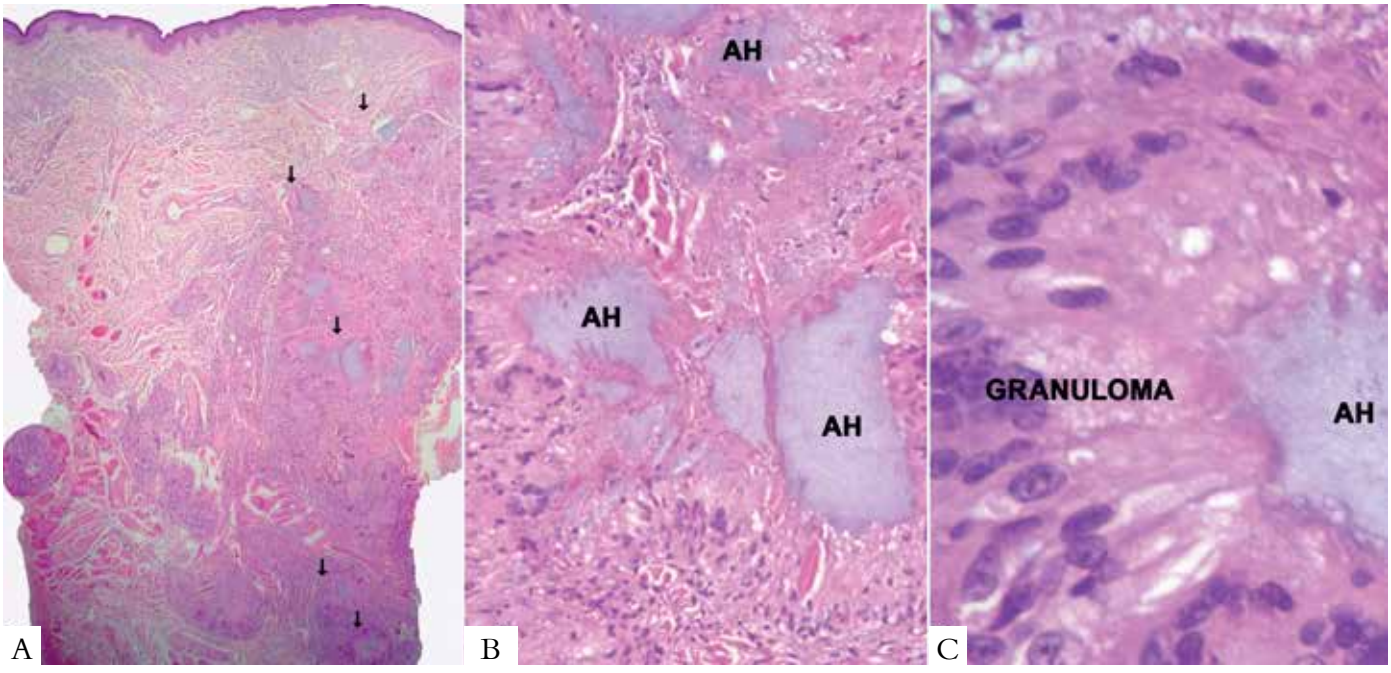

Figure 1: A: foreign body granuloma, medium and deep dermis; B: basophilic substance compatible with hyaluronic acid (HA); C: correlation of granuloma with the foreign body material

explain the granulomatous reaction as described in granulomas induced by interferon. [3] Another possibility is that an increase in the corticosteroid dose followed by rapid reduction may contribute to this process, despite the fact that the patient has denied taking prednisone doses greater than 20 mg/day.

Regarding the association with rheumatoid arthritis, some reports suggest the relative contraindication of filling procedures with HA in patients with lupus erythematosus and collagen diseases, nonetheless there is absence of descriptions mentioning rheumatoid arthritis.

