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Poderão ser aprofundados os temas específicos nas áreas de interesse da S&CD, algoritmos, compilações e estatísticas. Estes trabalhos têm formato livre, porem devem conter resumo não estruturado de até 100 palavras e conclusões ou considerações finais. Limite: texto até 6000 palavras, 10 ilustrações e 60 referências. Os artigos de revisão sistemática ou metanálises devem seguir orientações pertinentes (http://cochrane.org)

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É o relato de uma pesquisa investigativa original nas áreas de Cirurgia Dermatológica, Oncologia Cutânea, Tecnologia em Dermatologia e Dermatologia Cosmética. Exemplos: estudos experimentais, estudos clínicos, comparações e descrições de técnicas ou de métodos de avaliação, estudos de áreas afins (ex: estudos farmacêuticos em dermatologia cosmética). O texto deverá conter até 4000 palavras, 10 ilustrações e 35 referências e seguir o formato IMRDC (Introdução e objetivo, Métodos, Resultados, Discussão, Conclusão)

Resumo: deverá conter no máximo 200 palavras e ser estruturado seguindo os itens: Introdução, Objetivo, Métodos, Resultados e Conclusões. Não é permitido afirmar que os resultados ou outros dados serão apresentados ou discutidos.

Introdução: citar as razões que motivaram o estudo, descrevendo o estado atual do conhecimento sobre o tema. Utilizar o último parágrafo para especificar a principal pergunta ou objetivo do estudo, e a principal hipótese testada, se houver.

Métodos: Explicar como o estudo foi feito:

a-Tipo de estudo: descrever o seu desenho especificando a direção temporal (retrospectivo ou prospectivo), o tipo de randomização quando utilizada (pareamento, sorteio, sequenciamento, etc), se o estudo foi cego, comparativo, controlado por placebo, etc.

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c-Procedimentos: descrever as principais características das intervenções realizadas, detalhando a técnica e lembrando que o estudo de investigação deverá ser reprodutível.

d- Descrição dos **métodos** utilizados para avaliação dos resultados.

e- Inclusão da **análise estatística** descritiva e/ou comparativa com descrição do planejamento da amostra (representativa do universo a ser estudado), a análise e os testes estatísticos e apresentação dos níveis de significância adotados. A utilização de análises estatísticas não usuais é incentivada, porém neste caso, deve-se fazer uma descrição mais detalhada da mesma.

Resultados: descrever os principais resultados que devem ser acompanhados de estimativas pontuais e medidas de dispersão (p.ex., média e erro padrão) ou de estimativas intervalares (p.ex., intervalos de confiança), bem como os níveis descritivos dos testes estatísticos utilizados (p.ex. "p-value"). Os achados também devem ser interpretados sob o ponto de vista clínico.

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.

Conclusões: devem ser concisas e responder apenas aos objetivos propostos. A mesma ênfase deve ser dada para estudos com resultados positivos ou negativos.

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Descrição de novas técnicas ou detalhes de técnicas. Resumo não estruturado de até 100 palavras, introdução com breve revisão de literatura, métodos, resultados, discussão e conclusão. Limite: 1200 palavras, 8 ilustrações e 30 referências.

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Descrição de casos ou serie de casos de relevância nas áreas de interesse da S&CD, com descrição de tratamentos, complicações, etc. Resumo não estruturado de até 100 palavras, introdução com revisão de literatura, métodos, resultados, discussão e conclusão, sempre que pertinentes. Limite: texto até 1200 palavras, 8 ilustrações e 30 referências.

7 – CARTAS

Comentários objetivos e construtivos sobre matérias publicadas ou notas breves. Texto até 600 palavras, 2 ilustrações, e no maximo 5 referências.

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Vascular anomalies: review of classification, clinical and therapeutic aspects

Anomalias vasculares: revisão da classificação, dos aspectos clínicos e terapêuticos

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191131445

ABSTRACT

Vascular anomalies correspond to a broad spectrum of changes that fall into two main groups: 1) vascular tumors, which represent proliferative lesions, and 2) vascular malformations, caused by ectasia in vessels, whether capillary, venous or lymphatic. This article reviews the main vascular anomalies observed in dermatological practice, their main classifications and available treatments, focusing on the use of lasers and intense pulsed light to lighten cutaneous vascular lesions, especially those resulting from malformations.

Keywords: vascular Malformations; Hemangioma; Vascular neoplasms; Laser therapy; Intense pulsed light therapy; Dermatology

RESUMO

As anomalias vasculares correspondem a um extenso espectro de alterações que se dividem em dois grupos principais: 1) tumores vasculares, que representam as lesões proliferativas e 2) malformações vasculares, originadas por ectasias nos vasos, sejam elas capilares, venosas ou linfáticas. Este artigo revisa as principais anomalias vasculares observadas na prática dermatológica, suas principais classificações e tratamentos disponíveis, com enfoque na utilização de lasers e luz intensa pulsada para clareamento das lesões vasculares cutâneas, sobretudo naquelas decorrentes de malformações.

Palavras-Chave: *Vascular malformations; Hemangioma; terapia a Laser; Terapia de luz pulsada intensa; Dermatologia; Neoplasias vasculares*

INTRODUCTION

Vascular anomalies have a broad clinical spectrum, from an aesthetic-only cutaneous manifestation to life-threatening lesions. They predominate in children and young adults and can be classified into proliferative lesions (tumor) and vascular malformations.[1,2] Distinguishing these lesions is difficult due to their phenotypic diversity, and, not infrequently, the term "hemangioma" is misused to describe vascular malformations.[1,3] Due to the large number of diseases that constitute vascular anomalies, we review those of primary dermatological interest as well as their main therapeutic approaches.

Review Articles

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Classification of vascular anomalies

The oldest classification of vascular anomalies was described in 1863 by Virchow, who divided them into angioma simplex, cavernous angioma, racemic angioma, and lymphangioma, considering the pathology of the lesions.[1]

Over time, the nomenclature of vascular anomalies changed, and, in 1982, Mulliken and Glowacki proposed a classification that correlated the clinical presentation with the natural history and histopathology of the lesions, dividing them into two main types: hemangiomas and vascular malformations.[2,3] Analyzing the clinical evolution and cellular characteristics of 49 specimens of vascular lesions, the authors identified differences that supported the new nomenclature. Hemangiomas in the proliferative phase showed endothelial hyperplasia with 3H-thymidine incorporation (cell proliferation marker), subendothelial multi-laminated basement membranes formation, and were clinically characterized by rapid growth in early childhood. In the involution phase, hemangiomas showed histological fibrosis and fat deposition, low or absent 3H-thymidine cell aggregation, and clinical regression of the lesion. The endothelium of hemangiomas showed in the histology Weibel-Palade bodies, presence of alkaline phosphatase, and factor VIII production. On the other hand, they observed that vascular malformations revealed no incorporation of 3H-thymidine and maintained normal cellular structural characteristics.[4]

In 1996, the International Society for the Study of Vascular Anomalies (ISSVA) adopted the division of vascular anomalies into tumors and malformations, using this classification for over a decade.[1,3]

Starting in 2013, a group of ISSVA leaders sought to update the classification of vascular anomalies to describe new findings, including genetic and histological information. In 2014, this group added the description of diseases associated with vascular anomalies, such as Klippel-Trenaunay and Sturge-Weber Syndromes, for example.[1] The classic names: capillary hemangioma, cavernous hemangioma, and tuberous hemangioma were abolished.[2] Figure 1 summarizes the ISSVA classification adopted in 2014.

In 2018, ISSVA presented the evolution in the classification of these anomalies, with the identification of new genes implicated in some diseases (Chart 1).[5]

Also according to ISSVA, there are some provisionally unclassified vascular anomalies because they are not defined as tumors or malformations or because they have clinical and pathological characteristics still incompletely understood. Examples are: intramuscular hemangioma; angiokeratoma; sinusoidal hemangioma; acral arteriovenous tumor; multifocal lymphangioendotheliomatosis with thrombocytopenia/ cutaneovisceral angiomatosis with thrombocytopenia; PTEN harmatoma of soft tissue/ soft tissue angiomatosis; fibro-adipose vascular anomaly.[5]

It is essential to differentiate between malformations and vascular tumors that appear during childhood since the diagnosis can change the treatment direction and the outcome for the patient. It is also essential to know that vascular anomalies can have various effects on the child's psychosocial development because depending on their location, extent, and severity, it can cause significant aesthetic disfigurement.

1.1. Vascular tumors

Vascular tumors are neoplasms characterized by increased endothelial cell proliferation. Lesions usually overgrow, and most are not present at birth, following a phase of proliferation and subsequent involution. They can be classified as benign, locally aggressive, and malignant, based on cellular behavior.[1]

Infantile hemangioma, congenital hemangioma, tufted angioma, and pyogenic granuloma are examples of benign vascular tumors. Kaposiform hemangioendothelioma (KHE) exemplifies locally aggressive or borderline tumors. Angiosarcoma and epithelioid hemangioendothelioma, in turn, represent malignant vascular tumors, which we don't address here.[1,2]

1.1.1. Infantile hemangioma

Infantile hemangioma (IH) is the most common benign vascular tumor among children, with an incidence of 4% to 10%, most frequently observed in the cervicofacial region (80% of cases), in women, and in Caucasians.[1,2] It may have superficial (te-

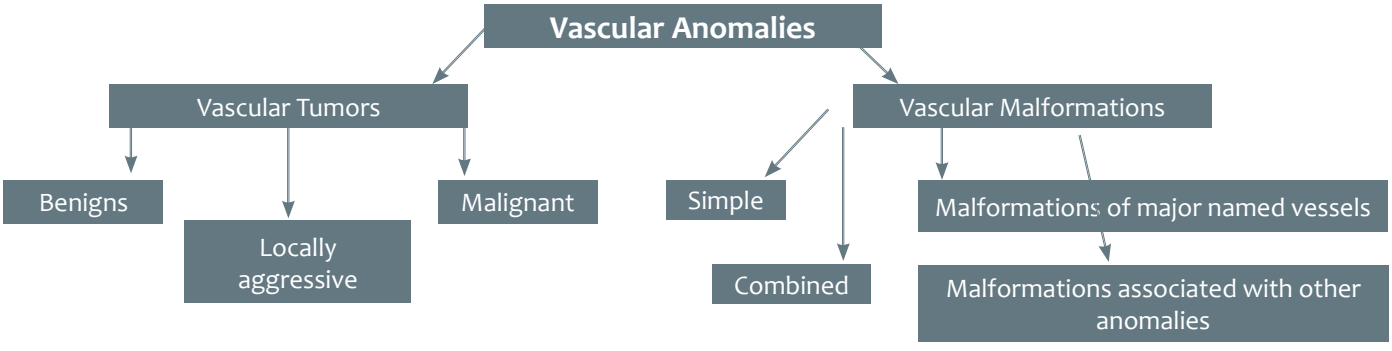

Figure 1: Classification of vascular anomalies
Source: *ISSVA (2014)*

Chart 1: Relationship of major vascular anomalies to their causal genes

Vascular Anomalies	Genes Involved
Benign Vascular Tumors	
Hemangioma Congênito	GNAQ/GNA11
Tufted Angioma	GNA14
Pyogenic Granuloma	BRAF/RAS/GNA14
Locally aggressive vascular tumors (borderline)	
Kaposiform hemangioendothelioma	GNA14
Malignant Vascular Tumors	
Angiosarcoma	MYC
Epithelioid hemangioendothelioma	CAMTA1/TFE3
Capillary Vascular Malformations	
Port-wine stain	GNAQ
Non-syndromic	GNAQ
Associated with ocular or central nervous system abnormalities	GNAQ
Associated with bone or soft tissue hypertrophy	GNA11
Lymphatic Malformations	
Microcystic/ macrocystic or mixed	PIK3CA
Venous Malformations	TEK (TIE2) /PIK3CA
Vascular Malformations Associated with Other Anomalies	
Klippel-Trenaunay Syndrome	PIK3CA
Parkes Weber Syndrome	RASA1
Sturge-Weber Syndrome	GNAQ
Maffucci Syndrome	IDH1/IDH2
Proteus Syndrome	AKT1
Bannayan-Riley-Ruvalcaba Syndrome	PTEN

Adapted from the International Society for the Study of Vascular Anomalies (2018)[5]

langiectatic macules and papules), deep (poorly delimited bluish nodules with fibroelastic consistency), or mixed components. In the first weeks of life, a phase of rapid growth is observed, up to eight to 12 months of age, when most IHs have reached their maximum growth. From then on, an involutive tumor phase begins, with color whitening and volume decrease. Approximately 20% to 50% of IHs involve leaving scarred areas with atrophy, hypopigmentation, fibrous adipose tissue, or residual telangiectasias.[2]

Immunohistochemistry is positive in all evolutionary stages of IH for GLUT-1, which is a glucose transporter generally expressed in brain microvascular endothelium, retina, endoneurium, and placenta, but it is not expressed in healthy skin. GLUT-1 positivity differentiates IH from vascular malformations and kaposiform hemangioendothelioma.[2] The most studied cytokines involved in the pathogenesis of IH are VEGF, b-FGF, metalloproteinases (MMP) 2 and 9, insulin-like growth factor (IGF), osteoprotegerin, and angiotensin-converting enzyme.

Treatment consists of follow-up when the lesions are small and without associated complications, as most IHs spontaneously involve.

In most cases, topical treatment is preferred. Still, immediate systemic treatment should be instituted in cases of potentially disfiguring hemangiomas, in the presence of risk of functional sequelae, or risk of airway obstruction. In 2008, the use of systemic beta-blockers for the treatment of IH was introduced, and propranolol has since been described as the drug of choice for these tumors.[2]

1.1.2. Congenital hemangioma

Congenital hemangioma is a vascular tumor that is completely formed at birth and has no postnatal proliferation. It can be identified intrauterine by obstetric ultrasound, usually in the third trimester of pregnancy. It presents as solitary exophytic plaques or masses of violet color and telangiectatic surface and may have hypochromic areas in the center and periphery. Immunohistochemistry is negative for GLUT-1 in these tumors.[2]

According to natural history, it is classified as rapidly involuting, partially involuting, and non-involuting.[1] The treatment of this hemangioma depends on its size, location, and presence or absence of associated complications, such as ulceration, bleeding, and pain. The application of pulsed dye laser can improve the superficial aspect of the lesion and has applicability in residual lesions of tumors that did not completely regress.[2]

1.1.3. Tufted angioma

Tufted angioma (TA) is a rare and benign vascular tumor, also known as Nakagawa's angioblastoma or progressive capillary hemangioma. It is most commonly located in the cervical region, shoulder, and upper trunk. Few cases are present at birth or associated with hyperhidrosis or hypertrichosis.[1] It presents a risk of association with the Kasabach-Merritt phenomenon, in which severe thrombocytopenia with mild to moderate coagulopathy occurs. There are no effective treatments for TA, and the use of interferon alfa (IFN-alpha) and laser is described.[2]

1.1.4. Pyogenic granuloma

Pyogenic granuloma is a common benign vascular tumor. Also described as lobular capillary hemangioma, most are acquired and manifest as an erythematous nodule or papule, usually with a scaly collar and bleeding surface. It can be localized in any region of skin and does not involve spontaneously. Therapeutic options include the use of topical timolol, electrocoagulation, laser, cryotherapy, and surgical exeresis.[2]

1.1.5. Kaposiform hemangioendothelioma

Kaposiform hemangioendothelioma (KHE) is a rare, locally aggressive vascular tumor. Some authors consider KHE and tufted angioma (TA) as spectra of the same disease.

KHE is present at birth or early in childhood and is more frequent in the trunk, extremities, and retroperitoneal region. Clinically, it is observed as an erythematous-brown macula or plaque that evolves into a poorly defined tumor of hard consistency, similar to tufted angioma. It is an immunohistochemical negative GLUT-1 tumor.[2]

Like TA, KHE is at risk of association with Kasabach-Merritt phenomenon.[2]

1.2. Vascular Malformations

Vascular malformations are caused by an alteration in angiogenesis during the embryological period, presenting vascular ectasia with normal endothelial growth.[1,6] They affect 0.3% to 0.5% of the population and are present at birth in 90% of cases. Also, they increase in length following the child's growth without spontaneous involution.[1,2,6] Although usually sporadic, vascular malformations may be familial and genetically determined.[6]

In 2018, Al-Olabi *et al.* studied sporadic vascular malformations with excluded genetic causes, sequenced the DNA from the tissue of patients with vascular lesions, and found the presence of multiple mosaic-activating variants in four genes of the RAS/MAPK pathway (KRAS, NRAS, BRAF e MAP2K1), commonly activated in cancer cases. They then tested the use of vemurafenib, a BRAF inhibitor, in an animal model with mutations in this pathway, and observed improvement in vascular lesions and re-establishment of blood flow in arteriovenous malformations.[7]

Vascular malformations are divided into four groups: simple malformations, combined malformations, malformations of major named vessels, and malformations associated with other anomalies (bone, soft tissue, visceral).[1]

1.2.1. Simple malformation

They are malformations composed of only one type of vessel: capillary, lymphatic or venous.

1.2.1.1. Capillary malformations

Capillary malformations consist of dilation of capillaries and/or postcapillary venules and mainly affect the skin and mucosa. They present from birth and generally persist throughout life. They may darken and become thicker as the child grows, manifest in isolation or be associated with increased soft and bone tissue.[1,6]

1.2.1.1.1. Port-wine stain

The Port-wine stain is a simple capillary congenital vascular malformation, usually of unilateral, segmental manifestation, without involution tendency.[2,6] Also known as flame nevus, it is commonly mistakenly referred to as "flat hemangioma". It has no predilection for sex and is less frequent in Asian and African American populations. It is the second most common congenital vascular malformation in childhood, characterized by capillary and venous ectasia in the dermis, which results in increased hemoglobin in the skin, giving it a more reddish or purpuric pigmentation.[8,9]

The Port-wine stain originates from irregularities in neural development and genetic mutations, which may be familial or sporadic.[6,8,9] It was recently associated with a mosaic mutation in GNAQ gene.[2,5]

Mutations in the expression of RASA 1 and vascular endothelial growth factor (VEGF) have also been implicated in the pathogenesis and progression of these lesions.[5,10]

In 1986, Smoller and Rosen documented a significant reduction in perivascular nerve fiber density in Port-wine stain compared to healthy skin.[11] Because neural mechanisms regulate cutaneous vascular flow, changes in nerve distribution would affect the development of these lesions.[8,9,11]

They are often seen in the distribution of dermatomes, involving one or more branches of the trigeminal nerve, when located on the face.[8,10]

It presents as a pink, red or purplish-colored macula or plaque on the skin that progressively darkens if not treated early and becomes hypertrophic or nodular with age in approximately two-thirds of patients at 50 years of age.[8,10]

Although it can be located in any region of the body, the face and cervical region are the most affected areas, especially in the distribution of dermatomes V1 (upper third of the face, innervated by the ophthalmic branch of the trigeminal nerve) and V2 (centrofacial region, innervated by the maxillary branch of the trigeminal), and, when present in these topographies, causes marked disfigurement.[1,2,8]

Port-wine stains located on the face may be associated with changes such as jaw hypertrophy, increased lip volume, bite deformity, and spontaneous gingival bleeding.[2]

When located on the face and neck, these stains respond better to laser treatment compared to those in other body areas.[12] The thicker lesions represent great therapeutic difficulty. Therefore, treatment should be conducted early, before thickening and as a way to prevent the development of psychosocial problems resulting from the functional or aesthetic impairment that the lesions cause.[8,13]

The possibility of recurrence or aggravation of capillary malformation even after its treatment should also be considered.

Michel *et al.* reported recurrence in 16.3% of patients with Port-wine stain treated with pulsed dye laser and noted that in children under 10 years of age there was no recurrence of the lesion.[14]

Port-wine stain manifests itself or in association with other changes, such as Sturge-Weber syndrome, Klippel-Trenaunay syndrome, and Proteus syndrome.[2]

1.2.1.1.2. Salmon patch

Also known as nevus simplex, Unna nevus, nevus flammeus nuchae, "angel's kiss" (when located on the glabella), "stork bite" (in the occipital region), the salmon patch occurs in 50% of newborns.[1,2]

It most often affects the midline of the head on the forehead, eyelids, glabella, or neck. Most present lightening or disappear over time, usually before the age of five, but lesions may persist to adulthood in 50% of patients when located in the neck and sacral regions.[1,2] It should be differentiated from the Port-wine stain, which tends to be more winemaking and unilateral.

1.2.1.1.3. Telangiectasias

Telangiectasias are small dilated vessels that manifest in childhood or puberty. Spider angioma, angioma serpiginosum, and unilateral nevoid telangiectasia are examples of primary telangiectasias.[2]

1.2.1.2. Lymphatic malformations

Lymphatic malformations (LM) consist of several lymphatic channels or dilated cysts, lined with endothelial cells with lymphatic phenotype.[1] They may be primary or secondary, localized, or diffuse. They are classified as microcystic, macrocystic, or mixed.

Microcystic LM, or circumscribed lymphangioma, is composed of abnormal microscopic lymphatic vessels, characterized by plaques surmounted by clear or violaceous vesicles.

Macrocystic LM, also known as cystic hygroma, is usually seen at birth or until the second year of life. It presents as a soft, translucent cystic mass with healthy skin coating.

Mixed LMs are more common in the cephalic segment, particularly in the malar region and in the mouth, and may lead to macroglossia. LM treatment includes compression, sclerotherapy, surgical exeresis, and laser.[2]

1.2.1.3. Venous malformations

Venous malformations (VM) are relatively rare congenital anomalies present at birth and not always evident.[2] They usually manifest as blue-colored lesions, when superficial, or as compressible masses, which may increase with exercise. They are the most common type of low-flow vascular lesions and account for about two-thirds of congenital vascular malformations.[1,2]

They present as sporadic and solitary lesions in 90% of patients and as familial multifocal lesions in 10% of them. May be associated with bleeding, aesthetic impairment, and difficulty breathing or eating.[15]

Imaging such as ultrasound, Doppler flowmetry, and magnetic resonance imaging (MRI) help determine the extent of tissue involvement and differentiate between high and low flow lesions.[16]

Venous vascular malformations, in general, are not eradicated. Its usual treatment is sclerotherapy, using solutions such as alcohol 95% or sodium tetradecyl sulfate 1% for small lesions. Surgery may also be performed after obliteration through sclerotherapy. Although surgical excision is the definitive therapy, anatomical and functional limitations and the possibility of aesthetic impairment often hamper its performance.[2]

1.2.2. Malformations of major named vessels

Malformations of major named vessels affect large-caliber veins, arteries, or vessels, usually axial. Congenital arteriovenous fistulas and persistent embryonic vessels are included in this group of malformations.[1]

Although they represent a significant clinical impact, they have few dermatological manifestations..

1.2.3. Combined malformations

Combined vascular malformations associate two or more malformations in the same lesion. Examples are: capillary and venous malformations; capillary and lymphatic malformations; venous and lymphatic malformations; capillary, lymphatic and venous malformations; capillary, lymphatic, venous and arteriovenous malformations.[5]

1.2.4. Vascular malformations associated with syndromes

Vascular malformations, whether simple, major named vessels, or combined, may be associated with bone, soft tissue, or visceral abnormalities.[5]

Chart 2 shows the principal syndromes of dermatological interest.

Although there are different therapeutic alternatives described for the treatment of cutaneous vascular malformations, such as percutaneous sclerosis, surgical resection, laser therapy, or a combination of them, there is not yet a method that guarantees the permanent cure of these lesions. Thus, their treatment is still a challenge to physicians.

1.2.5. Use of lasers and lights in vascular malformations

The word "laser" is an acronym for Light Amplification by Stimulated Emission of Radiation.[17] Its use in medicine began in the 1960s when Leon Goldman created the ruby laser to treat skin lesions.[9]

Before its use to treat cutaneous vascular malformations, local and systemic therapies were applied, such as hypertonic glucose injection, monoethanolamine oleate injection (Ethamolin, Farmoquímica S/A, Rio de Janeiro, Brazil) associated with glucose, morrhuate sodium injection, aethoxysklerol injection, ethanol injection, surgical excision, corticosteroid use, interferon, cryotherapy, arterial embolization, beta therapy, and bleomycin, with varied responses.[16,18]

Lasers and other light sources represent a breakthrough in dermatology for both cosmetic and non-cosmetic applications. They have been increasingly used to remove or lighten many vascular lesions that were once considered untreatable.[13,19,20]

The laser is considered the gold standard for treatment of cutaneous capillary malformation. However, its indication to treat hemangiomas remains controversial, and it is not recommended in arteriovenous malformations treatment.[9,17,21]

In the 1970s, the argon laser, which emits a continuous beam of blue-green light with wavelengths between 488nm and 514nm, was widely used to lighten cutaneous vascular lesions, but pigmentary changes and scarring were frequent due to the

Chart 2: Main syndromes related to vascular malformations of dermatological interest

Syndromes	Clinical features
Klippel-Trenaunay Syndrome	Capillary malformation + venous malformation +/- lymphatic malformation and enlargement of the affected limb
Parkes Weber Syndrome	Capillary malformation + arteriovenous fistula + limb overgrowth
Servelle-Martorell Syndrome	Venous malformation of limb + hypotrophy of affected limb
Sturge-Weber Syndrome	Facial and leptomeningeal capillary malformation + eye abnormalities +/- bone or soft tissue hypertrophy
Maffucci Syndrome	Venous malformation + spindle cell hemangioma + enchondroma
Proteus Syndrome	Capillary malformation + venous malformation +/- arteriovenous malformation + asymmetric growth + cerebriform connective tissue nevi
Bannayan-Riley-Ruvalcaba Syndrome	Arteriovenous malformation + venous malformation + macrocephaly and lipomatosis

Adapted from the International Society for the Study of Vascular Anomalies (2018)[5]

non-selective effects of this laser in the tissues.[2,13,22]

Ablative lasers such as carbon dioxide (CO2) 10,600nm and erbium:yttrium-aluminum-garnet (Er:YAG) 2,940nm lasers have also been used for this purpose. Although they did not reach the vessels, they aimed at destroying the lesion by absorbing laser energy by water from adjacent tissues. The 511nm and 578nm copper vapor laser represented an improvement over those already used. However, pulsed dye laser has replaced other lasers in the treatment of Port-wine stains.[13]

More recently, longer wavelength lasers - 755nm alexandrite laser; long pulse 1,064-nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser - have been used to treat vascular lesions with the advantage of deeper penetration in the skin.[22]

In 1983, Anderson and Parrish developed the theory of selective photothermolysis, allowing the understanding of the interaction between laser and treated tissue. The authors demonstrated that target chromophores selectively absorb specific wavelengths of light and produce thermal energy, enabling selective destruction of lesions with minimal damage to adjacent tissues.[23]

In vascular lesions, the target chromophores are oxyhemoglobin and deoxyhemoglobin, which absorb visible wavelengths of 400 to 780nm, with absorption peaks between 542 and 577nm.[22]

Port-wine stains were the most studied vascular malformations in laser therapy.[13]

1.2.5.1. Pulsed dye laser

Pulsed dye laser (PDL) emit lights of wavelengths between 585nm and 600nm and penetrate to a depth of up to 1.8mm.[2] They were introduced in 1989 and revolutionized the therapy of cutaneous vascular lesions, becoming the method of choice for treating vascular malformations such as Port-wine stains.[13,24,25] Its active medium is a fluorescent dye, which may be rhodamine 6G, fluorescein, coumarin, stilbene, umbeliferone, tetrazene, or malachite green.[13]

Older PDLs had a pulse duration of 0.45ms. Later models were developed with a longer pulse duration. Because they do not penetrate deep into the skin, their use became limited in the treatment of deeper localized lesions. Most patients require multiple sessions to improve Port-wine stains, yet not always achieving complete elimination of the lesion. Its main adverse event is the formation of purpura, which usually lasts between five and 14 days.[13]

There is a heterogeneity in the response of cutaneous vascular malformations to available therapies, and some factors that influence the unpredictability and resistance to pulsed dye laser treatment are described (Chart 3).[10] Centrofacial lesions, located in the V2 dermatome pathway, have a lower response than those located in the upper and lower thirds of the face, corresponding to V1 and V3 dermatomes, respectively.[10,26] Also, up to one-third of patients do not respond to treatment despite multiple sessions. Leg and hand lesions are less responsive to PDL treatment compared to facial injuries.[13]

The topical use of rapamycin and imiquimod showed antiangiogenic effects with encouraging results in improving the lightening of Port-wine stains when associated with pulsed dye laser.[11]

Cardoso *et al.* described, in 2006, the use of PDL to treat tufted angioma, which resulted in significant improvement of local pain and partial reduction of lesion size.[27]

In 2007, Chapas *et al.* first described the efficacy and safety of treating Port-wine stains with the high-energy pulsed dye laser in children under six months of age. Responses from 49 children submitted to 595nm V Beam® laser associated with dynamic cooling with cryogen tetrafluoroethane and energy ranging from 7.75 to 9.5J/cm^2 were assessed. This study showed good laser tolerance without atrophy or residual skin scarring and demonstrated the importance of early initiation of treatment of these malformations.[12] Bae *et al.* evaluated the outcome of the use of bipolar radiofrequency (RF) associated with pulsed dye laser and pointed out RF as an alternative for the treatment of Port-wine stains resistant to therapy with PDL alone in adults.[28]

1.2.5.2. Neodymium:yttrium-aluminum-garnet laser

Chart 3: Factors associated with resistance to the treatment of cutaneous vascular malformations using pulsed dye laser

Syndromes	Clinical features
Age at start of treatment	>1 year
Lesion size	>40cm²
Location	Centrofacial (V2 dermatome distribution)
Lesion Thickness	Hypertrophic or nodular injury
Number of Treatments	>5
Vessel Diameter	<20 µm
Vessel Depth	>400 µm dermoepidermal junction

Source: Savas, Ledon, Franca, Chacon, Nouri (2013).[10]

The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has a wavelength of 1,064nm. It acts by selective photocoagulation, and its great advantage is the greater depth of tissue penetration when compared to other lasers in the treatment of vascular lesions. It can penetrate the skin up to 4mm to 6mm, and it is also used for the treatment of Port-wine stains. The laser energy is transmitted through the superficial tissue layers and distributed to the deepest layers.[21]

Long pulse or continuous Nd:YAG lasers have been the method of choice for the treatment of venous malformations due to the wide experience and good results of their use.1[5]

Although most body tissues do not absorb this wavelength, pigmented tissues do absorb this wavelength better than unpigmented ones.[25]

Also, though the Nd:YAG laser has been shown to be effective in treating deep vascular lesions, it should be considered that its use at fluences slightly above the minimum purpuric dose may lead to complications such as scarring and dyschromia.[10,29]

Figure 2 shows an example of scar formation after the use of long pulse 1064nm Nd:YAG in hypertrophic capillary malformation located in the upper left lip.