By comparing the physical properties of HA-based cutaneous fillers, such as fluid gel proportion, HA modification extent, cross-linking percentage, particle size and module, it is possible to define the product's behavior and the depth to which it should be applied for a better clinical response. [4] For this reason, two different types of HA were used in the patient, with both apparently leading to reactions, since all filled areas were affected.

Comparing various cutaneous fillers, HA is an excellent choice for increasing lip volume and perilabial volumes due to its hydrophilic properties in the tissues.[3] The fillers containing non-animal origin HA can cause hematoma, edema and erythema more often. These complications are most common in the labial region, due to increased vascularization and tendency to edema in this area. Both of the fillers used in the present study were not derived from animals. The Restylane® line of products (QMed AB, Uppsala, Sweden) are produced by fermentation of *Streptococcus* cultures, partially cross-linked by Nasha technology (Non animal-stabilized hyaluronic acid). The product Restylane Fine Lines® has 20mg/ml HA and is indicated for the treatment of fine superficial wrinkles, such as the one in the perioral region. The Perfectha Deep® is HA based gel with high viscoelasticity, used in deeper wrinkles, such as the ones in the nasogenian folds. It contains 24 mg/ml HA, stabilized by hydrogen bonds, which allow the formation of a stable gel. The products were used at appropriate levels of injection. Both have low amounts of protein and endotoxin (<0.25 IU/g), with rare hypersensitivity reactions.

Side effects caused by cutaneous fillers are divided into intermediate (from 1 to 12 months after the procedure) and long term (12 months after the procedure). [3] Intermediate side effects involve local effects (edema, angioedema, skin induration, nodules) or systemic effects (fever, arthralgia, arthritis, skin and eye lesions, and dry mouth). Pain, erythema, edema and ecchymosis are expected during the first 2 weeks, however persistent edema has been reported. [5] In cases of granuloma caused by HA in the first weeks after filling, it is hypothesized that there is induction due to contamination by a protein during the procedure, possibly by the biofilm created around the implantation site. [6] Among the long-term side effects, granulomatous reactions are the most feared. Trauma and injection of other filling substances in the same location of the HA are possible causes for the onset of the process. In the present case, however, in addition to the late onset, the patient has denied undergoing any other procedure or aggression in the site over the past 30 months, ruling out these triggering factors. Late granulomatous or inflammatory reactions without associated factors have been reported in some cases after multiple HA injections.[3, 7] In most cases described, reactions have arisen within 18 months of the filling procedure, though they can occur up until 36 months, during the enzymatic degradation period.[7] In the present case, 30 months were required for the onset.

Despite the fact that late reactions to HA had persistent or recurring form in more than 20% of cases, an improvement of symptoms was observed in the present case as a result from systemic corticosteroid therapy, without recurrence. [3]

CONCLUSION

The ideal filler is still utopian, and it is necessary to evaluate risks and benefits on a case-by-case basis. It is indispensable that the patient be informed on the potential risks in advance. Rheumatoid arthritis, as well as the use of drugs such as leflunomide, might facilitate the occurrence of complications and should be contraindications for HA based filling procedures. Although uncommon, complications caused by HA implants can occur late on, after the average duration of the degradation period (18 months after the filling procedure).

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Letters

Soft tissues filling: not so minimally invasive

Preenchimento de tecidos moles: nem tão minimamente invasivo

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ABSTRACT

The dermal filling of soft tissue is a common practice. However there are potential serious complications associated. The authors are of the opinion that professionals who perform dermal filling procedures must have solid knowledge of anatomy and complete mastery of fillers injection technique. The behavior in potential cases of complications must be started early and conducted efficiently.

Keywords: Blindness; hyaluronic acid; injections

RESUMO

O preenchimento cutâneo de tecidos moles é uma prática frequente. No entanto há potenciais sérias complicações associadas. A opiniao dos autores é de que os profissionais que realizam procedimentos de preenchimento cutâneo devem possuir sólido conhecimento de anatomia e completo domínio da técnica de injeção de preenchedores. A conduta em potenciais casos de complicações deve ser iniciada precocemente e conduzida de maneira eficiente.