Alcántara-González *et al.* studied the efficacy and safety of using pulsed dye laser combined with Nd:YAG laser, showing good results in 30 patients aged 8 to 65 years who had mucous and cutaneous venous malformations.[15]

Van Drooge *et al.* presented, in 2013, the first case series showing the long-term effect of the long pulse 1.064nm Nd:-YAG laser on the treatment of hypertrophic areas in Port-wine stains. When evaluating the outcome in 32 patients with a mean age of 51.4 years, followed after a mean of 37 months from the last laser treatment, they observed good and excellent response in 91% of the hypertrophic areas and 63% of color improvement of the lesions treated, with report of hypopigmentation and residual scar in seven and 14 participants, respectively.[29]

Liu *et al.* assessed the role of the long-pulse, high-energy 1.064nm Nd:YAG laser in the treatment of isolated PDL-resistant Port-wine stains in 20 patients aged 16 to 46 years. The authors observed lightening over 90% of the lesions in 20% of participants, suggesting that the long-pulse 1.064nm Nd:YAG laser may be promising in the treatment of capillary malformations non-responsive to PDL.[30]

In 2017, Murthy *et al.* studied the response of long-pulse Nd:YAG laser treatment to cutaneous vascular malformations excluding Port-wine stains and showed good to excellent results in 66.7% of the patients assessed, with a mean of 4.6 laser sessions per patient. Most lesions were located in the head and neck (48%) and extremities (31%). They concluded that the laser used in the study is a therapeutic option in the management of symptomatic and stigmatizing lesions resulting from vascular malformations in children and adolescents.[31]

A prospective controlled study that sought to investigate the efficacy and safety of double wavelength laser (595nm pulsed dye laser + 1.064nm Nd:YAG laser) in the treatment of Port-wine stains showed no significant difference in outcome compared to treatment with pulsed dye laser alone.[32]

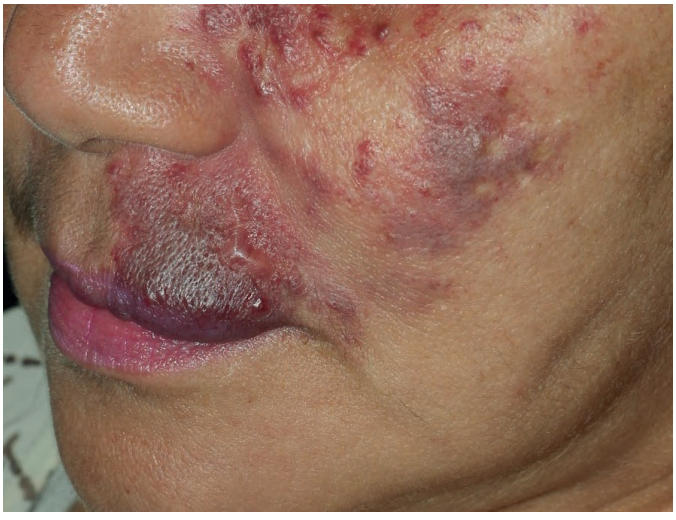

Figure 2: Patient developed scarring in the left supralabial region after treatment of facial Port-wine stain with long pulse 1064nm Nd:YAG ETHEREA® (VYDENCE Medical®, São Carlos, SP, Brazil); E:80J/ cm2/ DP:60ms/Spot:6mm over reddish papules.
E = energy; SD = pulse duration

Nd:YAG laser has also been used to treat angiokeratomas.[33] Figure 3 shows satisfactory response of lesions located on the buttocks, with reduced bleeding and local infections and consequent improvement in the patient's quality of life.

1.2.5.3. Potassium-titanyl-phosphate laser

The potassium-titanyl-phosphate (KTP) laser uses a 1.064nm Nd:YAG laser source, whose frequency is doubled using a KTP crystal, producing 532nm wavelength green light.2,10 KTP has already been used to treat vascular lesions with good results.[2,21]

A study comparing PDL with KTP laser found that it left less purpuric lesion immediately after treatment, although patients reported higher pain intensity with KTP.[10]

Kwiek *et al.* evaluated the response based on comparing three-dimensional photographs of 44 patients with facial capillary malformations treated with doubled frequency 532nm Nd:YAG laser (KTP) and concluded that 77.3% of them had at least a 50% improvement in lesion lightening, with a mean of 7.1 sessions per patient.[21]

1.2.5.4. Intense pulsed light

Intense pulsed light (IPL) is a non-coherent, high-intensity, polychromatic light source that emits light in a spectrum spanning 400nm to 1,200 nm wavelengths.[13] It resembles the laser by the mechanism of action based on selective photothermolysis but differs from it by the possibility of selecting pulse duration and wavelength using filters.

IPL is an effective treatment modality for a growing range of dermatological diseases, and it may represent a treatment of choice in some situations.[34]

In the pediatric population, different vascular lesions have been treated with IPL, including Port-wine stains.[21,25] Greater variability in pulse duration and fluency makes IPL useful in treating vessels of varying diameter and depth.[10]

In 2014, Adatto *et al.* studied the response of IPL in the treatment of Port-wine stains in 18 participants with Fitzpatrick skin phototypes to IV and a mean age of 32.1 years. The treatment was performed with two-wavelength tip: 500nm to 670nm and 870nm to 1200nm (LuxG™; Palomar Medical Technologies, Inc., Burlington, MA, USA) to achieve higher vessel specificity and avoid absorption by melanin. Response analysis was based on qualitative (subjective improvement scale, based on comparison of patient photographic records) and quantitative (erythema and pigmentation measurements in treated lesions using the photometric scale using DermaType ™; Palomar Medical; Technologies, Inc.) evaluations. The study showed efficacy and safety of the IPL use in the treatment of Port-wine stains in various anatomical locations, with minimal adverse events: transient pain, erythema, scabbing, and purpura.[35]

Campolmi *et al.* describe in 2011 the efficacy of the IPL use in the treatment of vascular lesions, solar lentigos, and actinic keratoses in 85 patients and concluded that IPL is an effective and safe measure for the treatment of these lesions, with better results observed in patients with Fitzpatrick skin phototypes I and II.[36]

Evidence suggest that IPL is a safe and effective modality for the treatment of capillary malformations. It may be especially useful for darker, more vascularized areas, but with minimal or absent nodular lesions.[34] Figure 4 shows good results obtained with the use of IPL in the treatment of Port-wine stain located on the face.

Faurschou *et al.* included, in a 2011 review, five randomized controlled trials involving patients with Port-wine stain to assess efficacy, adverse events, and satisfaction of participants after treatment with pulsed dye laser (PDL), long pulse Nd:YAG laser, and intense pulsed light (IPL). All studies showed lightening of lesions within three months of treatment. Adverse events described included pain, edema, hypo and hyperpigmentation, scabbing, blistering, hypertrophic scarring, and pyogenic granuloma. Participants preferred the PDL over the IPL result. It was also observed preference to the Nd:YAG laser when compared with the PDL, considering the shorter purpura duration time; PDL associated with cooling was preferred to PDL alone.[22]

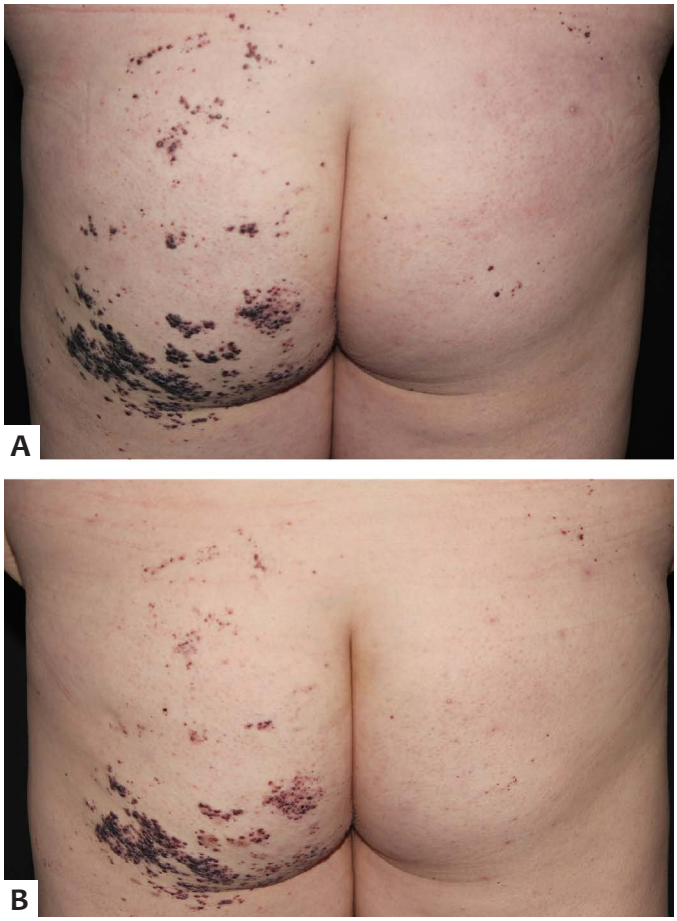

Figure 3: Angiokeratomas in the gluteal region. **A:** before and **B:** after three treatment sessions with ETHEREA® long pulse 1064nm Nd:YAG (VYDENCE Medical®, São Carlos, SP, Brazil); E:70J / DP: 30ms/Spot: 6mm.
E = energy; SD = pulse duration

Although laser and other light sources represent effective measures in the treatment of cutaneous vascular malformations, some care must be taken to avoid undesirable effects with their use. Table 4 presents measures to be adopted to reduce the risk of laser and intense pulsed light complications, based on the literature and clinical practice.[37]

1.2.5.5. Photodynamic therapy

Photodynamic therapy (PDT) is a photochemical reaction between a light source and a photosensitizing drug that produces reactive oxygen species (ROS) and induces cell death. Its first use was directed to the treatment of non-melanoma skin cancer and preneoplastic skin lesions. Some studies have shown that PDT can cause endothelial injury, vasoconstriction, thrombus formation, and blood flow stasis.[10]

In 2011, Xiao *et al.* assessed the outcome and complications of photodynamic therapy following intravenous use of hematoporphyrin monomethyl ether (HMME) photosensitizer followed by the application of a copper vapor laser on Port-wine stains in 507 Chinese participants. This study showed that in 29.8% of cases there was lightening higher than 50% in the treated lesions and 10% of participants had complications such as blistering, scabbing, eczema, hypo and hyperpigmentation, and photoallergy. The authors suggest PDT as a therapeutic option for Port-wine stains, especially in patients with high Fitzpatrick skin phototype and nodular vascular lesions.[38]

Although the role of PDT in vascular malformations treatment has been studied, its efficacy and safety have not been well established for this purpose.

The identification of somatic mutations in vascular anomalies is changing the understanding of these lesions, with potential targets for new pharmacotherapies being discovered.[39]

CONCLUSION

Vascular anomalies have a significant physical and psychological impact on patients. Knowledge of their characte-

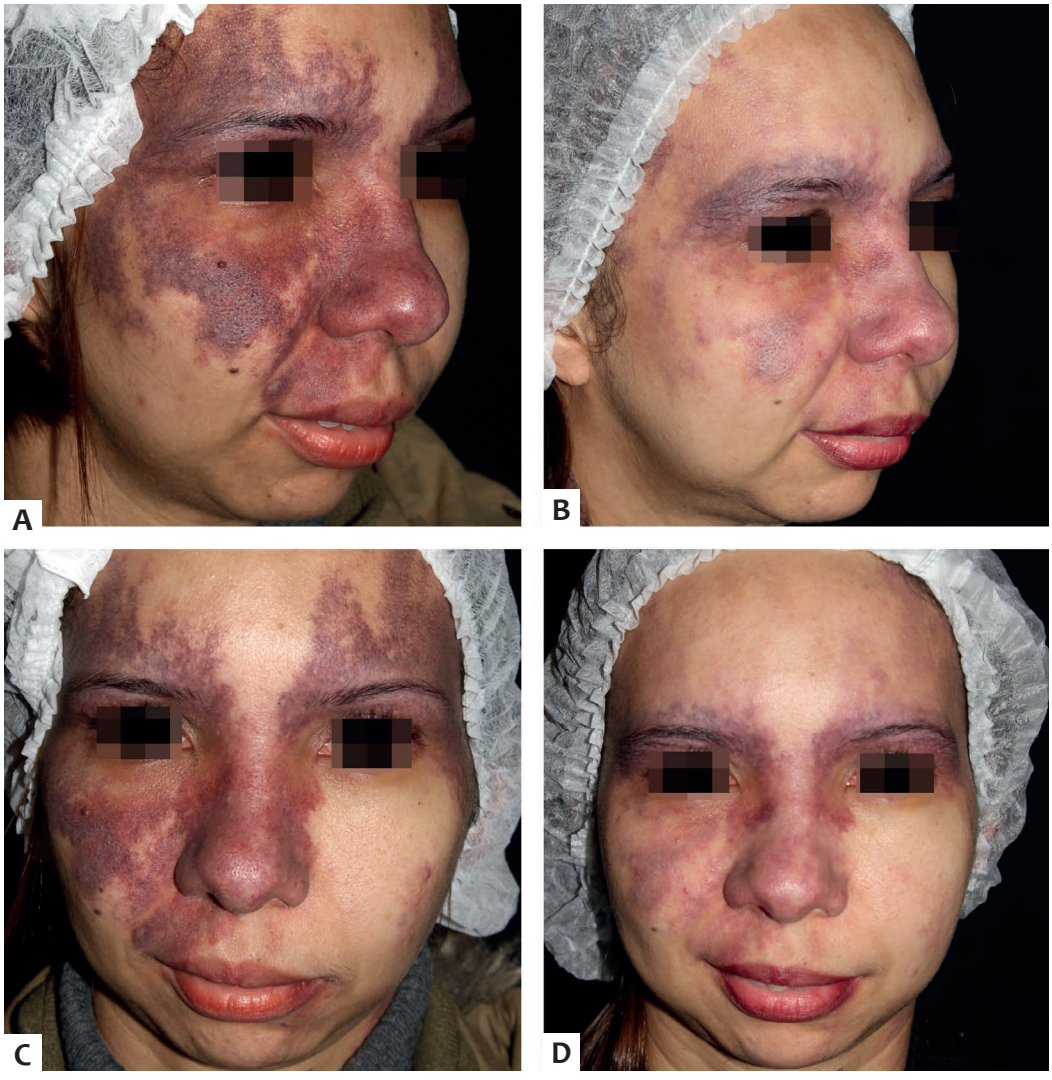

Figure 4: Female patient, 37 years old, with facial Port-wine stain. A and C: photos prior to treatment; B and D: photos after 10 sessions of ETHEREA® 540nm intense pulsed light (VYDENCE Medical®, São Carlos, SP, Brazil); E: 10J/cm2,SD: 10ms. E = energy; SD = pulse duration

Chart 4: Avoiding Complications with Laser and Light Sources
Know Your Laser Device - don't remember parameters and don't use preset settings from experiments with other laser devices.
Make sure your device is calibrated and always perform a maintenance routine.
Never shoot a laser without eye protection and on-site fire precautions.
Be sure to leave lasers and light fixtures in sleep mode before removing goggles.
Be aware of the endpoint you wish to obtain to avoid the appearance of: ● Nikolsky sign * (usually 5 minutes after firing) ● Second and third degree burns; ● Crescent Moon lesions; ● Charring fabric; ● Metallic gray pallor; ● Patient with severe pain during procedure.
Use active skin cooling as a means of reducing pain and the risk of burns.
Watch out for increased risk of complications by avoiding: ● Very high power flow or parameters in non-ablative devices; ● Inadvertent staking pulses.
Properly position and align the laser/ intense pulsed light handpiece, and cryogen to reduce risk of burns.

Source: Wanner, Sakamoto, Avram, Anderson (2016).[37]

* *Sinal de Nikolsky: descolamento epidérmico da derme subjacente, ao ser exercida pressão lateral na área afetada.*

ristics and classifications is essential to establish the correct diagnosis and initiate appropriate and early treatment, resulting in a better quality of life for patients. Psychological damage can be avoided if treatment is instituted before school age and before the onset of interaction with other children. With the introduction of laser use and the understanding of selective photothermolysis, there has been a considerable advance in dermatological therapy, especially with the use of pulsed dye laser for capillary malformations. Although numerous treatment options for vascular anomalies are available, and many have been investigated in the literature, therapeutic decision-making is still mainly based on expert opinion. In a not too distant future, we expect these cases to be conducted more successfully, with the use of different combinations of laser and other light sources, alone or in association with antiangiogenic agents and, promisingly, gene therapy when needed and well indicated. ●

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Treatment of cutaneous field cancerization

Tratamento do campo de cancerização cutâneo

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ABSTRACT

The cutaneous field cancerization corresponds to an area of skin chronically exposed to the sun. It contains actinic keratoses and other skin signs of photodamage caused by ultraviolet radiation. This field comprises the genetic alterations that form the basis of the process of cutaneous carcinogenesis. Actinic keratoses have the potential to be stable for years, to regress spontaneously or to become invasive carcinomas. There is a consensus in the literature that the treatment of the entire field cancerization is more effective than treating just isolated lesions since it is not possible to predict which of these lesions will evolve to invasive cancer. It is also effective in the prophylaxis and treatment of the existing clinically imperceptible incipient lesions. There are several therapeutic options for individualized actinic keratoses and the field cancerization, from self-applied topical drug therapies to interventional and surgical therapies.