Palavras-chave: *cegueira; ácido hialurônico; injeções*

The cutaneous injection of filling substances in soft tissues is a common practice. In 2014, 2.3 million injections were performed in the United States of America, corresponding to an increase of 253% when compared to 2000.[1]

This procedure has become a routine in the dermatologic and plastic surgery practice, with injections being described as minimally invasive. However, serious and irreversible, and potentially fatal complications can occur. Concomitantly, there is no formal or well-established training during the medical residence years and physicians depend on workshops and video-based self-learning to begin to perform the procedure. In addition, the injection of cutaneous fillers is sometimes carried out by general practitioners, who usually do not have any knowledge of anatomy. The increasing number of reports of serious complications in the literature is an alarming fact.

The cutaneous filler injection technique should be implemented in light of solid anatomical knowledge of the body part in question, for not only minor complications, but also severe and irreversible damage have already been reported.

In a recent literature review, 10 cases of blindness were found after filling injections in the face.[2] Two patients developed transient blindness and 8 developed permanent blindness in the affected eye. The injected substances were: bovine collagen, polymethylmethacrylate, hyaluronic acid and calcium hydroxyapatite. The nose was the most frequently injected area (root -1 patient, dorsum - 2 patients, tip - 2 patients). The remaining 5 cases included the following areas: forehead - 1 patient, glabella - 2 patients and glabella and malar region - 2 patients.

In another important study by The Korean Retina Society, 3 a nationwide survey found that 22 patients developed serious complications after undergoing filling injections in soft tissues. Considering hyaluronic acid injections, 5 patients had diffuse occlusions and 7 had localized occlusions. Long-term vision loss occurred in 43% of patients and 1 patient suffered brain lesion. Anterior segment ischemia has arisen as corneal edemas in 5 patients (39%), while the inflammation of the anterior chamber occurred in 7 patients (54%). The injected areas were as follows: glabella, nasolabial folds and nose (rhinoplasty for nasal increase).

These severe neurological and ocular complications result from the specific configuration of the facial vasculature, in which internal and external arterial branches connect. Embolization is linked to the arterial retrograde movement of the injected product (originating in the peripheral vessels and progressing into the ophthalmic artery system, close to the origin of the retinal artery). After the injection, the systolic pressure drives the filling material column into the ophthalmic artery and its branches. The same emboli might move further distally, reaching the internal carotid artery, causing cerebrovascular embolism and stroke.

Such incidents can be avoided by using a proper technique for the injection of the cutaneous filler. 4 Aspirating before injecting, injecting slowly at minimum pressure, performing additional injections, and employing blunt tip microcannulas are some of the techniques that help prevent intravascular injections. In case of development of ocular symptoms, the following procedures are recommended: urgently refer the patient to an ophthalmologist, inject from 300 to 600 UI (2 to 4 ml) hyaluronidase in the retrobulbar region, inject hyaluronidase in the area where the filler was applied. Such emergency management should be carried out within 90 minutes after application of the filler.[5]

Likewise, and with a higher frequency of cases reported in the literature, skin necrosis might also occur as a result of cutaneous filler injections.

Unfortunately, cases of blindness and skin necrosis resulting from the injection of cutaneous fillers are not always published – and when they are published, there is no explanation about the injection technique. In the context of the lack of a formal database aimed at recording serious complications, it is possible to conclude that such events are actually more frequent than professional applicators suppose. Thus, professionals who apply cutaneous fillers should be extremely cautious and use minimally invasive techniques, taking advantage of a robust knowledge of the vascular anatomy and safe injection techniques.

Plastic Surgery and Dermatological Societies should direct efforts to alert the relevant public about the alarmingly increasing number of serious complications resulting from the injection of cutaneous fillers in soft tissues.

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