Keywords: Actinic keratoses; Skin cancerization field; cutaneous carcinogenesis; squamous cell carcinoma

RESUMO

O campo cutâneo de cancerização corresponde a uma área de pele cronicamente exposta ao sol. Nela, são encontradas as queratoses actínicas e outros sinais cutâneos de fotodano causados pela radiação ultravioleta. Nesse campo, estão as alterações genéticas que constituem as bases do processo da carcinogênese cutânea. As queratoses actínicas têm potencial para ficarem estáveis por anos, regredirem espontaneamente ou se tornarem carcinomas invasivos. Há um consenso na literatura de que é mais eficaz o tratamento de todo o campo de cancerização do que apenas o das lesões isoladas, uma vez que, além de não se poder prever qual dessas lesões irá evoluir para câncer invasivo, também será feita a profilaxia e tratamento das lesões incipientes clinicamente imperceptíveis já existentes. Existem diversas opções terapêuticas para as queratoses actínicas individualizadas e para o campo de cancerização, desde terapias medicamentosas tópicas autoaplicadas até intervencionistas e cirúrgicas.

Palavras-Chave: *Queratoses actínicas; Campo de cancerização cutâneo; Carcinogênese cutânea; Carcinoma espinocelular*

Review Articles

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INTRODUCTION

The term "field cancerization" was first used by Slaughter in 1953 based on histopathological studies of oral mucosa neoplasms. It was observed that these lesions appeared in multifocal areas, with precancerous changes, and that the tissue around the primary tumor was histologically altered. It was also found that neoplasias, although multifocal, could coalesce, and that persistence of adjacent abnormal tissue following surgical excision of the primary lesion could explain recurrences and the appearance of new cancerous lesions in previously treated areas.[1] In addition to the oral mucosa, other organs may present a field cancerization, including the skin. Paul Unna made the first correlation between ultraviolet radiation and skin cancer in the late 19th century, describing the development of these lesions in chronically sun-exposed places in sailors.

Therefore, by definition, the skin field cancerization (SFC) is a chronically photoexposed skin area, damaged by the exposure to ultraviolet (UV) rays, that presents multiple actinic keratoses (AKs) and other signs of photodamage. The term "keratosis" refers to the thickening of the stratum corneum, and the term "actinic" refers to the origin by sun exposure. Currently, it is well established that the genetic alterations of these fields form the basis of the carcinogenesis process.[2]

ACTINIC KERATOSES

SFC is a group of alterations found in the areas chronically exposed to solar radiation, which determine the appearance of several foci of non-melanocytic neoplasms resulting from DNA damage, the AKs.[3] It occurs due to the cumulative doses of ultraviolet (UV) radiation absorbed over a lifetime. The AKs manifest as discrete intraepidermal lesions, typically presenting as rough, scaly, and sometimes keratotic papules or plaques. They can be found in all races and genders, but are much more common in men, light-skinned (Fitzpatrick phototype skin I and II), middle-aged or older individuals. More than 80% occur in the head (ears, frontal region, supraorbital prominence, nasal dorsum, malar region, and scalp of bald individuals), neck, and upper extremities (back of the hands and extensor surfaces of the forearms). They may present as a single lesion, but most often they are multiple lesions.[4]

In addition to the classic forms described above, there are some clinical variants of AK: hyperkeratotic AK, which manifests as a firm and infiltrated papule, covered by keratosic scale and rough on palpation; pigmented AK, which closely resembles solar lentigo; ant cutaneous horn, in which a conical projection is formed over the lesion, giving it a peculiar clinical aspect. Actinic cheilitis is the term used for AKs that appear on the lips, especially in the lower lip, resulting from the confluence of the lesions.[5]

Historically, AKs have been considered the most common premalignant skin lesions. However, some researchers prefer to classify them as in situ squamous cell carcinoma (SCC), as evidence has shown that they have histopathological criteria, genetic tumor markers, and p53 gene mutations identical to the SCC. Although 25% of AKs are estimated to have spontaneous regression, the risk of progression to invasive SCC ranges from 0.025% to 20% per year.[6,7] In recent decades, the incidence of AK has been increasing. The approximate prevalence in the 60 to 69 age group is 79% in men and 68% in women.[8] Recent studies show that AKs with atypical cells present only in the basal layer of the epidermis are the most common precursors of invasive SCC.[5]

SKIN FIELD CANCERIZATION

The SFC concept suggests that healthy skin around areas of AK supports the basis for clonal expansion of genetically altered neoplastic cells.[2] In clinical practice, defining SFC requires three factors: a determined skin region, multiple AKs, and at least one SCC within that region.[9] Histopathology of biopsies and optical coherence tomography (OCT) of skin areas suspected of SFC confirm that 79% of apparently healthy skin has evidence of dysplasia or occult carcinoma.[10] The SFC paradigm has two critical implications for the treatment of SCC. First, because SCC originates from multifocal areas with precancerous changes, and the presence of at least one SCC increases the risk of subsequent tumors by 42% within five years. Second, a clinical relapse of a completely surgically excised SCC may, in fact, represent not a relapse but the development of a new primary cancer.[11]

Despite all the advances in diagnostic methods, it cannot yet be predetermined which AKs will regress or which will evolve into a deep invasion. Because there are subclinical lesions, treatment must be performed on the isolated lesion and also on the entire field cancerization, considering that it is compromised with genetically altered cells.[12]

THERAPEUTIC OPTIONS

There are multiple options available for treating AK and SFC. The choice must be made taking into consideration:

1. The location, number, duration and clinical course of lesions;
2. The history of skin cancer, age, whether or not there is immunosuppression, and comorbidities;
3. The frequency and duration of sun exposure;
4. The physician's experience;
5. The treatment cost;
6. The patient's preference.[2,13]

Therapeutic measures are indicated both for the treatment of isolated lesions and for the field cancerization. The treatment of isolated lesions is based on the destruction of clinically apparent lesions and it is best suited for patients who have a small number of lesions and who have low-risk characteristics for invasive SCC.

Treatments for isolated AKs include cryosurgery with liquid nitrogen, curettage and electrocoagulation, dermabrasion, caustic application, and several types of lasers. All of these methods are effective, have variable costs and different adverse events such as pain, blistering, slow healing by secondary intention, and residual hypochromia. SFC therapy is directed to both clinically apparent and preclinical lesions and is, therefore, the

most recommended option for most patients.

Patients with multiple lesions may benefit from combined therapies, the destruction of isolated lesions, and concomitant treatment of SFC. Whatever the option, long-term monitoring is required to verify the healing or if new subclinical lesions have emerged.[2]

FIELD CANCERIZATION TREATMENT

The first step in controlling patients with multiple AKs and SFC is strict sun protection. Ultraviolet (UV) radiation is the initiator and promoter of tumor growth. Studies show that there is a reduction in the appearance of precursor lesions when UV radiation exposure is interrupted.[14]

The ultimate goal of SFC treatment is to remove all lesions, whether clinically apparent or subclinical, and to reduce the potential risk of SCC.[7,10] Topical drugs, photodynamic therapy (PDT), daylight PDT, and ablative procedures such as dermabrasion, lasers, and chemical peels are available. The advantages of topical therapies are that they are proven effective and can be self-administered, although they have the disadvantages of being generally long-term treatments with significant adverse events, which would decrease treatment adherence and increase the risk of relapse. On the other hand, PDT and ablative options are more expensive and need more post-procedure care because of the higher risk of complications (infections, hypopigmentations, unsightly scars, and relapses, among others).[2]

PHOTOPROTECTION

Several studies have shown that the regular use of photoprotection (sunscreen) is effective in preventing the progression of AK to invasive SCC and the emergence of new lesions. Thompson *et al.* conducted a randomized, placebo-controlled study involving 588 patients analyzing the remission rates of AK lesions after daily use of broad-spectrum sunscreen. The group that used sunscreens presented a higher rate of remission than the control group (OR = 1.53; 95% CI, 1.29–1.80) and a lower rate of new lesions emergence.15 There is a large number of sunscreen options on the market today, most of them with good quality, allowing the dermatologist to make a suitable, almost individualized choice for each patient. In addition to chemical photoprotection, patients subjected to constant or intermittent sun exposure, due to work or leisure, should be advised to use physical photoprotection, such as hats, clothing, umbrella, and others.

5-FLUOROURACIL (5-FU)

5-FU is a topical chemotherapy drug classified as a pyrimidine analog used as an antineoplastic agent. Its primary mechanism of action is the reduction of atypical cell proliferation and the induction of apoptosis by interfering with DNA and RNA synthesis in mutated cells. The drug causes intense inflammation, enhancing its antitumor effect .[3] 5-FU has been used in the clinical practice for over five decades and has the great advantage of its low cost. In Brazil, it is marketed as cream 5%, but it can be handled in other concentrations (0.5%, 1%, and 2%) and in vehicle lotion. According to a consensus published in 2007, 5-FU should be used twice a day for six weeks, reaching cure rates of 70% to 80%. But the same consensus reported recurrence rates of approximately 55%.[7]

It has important adverse events such as pruritus, prolonged erythema, ulceration, pain, and secondary pigmentation, making it difficult for patients to adhere to treatment. Also, prolonged use is another limiting factor.[11] The area to be treated should not exceed 500cm^2. When it is necessary to treat larger areas, it is advisable to do so in a staggered manner. It has a good indication for SFC treatment because it can show, through erythema and eczematization, apparently healthy areas, but with the onset of neoplasia.

In 2010, a pilot study was published in Germany using the combination of 5-FU 0.5% and salicylic acid 10% three times a week for four weeks in 15 patients with a mean of 66 AK lesions each. After 12 weeks, there was a complete response in 77% of patients, partial response in 21%, and no response in 2%. The authors concluded that the treatment was effective and very well tolerated.[7] Other publications support this therapy in other European countries.[3] Another study compared the results of the treatment of AKs located on the back of the hands with 5-FU 5% alone and in combination with tretinoin. This study concluded that the association with tretinoin was more effective than 5-FU alone.[7] A randomized, placebo-controlled study, published in 2015 by Pomerantz *et al.*, conducted a long-term follow-up of patients receiving a one-time field cancerization treatment with 5-FU 5% cream. The authors observed that there was a lightening of the precursor lesions of SCC that lasted for more than three years.[16] In another recent study, published in 2018, a randomized, double-blind clinical trial was conducted in 932 patients with a history of skin cancer (39% presenting a history of previous SCC). After a year, the authors identified a 75% reduction in SCC incidence after a single course of treatment with topical 5-FU 5% (5 patients with SCC in the 5-FU group *versus* 20 patients in the placebo group). They concluded that a single field cancerization treatment with 5-FU 5% cream could significantly reduce the incidence of SCC for at least one year. Further clinical trials are needed to support the use of this treatment, notably the SFC treatment repetition interval for high-risk patients.[14]

In another recent study, published in March 2019, Abby *et al.* conducted a prospective, randomized, double-blind, cohort trial. In this study, participants underwent therapy for face and scalp AKs with 5-FU 5% combined with calcipotriol 0.005%, while the control group received 5-FU 5% associated with vaseline. The treatment lasted four days. The incidence of squamous and basal cell carcinoma was evaluated for one, two, and three years. The authors concluded that there was a significant increase in erythema, a marked improvement in cellular immunity, and an induction of tissue-resident memory T cells against actinic keratoses, as well as a significant reduction in the risk of developing squamous cell carcinoma after three years of treatment.[17] Another low cost and effective option for the treatment of multiple AKs and SFC, especially in the forearms, is peels combining Jessner's solution and 5-FU 5% in propylene glycol. The application begins with one to three layers of Jessner's solution and then

a layer of 5-FU 5%. The patient is advised to wash the sites after 24 hours and completely avoid sun exposure by physical methods during this period. Six to eight applications are conducted, with biweekly or monthly intervals, depending on the patient's tolerability. Thus, it is concluded that, despite being an ancient drug, 5-FU remains one of the protagonists in the treatment of AKs and SCF.

RETINOIDS

For over 35 years, topical retinoids, especially tretinoin, have been used for various dermatoses, including acne, melasma, photoaging, and AK.[3] Tretinoin, or retinoic acid, is a molecule derived from vitamin A and the nuclear retinoid receptor mediates its mechanism of action.[18] The first use of tretinoin for AK was in 1962 by Stuttgen, and then several studies have shown generally low variable efficacy with this drug, both in the treatment of AS and in the prevention of skin cancer. Therefore, its use in the treatment of AK and SFC remains controversial, being more indicated for the treatment of photoaging than for SFC.[2]

DICLOFENAC SODIUM 3% IN HYALURONIC ACID

Diclofenac is a non-hormonal anti-inflammatory cyclooxygenase 2 (COX-2) inhibitor[10], an enzyme that, when activated, has been implicated in the carcinogenesis of tumors induced by UV radiation by promoting tumor growth, increasing cell proliferation, stimulating angiogenesis, and inhibiting apoptosis. The inhibition of this enzyme results in decreased prostaglandin production.[20] It has been used to treat AK and SFC at a concentration of 3% in a hyaluronic acid gel vehicle twice a day for a period of 60 to 90 days. There is slight or moderate irritation at the application site. The mechanism of action is by apoptosis induction. Several phases 3 and 4 studies have shown the efficacy of complete lesion resolution of 33% to 50% between 60 and 90 days of treatment.[21-24] One of them, a meta-analysis of three randomized trials comprising 364 patients, found a cure rate of 40%. In 2010, Ulrich *et al.* published a randomized, placebo-controlled study evaluating topical diclofenac 3% in transplant patients with multiple AKs. The authors observed a complete response in 41% of the AKs, a decrease in the number of lesions, and, despite being a high-risk group, they identified no patients with invasive SCC at 24 months of follow-up. The authors concluded that the treatment is effective and well-tolerated.[25] Nevertheless, this therapeutic option requires proper patient compliance due to the long duration of use. According to the British Association of Dermatologists Therapy Guidelines, the level of recommendation for diclofenac gel in the treatment of SFC and AK is B, and the quality of evidence is I.[2]

PIROXICAM

Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) with a mechanism of action similar to diclofenac. It is a potent inhibitor of cyclooxygenase 1 (COX-1) and suppressor of proteinases related to tumor growth.[26] Babino *et al.* used this drug at a concentration of 0.8% incorporated into photoprotection products applied twice a day for six months and found a clear improvement in AKs.[27]

DOBESILATE

Dobesilate is used for the secondary prevention and progression stabilization of mild to moderate nonproliferative diabetic retinopathy. It also improves the clinical manifestations of chronic venous insufficiency (CVI) of the lower limbs. Its mechanism of action is to inhibit the vascular endothelial growth factors (VEGF) and fibroblast growth factors (FGF). Studies with this drug are still in preliminary stages. It has been used at 2.5% and 5% concentrations in cream for AK and basal cell carcinoma and has been showing to be effective, safe, and well-tolerated.[28,3]

IMIQUIMOD

Imiquimod is considered a nonspecific immunomodulator that acts as a toll-like receptor 7 agonist. These receptors are located on the surface of dendritic cells, monocytes, macrophages, and Langerhans cells. When imiquimod activates them, they induce apoptosis and lead to the release of cytokines and chemokines, including tumor necrosis factor-alpha (TNF–α), interferon c (INF-c), and interleukins. This release determines an influx of inflammatory cells within the lesions and, consequently, their cell-mediated destruction of the innate immune response.[3] Although its mechanism of action is not yet fully elucidated, it has a recognized antiviral and antitumor action. It is a well-studied drug in the treatment of AKs, notably in non-hyperkeratotic or hypertrophic lesions located on the face and bald area. It is marketed in Brazil in 5% cream. The application should be three times per week for 16 weeks over an area of up to 25cm^2, and determine cure rates ranging from 45% to 84%, according to several well-conducted placebo-controlled studies.[29, 30, 31] In these studies, recurrence rates were approximately 10% in the first year and 20% in the second year. The FDA has approved other concentrations, such as 3.75% and 2.5%, but they are not sold in Brazil. These lower doses were also effective, with shorter use time and fewer adverse events.[32] Its drawbacks are the long treatment duration and important local adverse events such as erosion, ulceration, blistering, pain, and residual hypochromia. When applied to large areas, even systemic symptoms (malaise, headache, and fever) may occur. For these reasons, adherence to treatment is more difficult and should be very clear to patients.[2,3]

RESIQUIMOD

It is an emerging therapy that also acts as an immunomodulator by the toll-like receptor 7 and 8 agonist mechanism. It induces a more intense response of myeloid dendritic cells and a higher expression of TNF-α and interleukin 12 than imiquimod.[4] It was used in a European gel vehicle study with four different concentrations (0.01%, 0.03%, 0.06%, and 0.1%) once a day, three times a week for four weeks in a 25cm2 area on the face and/or bald area. High cure rates were observed at all concentrations (ranging from 40% to 74.6%), with the highest rates at the highest concentrations. The authors concluded that all concentrations are effective, but the lowest (0.01% and 0.03%) were better tolerated.[33]

INGENOL MEBUTATE

Ingenol mebutate is the most recently introduced substance for the treatment of SFC. FDA approved it in January 2012. It is a macrocyclic diterpene ester taken from *Euphorbia peplus*, a plant native to most of Europe, northeast Africa, northwestern Asia, Australia, New Zealand, North America, and temperate regions. The mechanism of action, although not yet fully elucidated, seems to be due to two mechanisms: rapid lesion necrosis within a few hours, direct cytotoxic effect on keratinocytes, followed by the production of inflammatory cytokines and induction of dense inflammatory infiltrate consisting of neutrophils and eosinophils. What sets it apart from the other therapeutic agents mentioned is the short duration of treatment, which is two to three days, contributing to higher patient compliance.

It is commercially available in two gel vehicle concentrations: 150mcg/g and 500mcg/g formulated in propyl alcohol-based gel. The former is given once daily for three consecutive days on the face and/or scalp, and the latter is administered once daily for two consecutive days on the trunk and/or extremities. It can be used to treat localized lesions and/or SFC. After topical application, it crosses the stratum corneum and exerts its action on the dermis and hypodermis with minimal systemic absorption. Each single-dose package is sufficient to treat an area of 25cm^2. Phases 2 and 3 studies showed higher efficacy than placebo, in which the number of lesions on the face and scalp reduced a mean 83% and on the back and limbs, a mean 75%.[34,35] High sensitivity pharmacokinetic studies did not detect systemic absorption of ingenol mebutate, and its metabolites do no affect cytochrome P450.[36]

The main adverse events are erythema, edema, pruritus, erosion, and blistering, with varying intensities. These events usually disappear spontaneously within two days on the face and bald area, and within four days on the body and extremities.[37] In early May 2019, the laboratory responsible for marketing the product in Brazil announced its discontinuation to the Brazilian Society of Dermatology.

PHOTODYNAMIC THERAPY (PDT)

Photodynamic therapy (PDT) is a therapeutic option for SFC already well established in the literature. It is based on the photoactivation of protoporphyrin IX. It acts through the interaction between a photosensitizing agent and a light source, which produces reactive oxygen species (ROS). The most commonly used photosensitizing agents are 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL), which preferentially accumulate within AK cells where they become protoporphyrin IX. They are applied topically to the skin at intervals ranging from 1 to 18 hours before being exposed to a visible light source. They absorb this light and generate reactive oxygen species that determine microvascular damage, inducing a local inflammatory reaction and cell death. Because the conversion of prodrugs to protoporphyrin IX is increased in malignant and premalignant cells, treatment is relatively selective for SCC precursors.[3]

Several published studies show good results in the treatment of AKs, SFC, and superficial basal cell carcinomas (BCC), mainly in less hyperkeratotic lesions. The association with the previous curettage seems to increase the efficacy. Pain at the time of application is the most commonly reported adverse event, followed by photosensitization. According to a European guideline, published in 2013, with evidence B and quality I, PDT in the treatment of the field cancerization in transplant patients can prevent the emergence of new AKs and their transformation into invasive SCC. They also reported that in immunocompetent patients, this therapy showed a significant delay, on average six months, in the appearance of new lesions. According to these guidelines, this prophylactic effect is because PDT decreases the p53 expression, a marker of skin cancer.[38] Szeimies *et al.*, in a study published in 2012, concluded that MAL-PDT treatment decreases the carcinogenic potential in the skin field cancerization and partially reverses the intrinsic and extrinsic signs of skin aging due to dermal collagen deposition.[39] In a randomized controlled trial, the results of the treatment of multiple AKs on the face and scalp with ALA-PDT versus TCA 35% peel in 28 patients were compared using new and pre-existing lesions count as assessment base. Patients were examined at one, three, six, and 12-month intervals. They found that PDT was significantly more effective than TCA 35% peel, with a cure rate of 73.7% *versus* 48.8%. The cosmetic result was similar in both treatments.[40]

More recently, an alternative form of PDT has been developed using the MAL photosensitizer. Instead of using an artificial light source, single two-hour exposure to indirect sunlight activates MAL. There is higher tolerability, shorter treatment duration, and the cost is lower because it does not require an artificial light source. There are studies showing the same efficacy as conventional therapy with fewer adverse events.[41,42,43] Neither PDT, and probably any other therapeutic option, can eliminate the precursors of skin cancer. Therefore, like the others, repeated treatments are necessary to prevent the onset of SCC.[11] A limiting factor is the treatment cost. Currently, in Brazil, there are problems with the supply and acquisition of photosensitizers, which has hindered its use.

CRYOTHERAPY

The cryotherapy is a destructive technique that uses direct application of liquid nitrogen (or more rarely other cryogens) to freeze skin lesions. Keratinocyte is destroyed at -40 °C to -50 °C, and liquid nitrogen reaches -196 °C, making it a very effective agent. It is best indicated for the treatment of individualized and discrete AK since the effect is smaller in larger and thicker lesions.[44,45] The application time varies from five to 15 seconds but may reach up to 30 seconds in thicker lesions. The procedure must be performed inside and around the lesion and must reach a freezing range of 2mm to 4mm to destroy it.[3] Despite being a widely used treatment, few studies determine its real efficacy, application frequency, duration, intensity, and appropriate temperature. This lack of uniformity leads to different results.[46] One of the cryotherapy advantages is that, in general, only one application is required. Cure rates range from 75% to 99%.[43,47] In 2008, Kaufmann *et al.* published a randomized, multicenter, comparative study on the safety and efficacy of PDT with MAL *versus* cryotherapy in the treatment of AK on

the extremity in 121 patients. Complete response with cryotherapy after 24 weeks was 88%.48 Some studies show increased efficacy of this technique when combined with other topical treatments, such as imiquimod, diclofenac, and ingenol mebutate. Adverse events may arise during treatment, such as erythema, pain, blistering, and scabbing of varying intensity, as well as the possibility of residual hypopigmentation.

SYSTEMIC RETINOIDS

Patients with SFC and a high risk of developing SCC may benefit from systemic treatment with acitretin. Studies in animal models have shown that this drug can suppress proliferation, promote keratinocyte differentiation, and induce tumor regression. In humans, acitretin was used in 30 mg/day in renal transplant patients for six months, and there was an 88% reduction in the incidence of SCC. However, there was an increased incidence in both acitretin and placebo control groups with therapy discontinuation.49 Therefore, this drug was not able to eliminate SCC precursors, and thus therapy should be administered over a long time, with all known adverse events (xerosis, mucositis, hepato-toxicity, hyperlipidemia, and others) and teratogenicity.[50]

SURGERY AND LASER

Surgical treatment is restricted to isolated and/or localized lesions. It is indicated for individuals at high risk or for those who have already undergone malignant transformation. The most commonly used techniques are curettage and electrocoagulation, as well as surgical excision. Ablative and non-ablative lasers are being investigated as monotherapy and in combination with other SFC therapies, and they have shown promising results.[51,52] A limiting factor of laser therapy is its high costs.

CONCLUSIONS

We can draw some practical conclusions from all that have been described to contribute to the daily conduct of dermatologists.

1. The concept of skin field cancerization (SFC) is well-grounded in the literature.

2. Although some clinical and histopathological data suggest some AKs to have a higher or lower potential to become invasive carcinoma, it is not yet possible to predict which one will evolve.

3. As a result, it is necessary to perform the treatment in all areas where there are lesions likely to transform and not only in individualized lesions.

4. There are numerous therapeutic options available, with evidence of varying favorable outcomes. It is up to the dermatologist to choose the most appropriate for each case, considering several factors, such as effectiveness, time of use, adverse events, comorbidities, and costs.●

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Transcriptional profiles of melanogenesis and genes related to enzymatic antioxidants in skins with periorbital hyperpigmentation

Perfis transcricionais da melanogênese e genes relacionados a antioxidantes enzimáticos em peles com hiperpigmentação periorbital

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ABSTRACT

Introduction: Identifying the causes of periorbital hyperpigmentation is crucial in selecting the best treatment. The identification of transcriptional profiles that may be related to hyperpigmentation around the eye area could contribute to a new approach in the treatment of periorbital hyperpigmentation – the gene therapy.

Objective: This study aims to assess the transcriptional profile of melanogenesis, and genes related to enzymatic antioxidants in skins with periorbital hyperpigmentation.

Methods: Based on clinical evaluation, 49 healthy volunteers were classified with or without periorbital hyperpigmentation. Genetic profiles of melanogenesis-related genes: microphthalmia-associated transcription factor (MITF), pro-opiomelanocortin (POMC), melanocortin 1 receptor (MC1R), tyrosinase (TYR), tyrosinase 1-related protein (TYRP1), and intracellular antioxidants - glutathione reductase (GR), glutathione peroxidase 1 (GPx-1), glutathione s-transferase (GST-1) - were determined by the polymerase chain reaction technique in real-time.

Results: MITF, TYR, and TYRP1 gene expressions were significantly higher in the periorbital hyperpigmentation group ($p<0.01$). GR, GPx-1, and GST-1 gene expressions were comparable between the groups with and without periorbital hyperpigmentation.

Conclusions: The results of this study suggest that MITF is the primary regulator of melanin deposition in skins with periorbital hyperpigmentation. Up-regulated MITF is closely associated with increased TYR and TYRP1. These findings are essential in proposing a new therapeutic approach in the treatment of periorbital hyperpigmentation.

Keywords: Hyperpigmentation; Melanins; Microphthalmia-associated transcription factor

RESUMO

Introdução: *A identificação das causas da hiperpigmentação periorbital é crucial na seleção do melhor tratamento. A identificação de perfis transcricionais que podem estar relacionados com a hiperpigmentação ao redor das áreas oculares poderia contribuir para uma nova abordagem no tratamento da hiperpigmentação periorbital, -a terapia genética-.*

Objetivo: *Este estudo tem como objetivo avaliar o perfil transcricional da melanogênese e genes relacionados a antioxidantes enzimáticos, em peles com hiperpigmentação periorbital.*

Métodos: *Com base na avaliação clínica, 49 voluntários saudáveis foram classificados em grupos com ou sem hiperpigmentação periorbital. Perfis genéticos de genes relacionados à melanogênese: -fator de transcrição associado à microftalmia (MITF), pró-opiomelanocortina (POMC), receptor da melanocortina 1, (MC1R), tirosinase (TYR), proteína relacionada à tirosinase 1 (TYRP1)-, e antioxidantes intracelulares: -glutationa redutase (GR), glutationa peroxidase 1 (GPx-1), glutationa s-transferase (GST-1)- foram determinadas pela técnica de reação em cadeia da polimerase em tempo real.*

Resultados: *as expressões dos genes MITF, TYR e TYRP1 foram significativamente maiores no grupo com hiperpigmentação periorbital.($p<0,01$). As expressões gênicas de GR, GPx-1 e GST-1 foram comparáveis entre os grupos com e sem hiperpigmentação periorbital.*

Conclusões: *Os resultados deste estudo sugerem que o MITF é o principal regulador da deposição de melanina em peles com hiperpigmentação periorbital. O MITF com regulação positiva está intimamente associado ao aumento da TYR e TYRP1. Esses achados são importantes na proposição de uma nova abordagem terapêutica no tratamento da hiperpigmentação periorbital.*

Palavras-chave: *Hiperpigmentação; Melaninas; Fator de transcrição associado à microftalmia*

Original Article

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INTRODUCTION

Periorbital hyperpigmentation (POH), commonly known as dark circles under the eyes, features as bilateral, homogenous hyperchromic macules and patches primarily involving the lower and/or upper eyelids. In some severe cases, it extends to eyebrows, malar regions, temporal regions, and lateral nasal root. [1] POH is one of the most common cosmetic concerns, and it is notoriously resistant to treatment.

The data on the incidence and prevalence of POH is very scarce, and its pathogenesis remains elusive. It is believed that excessive pigmentation, thin and translucent lower eyelid skin, shadowing due to skin laxity and venous congestion are the main causative POH factors. Congenital and genetic factors are also the predisposing factors to POH development.[2, 3] Recently, Verschoree *et al*. assessed the melanin and hemoglobin distribution using a non-invasive method, i.e., spectrophotometric intracutaneous analysis (SIA)scopy, in the Indian population, suggesting that melanin deposits and blood stasis may play a role in POH.[4] On the other hand, histology studies revealed that periorbital biopsy of Japanese and Brazilian patients showed dermal melanin deposit, which could be the main factor contributing to POH.[5, 6] Nevertheless, these authors did not mention the primary causes that may lead to melanin deposition surrounding eye areas. Other than limited histological studies on POH skin, to the best of our knowledge, the roles of pigmented-related gene expression in POH has not been elucidated yet.

Studies have shown that the microphthalmia-associated transcription factor (MITF) modulation can alter skin pigmentation in dark-skinned Yucatan swine.[7] On the other hand, MC1R has also been reported to be highly polymorphic, and its genetic variants are associated with various pigmentation phenotypes in the skin, hair, and eyes.[8] Surprisingly, its gene variants are also associated with an increased risk for hyperpigmentation disorders, i.e., cutaneous melanoma, which is largely independent of skin type and hair color.[9] Tyrosinase-related protein 1 (TRP-1) and tyrosinase-related protein 2 (TRP-2) present in the membrane of melanosomes are proteins similar to tyrosinase. Their precise role is nuclear, but it has been proposed that TRP-1 acts on the activation and stabilization of tyrosinase, melanosome synthesis, increased eumelanin/pheomelanin ration, and also against oxidative stress.[10]

This study assumes that deregulation of pigmentation--related gene expression might involve POH development. Furthermore, it raises the hypothesis that deregulation of intracellular enzymatic antioxidants might be associated with overregulated melanogenic gene expression.

METHODOLOGY

Ethical Approval of Studies

Medical Research & Ethics Committee (NMRR-13-1267-16770) and Sunway Medical Center Independent Research Ethics Committee (011/2013/ER) were obtained prior to the commencement of the study.

Subject recruitment

Healthy subjects requested for blepharoplasty in Lim Plastic and Surgery Clinic (Kuala Lumpur, Malaysia) and Sunway Medical Centre (Selangor, Malaysia) were randomly invited to participate in this study. Subjects diagnosed with nevus of Ota, nevemelanocytic nevi, café-au-lait, Hori's nevus, ephelides, localized post-inflammatory hyperpigmentation due to a recognizable insult, cutaneous inflammatory diseases/ulceration, allergies/asthma, hyperpigmentation associated with systemic diseases, i.e., Addison's disease, were excluded from the study.

A total of forty-nine (n=49) subjects had been recruited. Written informed consent was obtained from each subject. Plastic surgeons evaluated the periorbital areas and classified them into pigmented (POH) or non-pigmented (Non-POH) eyelid skins. The excised eyelid skins following blepharoplasty were collected and kept in 10% formalin for histological analysis or RNAlater® RNA stabilization reagent solution for gene expression study. The specimens were processed within 3 days of upon sample collection.

Histological Analysis

Paraffin-embedded skin tissues were processed for the Fontana-Masson silver stain to observe the melanin deposition and pattern of distribution in eyelid specimens. The depth of melanin distribution, i.e., down to papillary dermis or down to reticular dermis, was reported.

Total RNA extraction and cDNA conversion

A small portion of biopsy specimens was preserved in RNAlater® RNA stabilization reagent (Qiagen, Germany). Specimens were homogenized using gentleMACS M tubes (Miltenyi Biotec, Germany). Total mRNA was extracted using RNeasy® Lipid Tissue Mini Kit (Qiagen, Germany). Reverse transcription-polymerase chain reaction (RT-PCR) was conducted with High Capacity RNA-to-cDNA Kit. Up to 2µg of total RNA was used in the conversion of RNA-to-cDNA in a 20µl reaction. The reaction consisted of 10 µl of 2× RT Buffer, 1µl of 20× Enzyme Mix, 2µg of RNA, and sufficient quantity of nuclease-free H2O up to the final volume of 20µl.

Gene Expression Assay

A real-time PCR technique was utilized to determine the level of mRNA expression associated with melanogenesis as well as the antioxidant defense system. The genes which have been quantified were microphthalmia-associated transcription factor (MITF), proopiomelanocortin (POMC), and melanocortin 1 receptor (MC1R), tyrosinase (TYR) and tyrosinase-related protein 1 (TYRP1), glutathione reductase (GR), glutathione peroxidase-1 (GPx-1) and glutathione s-transferase-1 (GST-1). Beta-actin (ACTB) acts as the housekeeping gene. Taqman® Gene Expression Assays were purchased from Applied Biosystem with gene code Hs01117294_m1 (MITF), Hs01596743_m1 (POMC), Hs00267167_s1 (MC1R), Hs00165976_m1 (TYR), Hs00167051_m1 (TYRP1), Hs00167371_m1 (GR), Hs00829989_gH (GPx-1), Hs00220393_m1 (GST-1) and Hs99999903_m1 (ACTB).

The real-time PCR was conducted in 20 µl reaction mixture consisting of 2µl of template cDNA, 1µl of Taqman® Gene Expression Assay and Taqman® Fast Advanced Master Mix. The sample was first denatured at 95 °C for 20 s, followed by 40

cycles of denaturing step at 95 °C for 1 s and annealing step at 60 °C for 20 s. The data was collected at the end of each annealing step. Relative expression of mRNA was determined by the comparative 2-ΔΔCT method.

Statistical analysis

Quantitative data were analyzed using statistical software, SPSS 18.0. Normally distributed continuous data were analyzed using parametric statistical test and expressed as mean and standard deviation. Categorical data were analyzed via chi-square test.

RESULTS

A. Demographic Data and association with POH

Forty-nine (10 men and 39 women) with a mean age of 52.9 ± 9.2 years old met the inclusion criteria and agreed to participate in the study. A total of 47% (n=23) of subjects were evaluated with POH, and 53% (n=26) were categorized into the non-POH group. A total of 67.3% of the subjects were Fitzpatrick skin phototype III, while 22.3% were phototype IV, 8% were phototype I, and 2% were phototype V. Pearson Chi-square showed that Fitzpatrick scale was not associated with the POH group (c2 = 2.675, p=0.445). However, the Pearson Chi-square showed that the invagination of melanin deposit into the dermal layer was more prominent in the POH group compared to the non-POH group (c2 =8.349, p<0.05, Table 1).

B. Gene Expression Study

MITF, TYR, and TYRP1 gene expressions were significantly higher in the POH group (p<0.01, graph 1). Gene expressions of GR, GPx-1, and GST-1 were comparable between POH and non-POH groups (Table 2).

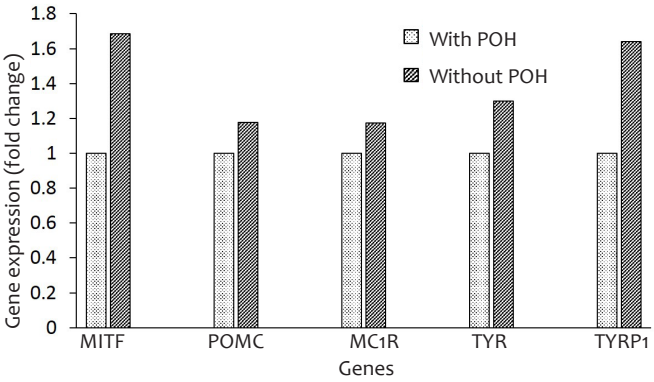
DISCUSSION

The findings of this study suggest that (i) dermal hyperpigmentation could be the predominant underlying cause of periorbital hyperpigmentation, which may be associated with (ii) the overexpression of MITF, TYR, and TYRP1, which in turn triggers the melanogenesis in periorbital skins.

In agreement with the findings of this study, growing evidence showed that pigmentation surrounding the eyelids is not restricted in the epidermal layer but also deep in the dermal layer, and it is resistant to treatments.[2, 6, 11-14] Macrophages normally phagocyte melanin that falls into the reticular dermis to form melanophages, causing a bluish appearance. Dermal hyperpigmentation is less responsive to common depigmenting agents. Partially, it occurs because most of the depigmentation therapies focus on epidermal hyperpigmentation, and they are not effective in eliminating dermal melanophages. The findings of this study suggest that incorporating topical depigmenting agents to transdermal drug delivery may be beneficial in reducing dermal hyperpigmentation. For instance, using a transdermal vehicle like synthetic peptide ACSSSPSKHCG (TD1) and oligoarginine (R8) could be beneficial in treating periorbital hyperpigmentation. However, which therapeutic molecule should be delivered to the dermal layer to achieve the maximal therapeutic effect? Extensive studies focus on the depigmenting roles of TYR inhibitors, but scarce have considered MITF as a drug target for treating hyperpigmentation disorders, especially periorbital hyperpigmentation.

Topical eye creams, mainly tyrosinase-inhibiting agents, i.e., hydroquinone, azelaic acid, tretinoin, and kojic acid, are widely used as depigmenting agents.[15, 16] Nevertheless, their therapeutic effects are inconsistent and unsatisfying in treating periorbital hyperpigmentation. Laser and intense pulsed light treatments are newer approaches to remove the pigments under the eyes.[17] Still, these therapies are relatively more expensive and require high skilled professions to conduct the treatment procedure. Therefore, innovative strategies are required to identify new drug targets. This study proposes that targeted suppression of MITF rather than its downstream melanogenic genes such as TYR and TRP1 would be a better candidate for a new generation of depigmenting agents.

MITF is a key regulator involves in melanocytic development, and pigmentation. It is a critical regulator of survival, proliferation and differentiation of pigment cells, melanocytes.[10] The three most commonly known signal pathways, which are cAMP-dependent (via MC1R), Wnt, and ERK (via c-Kit receptor) signaling pathways, control the MITF activity. Binding of α-MSH (also known as proopiomelanocortin, POMC) to its plasma membrane receptor, MC1R activates the cAMP-de-



** p<0,01 compared to the group without POH

GRAPH 1: *Fold change of gene expression in groups with and without POH*

TABLE 1: DEPTH OF MELANIN DISTRIBUTION AND ITS ASSOCIATION WITH POH GROUP

POH Classification/ Depth of melanin distribution	POH (n = 26)	Non-POH (n = 23)	Total (n)	Pearson Chi-square
Papillary dermis	11	19	30	(c2 =8.349. p<0.05)
Reticular dermis	15	4	19	
Total (n)	26	23	49	

Pearson chi-square test showed that the depth of melanin distribution was associated with the POH group (p<0.05).

TABLE 2: PEARSON CHI-SQUARE TEST SHOWED THAT THE DEPTH OF MELANIN DISTRIBUTION WAS ASSOCIATED WITH THE POH GROUP (P<0.05).

Gene/Group	Gene Expression (*Fold-change*)	
	Non-POH	HPO
GR	1 ± 0.51	0.90 ± 0.41
GPx-1	1 ± 0.93	0.86 ± 0.68
GST-1	1 ± 0.48	1.06 ± 0.49

pendent pathway, and eventually increases MITF activity, and therefore stimulates melanogenesis.[10] The findings of this study suggest that overexpression of MITF is unlikely via the activation of α-MSH-MC1R signaling pathway. It has been demonstrated that regardless of the high or low level of MC1R, elevated intracellular cAMP triggered by forskolin leads to induction of the TYR, and TYRP1 promoters.[18] Further investigations on the association of MITF with increased intracellular cAMP, Wnt and ERK signaling pathways might provide more insights into the underlying mechanism of MITF overexpression in hyperpigmented eyelids.

This study has shown that MITF is highly expressed in periorbital hyperpigmented skins and closely associated with the degree of melanin production. Therefore, this study proposed that MITF is a potential therapeutic target molecule in treating periorbital hyperpigmentation. Earlier studies showed that the silencing of MITF gene expression via small interfering RNA (siRNA) technique, MITF-siRNA (a negative modulator of MITF), significantly reduced the TYR, TYRP1, and MC1R levels, and, therefore inhibit melanogenesis in melanoma cell culture.[19] Furthermore, in a clinical study, the topical application of MITF-siRNA cream with transdermal vehicles significantly improved facial hyperpigmentation lesions.[19] As the underlying cause of dark circles under the eyes is similar to melasma, which is mainly due to overexpression of MITF and melanin deposition in the dermal layer, this study suggests that MITF-siRNA probably exerts the similar therapeutic effect in skins with periorbital hyperpigmentation.

In addition to MITF-siRNA strategies, compounds, or drug molecules able to interfere with MITF, post-transcriptional regulation can be utilized to modulate the pigmentation process. DKK1 (dickkopf-1) is found predominantly in hypopigmented palmar and plantar areas and exhibits suppression activities on MITF, therefore inhibiting melanocyte growth and pigment production.[20] This study postulates that targeted DKK1 stimulation could be a viable approach to modulate the overexpressed MITF in periorbital hyperpigmented skins. Therefore, there is two crucial conditions in designing a new therapeutic agent in treating periorbital hyperpigmentation, i.e., (i) it should be a small molecule and able to be delivered to transdermal layer, (ii) it should be able to enter the cell and suppress the MITF expression.

Exposure to ultraviolet (UV) irradiation and oxidative stress has been associated with the pathogenesis of periorbital hyperpigmentation.[1, 21, 22] UV has been shown to trigger the expression of MITF, tyrosinase, and MSH, which eventually leads to the production of melanin pigments.[10] UV irradiation is also known to induce the production of reactive oxygen species (ROS) in human skin, resulting in oxidative stress and photodamage to the skin. Antioxidants have been widely used for depigmentation in skin products, including eye creams, to reduce skin damage and melanin deposition.[2, 23] Nevertheless, this study showed that there is no significant difference in gene expressions of the major intracellular enzymatic antioxidants like glutathione reductase (GR), glutathione peroxidase (GPx), and glutathione-s-transferase (GST) in hyperpigmented and non-hyperpigmented eyelid skins. These findings suggest that periorbital hyperpigmentation is unlikely due to inadequate intracellular antioxidants.

In conclusion, the findings of this present study suggest that MITF is the master regulator for melanin deposition in POH skins, upregulated MITF is closely associated with increased TYR and TYR1. These findings are essential in proposing a new therapeutic approach in POH treatment. ●

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Original Article

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Comparative split-face study between pulse-in-pulse intense pulsed light therapy and 5% retinoic acid peel for melasma treatment

Estudo comparativo, split face entre luz intensa pulsada com modo pulse-in-pulse e peeling de ácido retinoico 5% para o tratamento do melasma

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ABSTRACT

Introduction: Melasma is a highly common dermatosis that has numerous therapeutic alternatives but tends to be a therapeutic challenge due to its refractory and relapsing nature.
Objective: Comparison between intense pulsed light with pulse-in-pulse mode (IPL-PIP) and retinoic acid peel (RAP) for melasma treatment.
Methods: We conducted six bi-weekly IPL-PIP sessions in the left hemiface and three-monthly RAP sessions in the right hemiface. The Melasma Area and Severity Index (MASI) and MelasQol questionnaires were applied before and one month after the last treatment session.
Results: We observed a reduction of approximately 33% in hemiface MASI with RAP and of 35% in hemiface with IPL-PIP, showing significant improvement of melasma with both methods. There was no statistically significant difference between the two groups. Both practices were well tolerated by patients, but RAP had more reports of adverse events than IPL-PIP. There was a substantial improvement in the quality of life of the patients with both therapeutic methods.
Conclusions: RAP and IPL-PIP are effective in treating melasma and improving patients' quality of life. There was no statistical difference between the methods concerning lesion clearance and quality of life of patients.
Keywords: Chemexfoliation; Light; Melanosis; Retinoids

RESUMO

Introdução: *Melasma é uma dermatose com alta prevalência, que possui inúmeras alternativas terapêuticas, porém tende a ser um desafio terapêutico por sua natureza refratária e recidivante.*
Objetivo: *Comparação entre a luz intensa pulsada na modalidade pulse-in-pulse (LIP-PIP) e o peeling de ácido retinoico (PAR) para o tratamento do melasma.*
Métodos: *Foram realizadas seis sessões quinzenais de LIP-PIP na hemiface esquerda e três sessões mensais PAR na hemiface direita. Foram aplicados os questionários Índice de Gravidade para o Melasma (MASI) e MelasQol antes e um mês após a última sessão do tratamento.*
Resultados: *Redução de cerca de 33% no MASI da hemiface com PAR e de 35% na hemiface com LIP-PIP, mostrando melhora significativa do melasma com ambos os métodos. Não houve diferença estatisticamente significante entre os dois grupos. Ambos os métodos foram bem tolerados pelas pacientes, porém o PAR apresentou mais relatos de efeitos adversos que o LIP-PIP. Houve melhora significativa na qualidade de vida das pacientes estudadas com os dois métodos terapêuticos.*
Conclusões: *O PAR e o LIP- PIP são efetivos para o tratamento do melasma e para a melhora da qualidade de vida dos pacientes. Não houve diferença estatística entre os métodos em relação ao clareamento da lesão e à qualidade de vida de seus portadores.*
Palavras-Chave: *Abrasão química; Luz; Melanose; Retinoides*

INTRODUCTION

Melasma is a benign and acquired dermatosis, whose prevalence can reach up to 24% in women in some populations.[1] It is characterized by hyperpigmented and asymptomatic spots in photo exposed areas. It is more common in women and patients with higher Fitzpatrick skin phototypes. Genetic, hormonal, vascular, visible light, and ultraviolet light factors are considered the main causal factors.[2] According to the literature, this dermatosis, although asymptomatic and with a benign course, causes a significant negative impact on patients' quality of life (QoL), interfering in the psychosocial, family and professional spheres.[3]

Due to its refractory and recurrent nature, melasma can be a therapeutic challenge. Although there are numerous therapeutic options, none is considered to have the potential for total and definitive improvement. Response to treatments varies widely among patients, requiring, in most cases, combinations of methods and individualization according to tolerability and clinical response.[4] Thus, this study aims to compare the effectiveness, tolerance, adverse events, and quality of life of patients with melasma treated in a hemiface with a traditional and widely known option (retinoic acid peel - RAP) and in the other with a promising but still little studied option (intense pulsed light with pulse-in-pulse mode - IPL-PIP). This technology emits the same wave as IPL but fractionates the pulse duration of 10 ms into 100 sub-pulses of 40 μs. Through these fractional pulses, PIP can remove more gently the unwanted pigmentation without aggravating or exacerbating melasma.[5]

MATERIALS AND METHODS

This is a split-face, single-center, clinical trial conducted in 17 patients with melasma. The inclusion criteria were the presence of clinically typical melasma lesion, located on the face, bilateral, in patients with Fitzpatrick skin phototype I and IV.[2] The exclusion criteria were pregnancy, lactation, use of oral medications that influenced melasma treatment (such as oral contraceptives), skin lighteners (or bleachers), and laser or light treatment for melasma for six months before inclusion. The institution's research ethics committee (UFCSPA) approved the study, and all patients signed an informed consent form (ICF).

The face was cleaned with 2% chlorhexidine aqueous solution and gauze. On the IPL-PIP hemiface, (Multiwave Laser Toning of LMG Solon, Guaxupé, MG, Brazil), a thin layer of water-based gel was applied, and the session started at 550 nm to 800 nm wavelength, fluency 12 J/cm^2 to 15 J/cm^2, two to three times until reaching mild erythema that disappeared in approximately 40 seconds. Treatments were administered to the left hemiface at two-week intervals with a total of six ILP-PIP sessions. The right hemiface was treated using RAP 5% once a month in a total of three sessions. The patients were instructed to wash the RAP with soap and water after six hours of its application. After each session, patients received a form with guidelines and care to be taken after the procedure, especially strict 4/4 hour photoprotection with Minesol Actif® SPF 80 (Johnson & Johnson do Brasil Indústria e Comércio de Produtos para Saúde Ltda., São Paulo, SP, Brazil) provided by the researchers, and no other topical medications were used. In this same form, patients should describe possible adverse events if they occurred.

Two researchers assessed the modified MASI score at the beginning of the protocol and one month after the last treatment, and the patients answered a quality of life questionnaire (MelasQoL-BP).[3,6]

Statistical analysis was performed using absolute and relative distributions, as well as measures of central tendency and variability. Regarding the comparison of the means assessed during the follow-up, the study of the data distributions for normality was conducted using the Shappiro Wilk test. In the comparison of continuous variables between two dependent groups (pre- and post-treatment evaluation as well as comparison between the hemifaces), the t-Student and Wilcoxon tests were used. The magnitude of the differences was calculated from the effect size, where an effect size of 0.20-0.49 was considered small; 0.500.79, moderate; and ≥0.80, large magnitude effect. Data were analyzed using the Statistical Package for Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA, 2008) for Windows. For the statistical decision criteria, the significance level of 5% was adopted.

RESULTS

The comparative study between melasma treatment with ILP-PIP and RAP 5% initially involved 17 patients. We excluded one patient after the first session because she presented post-inflammatory hyperpigmentation on the IPL-PIP hemiface. Two other patients were excluded from the study due to loss to follow-up. Therefore, the results were analyzed based on a sample of 14 female patients, aged 32 to 47 years (mean 41 years and SD ± 4,6), and with a predominance of Fitzpatrick skin phototype III in 43% of the patients (Table 1).

Analysis of pre- and post-treatment MASI indices showed a significant improvement in melasma with both therapeutic modalities (p=0.002). The individual analysis of each hemiface with its respective intervention evidenced the same significant reduction in severity (p=0.001 for RAP and p=0.012 for ILP-PIP). ILP-PIP presented a slight 2% superiority in improving melasma, but with no statistical significance (Table 2).

Table 3 shows adverse events with both techniques. RAP presented significantly more burning (78.5% of patients; p=0.047) and peeling (100% of patients; p=0.001) than ILP-PIP (burning in 21.4% of patients and peeling in no patients). Regarding other unwanted events, the differences observed between the treatments were not significant.

Table 1: Absolute and relative distribution by age and phototype

Variable	Total sample (n=14)	
Age (mean ± standard deviation)	**41** ± 4.6 (32 – 47)	
Phototype	**N.**	**%**
I	2	14.3
II	2	14.3
III	**6**	**43**
IV	4	28.5

Regarding the assessment of the quality of life of patients with melasma, there was a significant improvement with both treatments (p=0.045) demonstrated by reducing the MelasQoL--BP score by approximately 20%. The effect size of melasma treatment on patients' quality of life was classified as moderate (*dCohen*= = 0.641) (Figure 1 and Table 4).

DISCUSSION

Melasma is considered a chronic dermatosis with numerous therapeutic options, but not always enough to achieve satisfactory and lasting improvement.[4,7] Over the last decades, studies have shown that its presence goes far beyond a simple change of aesthetic nature to acne with a significant impact on the qua-

Table 2: MASI mean, standard deviation and median in pre and post-use assessments of ILP-PIP in the left hemiface and RAP in the right hemiface for melasma treatment Melasma Area and Severity Index

Melasma Area and Severity Index	Assessment (n=14)								Difference Post-Pre[G]
	Pre-treatment			Post-treatment					
(MASI)	Mean	SD	Median	Mean	DP	Median	pø	Cohen' D[B]	
MASI Mean RAP-PIP	8.4	4.0	7.5	5.5	3.4	4.5	0.002	-0.719	-2.9 (34.5%)
MASI RAP	8.5	4.2	8.0	5.7	3.5	5.0	0.001	-0.667	-2.8 (32.9%)
MASI PIP	8.3	4.2	8.0	5.4	3.3	5.0	0.012	-0.709	-2.9 (34.9%)
pø		>0.999			0.896				

Ø: *Wilcoxon test;*
B: *Estimation of post-treatment effect size compared to pretreatment: evaluation*
G: *Difference between pre and post treatment means - n (%)*

Table 3: Absolute and relative distribution of adverse events reported by patients

Adverse events	Right and left hemifaces				*p* (value)§
	RAP 5%		ILP-PIP		
	n	%	n	%	
Erythema					0.874
No	10	71.42	13	92.85	
Yes	4	28.68	1	8.25	
Scabbing					>0.999
No	11	78.57	14	100.0	
Yes	3	21.42	0		
Peeling					0.001
No	0	0	14	100	
Yes	14	100.0	0	0	
Pain					>0.999
No	12	85.71	14	100.0	
Yes	2	14.28	0		
Burning					0.037
No	3	21.42	13	92.85	
Yes	11	78.57	1	8.25	
Hyperchromia					---
No	14	100.0	14	100	
Yes	0	0	0	0	

§ McNema Test

lity of life of its carriers.[3,8] Thus, we continue looking for new therapeutic options that are promising and effective for its treatment. In melasma, high-fluency laser and ILP treatments to treat pigments are not helpful because they can aggravate melasma.[5] PIP does not raise the temperature of the target tissue enough to destroy it, gradually increasing skin temperature, thus being safer than conventional ILP. It applies a very low fluency and does not destroy active melanocytes with melanosomes.[5,9] Previous experience showed that PIP has induced clinical improvement with fewer treatment sessions (4-6), and may have the additional benefit of avoiding possible adverse events.[9] We chose to use RAP 5% as a PIP system control as it is a well-known, effective, and scientifically documented traditional treatment alternative for melasma.[10,11]

Our study demonstrated a significant improvement of melasma with both treatment modalities in the Melasma Area and Severity Index (MASI) analysis but without superiority between the two intervention methods. However, the PIP system showed a slight superiority of 2% over RAP, which may represent a tendency to significance with the increase of the studied sample.

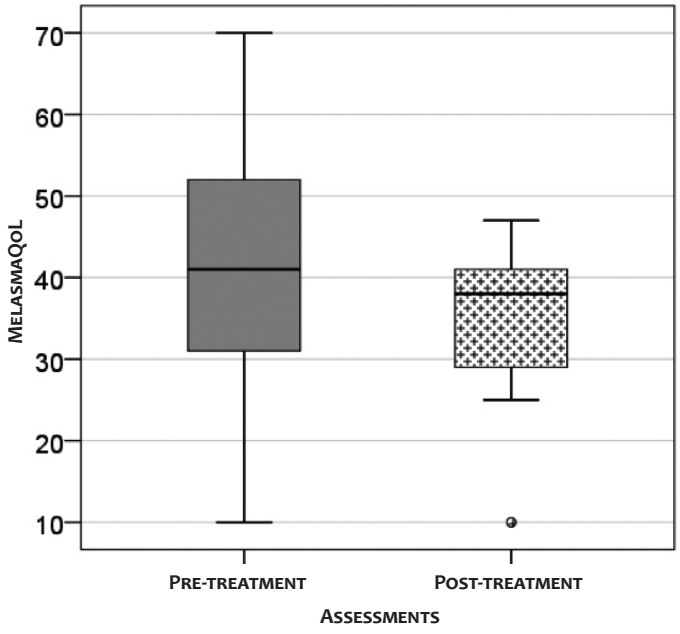

Figure 1: Quality of life assessment of patients with melasma before and after treatment (Box Diagram)

RAP presented significantly more adverse events than PIP. The presence of burning and peeling, already well described and expected with RAP, confirmed this fact. Although very common, they were described as mild and transient. In the evaluation of PIP para effects, only one patient reported mild erythema, which is a very comfortable procedure with no recovery time to return to daily activities. However, it's essential to remember that a patient was excluded from the study after a PIP session due to the presence of post-inflammatory hyperpigmentation in the hemiface where this treatment was applied. In addition to suspending her follow-up in the study, we recommended the topical use of hydroquinone 4% and strict photoprotection. In approximately 15 days, the patient had a total improvement of this dyschromia.

In this study, we also assessed the impact on patients' quality of life (QoL) secondary to melasma, and our findings corroborated the worldwide literature showing its decrease. After treatment, there was a significant improvement in the quality of life of the study patients, measured with moderate impact. This fact reinforces the importance of always offering some therapeutic options to patients, regardless of total or partial improvement, because, despite their chronic and relapsing course, patients experience improvement in their quality of life.

CONCLUSION

Both RAP 5% and PIP systems are significantly effective options for melasma treatment. Despite a slight tendency for the superiority of IPL-PIP over RAP, we found no significant difference between them. Regarding adverse events, RAP is significantly accompanied by burning and peeling, but mildly and transiently. PIP, on the other hand, does not present discomfort and does not require recovery time by patients, but it is a more expensive therapeutic option, in addition to one patient having post-inflammatory hyperchromia. We emphasize the need for further studies with larger samples.

Table 4: Mean, standard deviation and medians for pre and post intervention quality of life assessments

Variables	Assessments (n=14)						*p* (valor)
	Pre-treatment			Post-treatment			
	Mean	SD	Median	Mean	SD	Median	
Quality of life							
(MelasmaQol-BP)	42.2	14.9	41.0	33.7	11.6	38.0	**0.045Ø**
Cohen' D[A]				0.641			

Ø: *Wilcoxon Teste;*
Variable with asymmetric distribution (Shapiro Wilk <0.100)
A: *Estimated size of post-treatment effect compared to pretreatment*

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Superficial application technique with cohesive polydensified matrix hyaluronic acid for the treatment of lines and wrinkles

Técnica de aplicação superficial com ácido hialurônico de matriz coesiva polidensificada para o tratamento de linhas e rugas

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ABSTRACT

Introduction: During aging, the skin undergoes structural, cellular, and molecular changes that alter its mechanical properties as well as its biological and physiological functions. These changes manifest as loss of elasticity, and turgor, with consequent appearance of fine wrinkles, lines, and creases that are difficult to resolve, being considered a therapeutic challenge.

Objective: To describe the technique of applying cohesive polydensified matrix hyaluronic acid for the treatment of superficial wrinkles.

Materials and methods: In this retrospective and observational study, the technique of superficial and transverse application to superficial wrinkles with cohesive polydensified matrix hyaluronic acid was performed in women with this type of wrinkles in the perioral, periorbicular and lateral regions of the face, which did not disappear after treatment with botulinum toxin, facial volumization with fillers and technology. The study was conducted over 22 months between 2016 and 2018. The degree of improvement was assessed by a questionnaire applied to the patients who observed paired standardized photographs taken in the previous period and one month after the treatment.

Results: The technique was performed on 40 women aged 55 to 80 years, whose response to the evaluation questionnaire was improved between 90% and 100% after one month of treatment.

Conclusions: The technique of superficial and transverse application to wrinkles with cohesive polydensified matrix hyaluronic acid proved to be an excellent option for the treatment of affected areas, without significant adverse events and/or Tyndall effect, with a high degree of patient satisfaction.

Keywords: Hyaluronic acid; Skin aging; Skin care

RESUMO

Introdução: *Durante o envelhecimento, a pele sofre modificações estruturais, celulares e moleculares que alteram as suas propriedades mecânicas e também as suas funções biológica e fisiológica. Estas se manifestam por perda de elasticidade e turgor, com consequente aparecimento de rugas finas, linhas e vincos de difícil resolução, sendo consideradas um desafio terapêutico.*

Objetivo: *Descrever a técnica de aplicação de ácido hialurônico de matriz coesiva polidensificada para o tratamento de rugas superficiais.*

Materiais e métodos: *Neste estudo retrospectivo e observacional, a técnica de aplicação superficial e transversal às rugas superficiais com o ácido hialurônico de matriz coesiva polidensificada foi realizada em mulheres portadoras deste tipo de rugas nas regiões perioral, periorbiculares e laterais da face, que não desapareceram após tratamentos com toxina botulínica, volumização facial com preenchedores e aplicações com tecnologias. O estudo ocorreu durante 22 meses entre os anos de 2016 e 2018. O grau de melhora foi avaliado por meio de questionário aplicado às próprias pacientes que observaram fotografias padronizadas pareadas feitas no período prévio e um mês após o tratamento.*

Resultados: *A técnica foi realizada em 40 mulheres com idade entre 55 e 80 anos, cuja resposta ao questionário de avaliação foi melhora entre 90 e 100% após um mês de tratamento.*

Conclusões: *A técnica de aplicação superficial e transversal às rugas com o ácido hialurônico de matriz coesiva polidensificada mostrou-se uma excelente opção para o tratamento das áreas afetadas, sem descrição de efeitos adversos importantes e/ou efeito Tyndall, com alto grau de satisfação das pacientes.*

Palavras-chave: *Ácido hialurônico; Envelhecimento da pele; Higiene da pele*

Original Article

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INTRODUCTION

Extracellular matrix (ECM) remodeling is a continuous multistep process involving localized degradation of matrix components, followed by cytoskeleton rearrangement, cell translocation, and deposition of new constituents. Evidence shows that TGF-β plays a central role in ECM biosynthesis, either by controlling collagen synthesis and degradation by binding to fibroblast cell membrane receptors and activating their genes or by inhibiting the action of metalloproteinases (MMPs). Although a variety of molecular mechanisms regulates each of these steps, the presence of proteinases controls the initial stage - especially MMPs such as collagenase, gelatinase, and metalloelastase, capable of initiating the fragmentation process of ECM native macromolecules, predominantly collagen I and IIII.[1]

During aging, all skin undergoes structural, cellular, and molecular changes that alter not only its mechanical properties but also its biological and physiological functions.[1,2,3] The changes caused by skin aging are the result of a normal physiological process aggravated by photoaging, which is also responsible for the appearance of stains, fine wrinkles, and dilated vessels, as well as surface roughness and skin cancer.[4]

Structurally, during chronological aging, the epidermis becomes thinner, dehydrated, and at the dermal-epidermal junction, the villi become flattened. The papillary dermis is the most affected, with fibroblast activity compromised by changes in cell morphology and metabolism, reduced proliferative potential, loss of response to growth factors, decline in ECM protein production, and increased expression of proteases involved in ECM degradation. Thus, the elastic fibers decrease in number and diameter; collagen synthesis reduces and its degradation increases due to elevated levels of metalloproteinase type I (collagenase), impacting the deposition, orientation, and size of fibers, which appear disorganized, more compact and granular. As a result, fibroblasts slowly lose their adhesion points with collagen fibers, changing their shape from fusiform to rounded. It affects its metabolic functions, creating a vicious circle. The reticular dermis becomes disorganized and degraded, with fragmented fibers.[5,6] Photodamage tends to aggravate this process, especially in the papillary dermis, reducing the synthesis of type I procollagen and increasing collagenase levels, which generates more collagen degradation products and inhibits the synthesis of new collagen.

Chronological aging and photodamage also affect the ground substance, reducing the number of mucopolysaccharides, glycosaminoglycans, and proteoglycans, especially hyaluronic acid, altering dermal hydration, negatively influencing skin turgor, and modifying its biomechanical properties.[3] Clinically, it is observed dry skin with loss of elasticity and consequent appearance of fine wrinkles, lines, and creases that are difficult to solve. These are considered a therapeutic challenge since they do not always disappear with botulinum toxin applications, facial volumization, and/or use of technologies (Figures 1A-C).

OBJECTIVE

This was a retrospective and observational study to describe the technique of superficial application of cohesive polydensified matrix hyaluronic acid and to evaluate the degree of satisfaction of the treated patients.

MATERIALS AND METHODS

Patient care was conducted in a private clinic for 22 months between 2016 and 2018, according to ethical guidelines indicated by the Declaration of Helsinki. The applications were performed in female patients with medium depth wrinkles and/or superficial creases in the perioral, periorbital, and lateral areas of the face that had not been resolved by previous botulinum toxin treatments for expression wrinkles, facial volumization by fillers, or by treatments with technologies. The product of choice was Belotero Soft® (Merz Brasil, São Paulo, SP) because of its indication for subepidermal applications. The degree of improvement was assessed by a questionnaire administered to patients after observing their own paired standardized facial photographs taken before and one month after the treatment.

TECHNICAL DESCRIPTION

We performed the applications under topical anesthesia at the site to be treated, according to the manufacturer's specifications and after the application of cold compresses for a few minutes to minimize pain and bruising.

The applications were in all regions of the face affected by

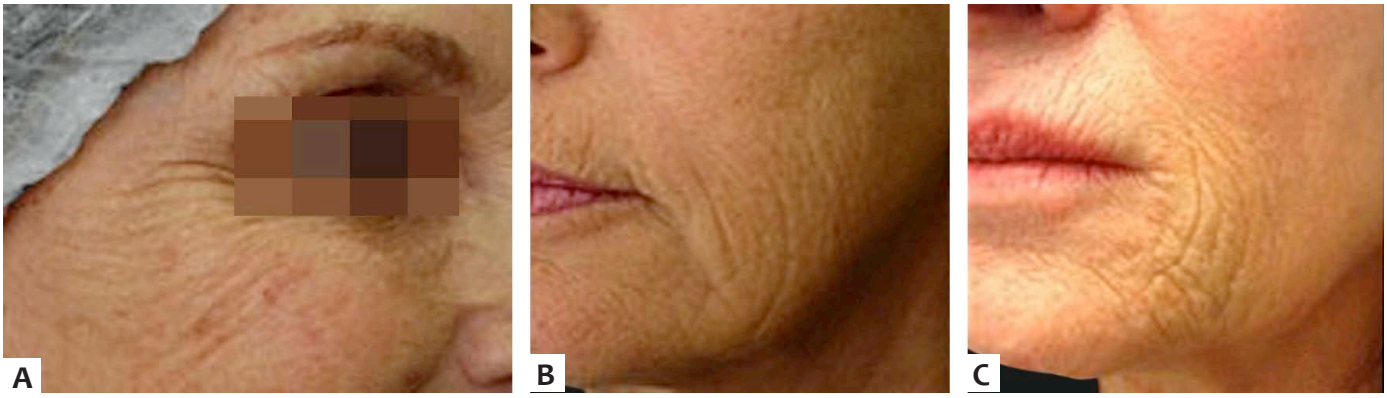

Figure 1: Creases and lines caused by dermal thinning and dehydration, which didn't disappear with botulinum toxin **(A)**, face volumization **(B)**, or technologies **(C)**

wrinkles and creases, perpendicular to the lines for the treatment of the entire affected area. They were applied to the superficial dermis in retro-injection, with the entrance of the full length of the 13mm 30G 1/2 needle at an angle of 10 to 12 degrees, that is, practically parallel to the skin surface, allowing the needle to be visualized (Figure 2). The needle bevel was normally upward, especially in thin skins, as downward placement could limit the application to the superficial dermis. The multiple implant placement lines were made about 5mm apart, with a small amount of product deposition (approximately 0.03mL), creating a slight elevation until the entire affected area was treated. All patients received 2mL of the product, 1mL in each hemiface, with distribution in all affected areas. After application, the treated areas were gently massaged to facilitate the horizontal spreading of the product, allowing the disappearance of any undulations on the skin surface, for better final correction. At the first sign of hematoma formation, digital compression was performed to prevent its progression.

RESULTS

Applications were performed on 40 women, aged 55 to 80 years (mean age 70.4 years). Improvement in facial lines was immediate in all cases (Figures 3-6). In some patients, two applications were necessary (Figure 7), according to the degree of skin atrophy, depth of lines and creases, or if the increase of the treated area volume was the desired objective that could be achieved uniformly and gradually, resulting in a very natural look. The treated patients were very satisfied with the results, assessing the degree of improvement. The achieved effects lasted for at least one year (Figure 7C).

DISCUSSION

The contribution of the dermis to the structure and function of the skin is crucial as it nourishes and shapes the epidermis, gives elasticity, resistance, tensile strength, protects the body from mechanical injuries, collaborates in thermoregulation

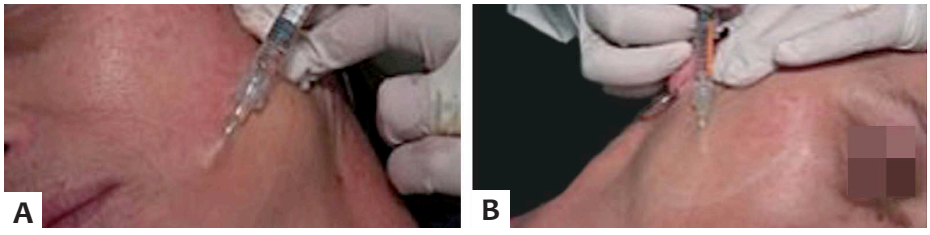

Figure 2:
Retro-injection application with full needle insertion at 10-degree angle

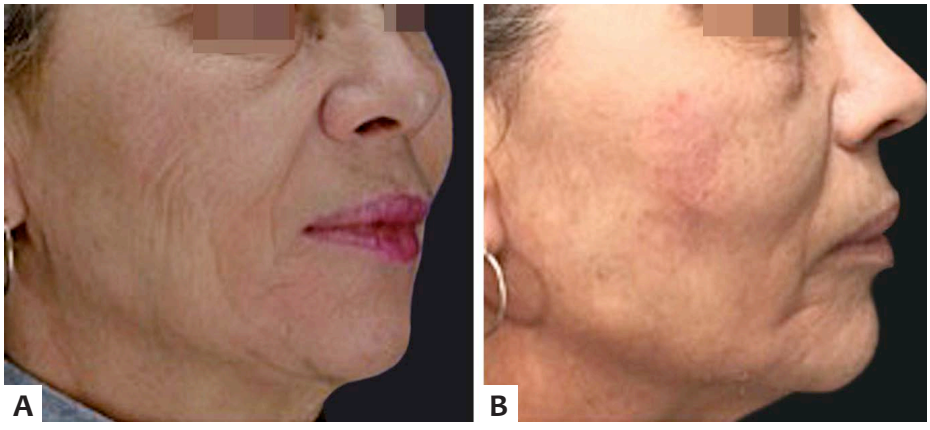

Figure 3.
Pre-application (A) and immediately after (B) application for the treatment of lines on the side of the face

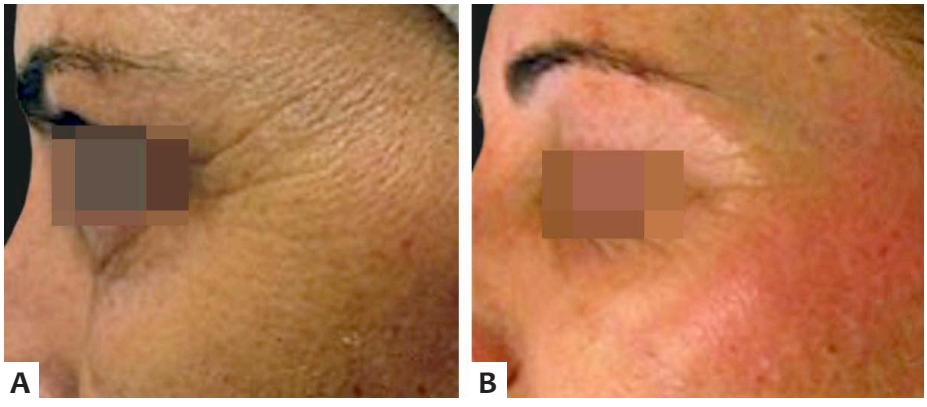

Figure 4.
Pre-application **(A)** and immediately after **(B)** application for the treatment of periorbital lines, 15 days after botulinum toxin

and contains sensory receptors, besides regulating the healing process.[5]

The amorphous or ground substance is mainly responsible for maintaining the dermal structure because it retains hydration; confers elasticity; helps the skin return to its original shape by facilitating the movement of fibers; protects and surrounds the fibers and cells; and promotes nutrient distribution.[5,6]

During aging, the dermis undergoes significant changes in the composition, thickness, and biomechanical properties of the extracellular matrix, thus reducing its turgidity and elasticity. Consequently, lines, wrinkles, and grooves appear.[7] Hyaluronic acid gels implant directly into the dermis may be a strategy to replenish the ground substance and increase the dermal thickness, thus restoring the mechanical properties of the skin.

Filling techniques with deep or intradermal injections or subdermal injections are especially pertinent for less cross-linked gels and/or hyaluronic acid at low concentrations, which are indicated to treat fine wrinkles directly in areas such as the periorbital or perioral region. Applications should be made at depths indicated by the risk for the Tyndall effect or visualization of the injected material.

However, recent technological advances have introduced new dermal fillers with unique characteristics, such as cohesive polydensified matrix hyaluronic acid used in the group of

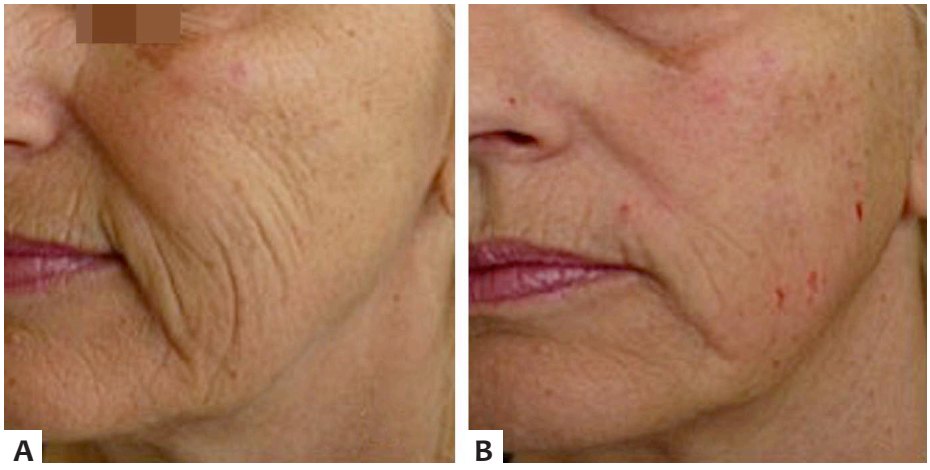

Figure 5.
Pre-application **(A)** and immediately after **(B)** application with immediate improvement of periorbital lines and lateral face

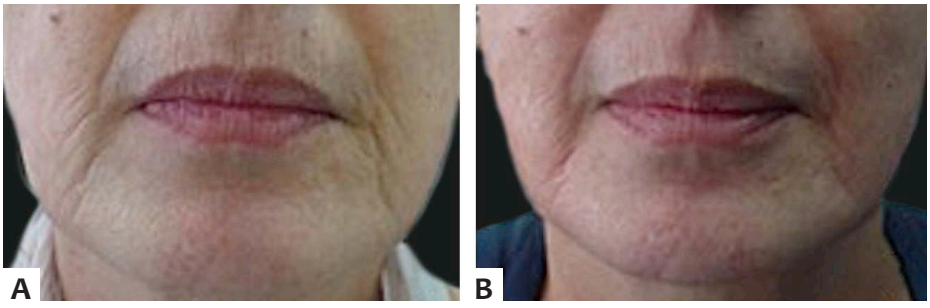

Figure 6.
Pre-application **(A)** and one month after **(B)** a single application for the treatment of the perioral and lateral lines at the corners of the mouth

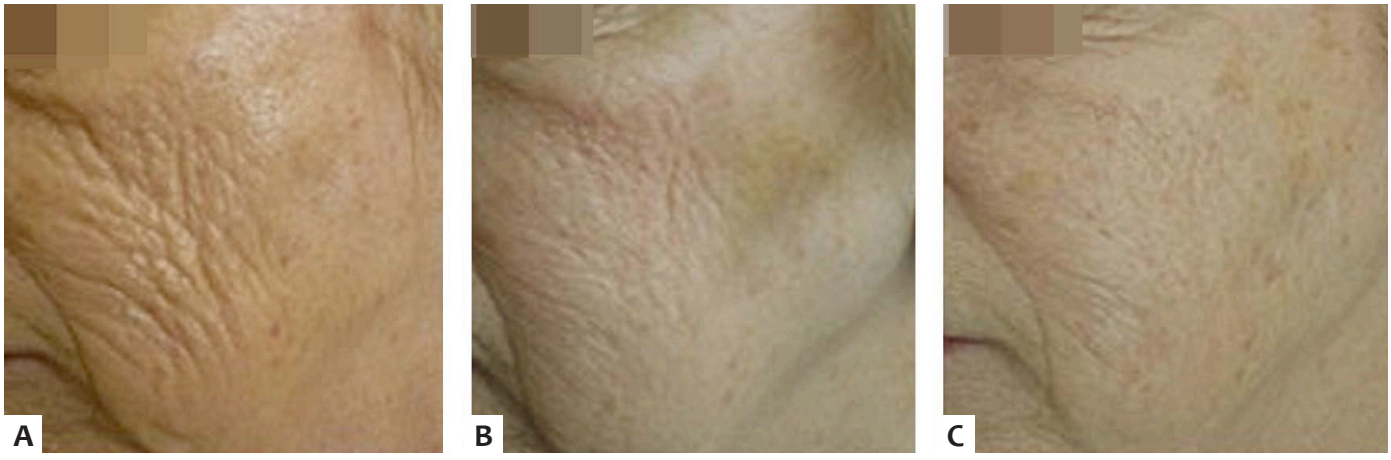

Figure 7. Pre-application **(A),** seven days after the first application **(B)** and one year after second application **(C)**

patients included in the present study. It presents particles of varying sizes and is produced by two cross-linking cycles with butanediol diglycidyl ether (BDDE), which results in a dermal filler gel with higher and lower density zones, giving the product the following characteristics: low viscosity, low elasticity (G´), high tan and high cohesiveness, which maintain affinity between gel molecules and allow tissue expansion in the superficial dermis with a predominant horizontal vector, resulting in high dermal integration and dermal volumization without changing its architecture.[2,8,9] Therefore, these rheological properties determine the distribution evenly within the dermis without the risk for the Tyndall effect.[9] Histological images with various stains and an ultrasound scan of the treated skin demonstrate a cohesive and homogeneous appearance that confirms the high degree of dermal integration and isoechogenicity regarding the adjacent dermis.[2,8] These product properties allow its application in the superficial reticular dermis with natural results and without risk of skin undulation.

Thus, we chose to apply the Belotero Soft cohesive polydensified cohesive matrix hyaluronic acid (Merz Farmacutica Comercial Ltda, São Paulo, SP, Brazil), due to its rheological characteristics, using the superficial transverse retro-injection technique, to wrinkles in the periorbital and perioral regions, in addition to those located on the lateral regions of the face, which did not disappear after botulinum toxin, filling or technologies.

The retro-injection application technique allows the homogeneous distribution of the product throughout the affected area, presenting improvement of the skin thickness and not only of the lines, keeping the mobility of the treated area, and the natural appearance, without the visualization of the material due to its high tissue integration.

The applications were practically painless and with little bruising, probably due to their depth in the dermis. We should highlight the fact that there was no description of the Tyndall effect in the treated patients, in agreement with the data obtained by Kuhne (2012) and Micheels (2013).[10,2]

There was a high degree of patient satisfaction with the treatment, with significant improvement of lines and wrinkles, as well as improvement of turgor and overall skin appearance with a single application. Still, some patients requested a second application due the thin skin thickness, the depth of the lines and wrinkles, and the extent of the affected areas.

The long-term cosmetic benefits on aging skin can be attributed not only to gel application (immediate response) but to fibroblast elongation promoted by cross-linked hyaluronic acid injection and concomitant release of TGF-, which stimulates the synthesis of dense bands of mature collagen markedly, partially restoring the extracellular matrix components.[6,11]

It should be noted that patients under the effect of muscle relaxation promoted by botulinum toxin were informed about the possibility of relapsing of some facial lines, in the case of expression, after the return of the movements.

CONCLUSION

The cohesive polydensified matrix hyaluronic acid proved to be the ideal filler for the treatment with the technique of superficial and transverse application of wrinkles and superficial creases, located in the periorbital, perioral and lateral regions of the face, caused by skin aging, which did not disappear after the treatment with botulinum toxin and/or face volumization and/or technology treatments, and no Tyndall effect or other adverse events were observed.●

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New facial rejuvenation technique with Hyaluronic Acid: Delta V Lifting

Nova técnica de rejuvenescimento facial com ácido hialurônico: delta V lifting

Original Article

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ABSTRACT

Introduction: Facial aging occurs due to loss of facial volume and altered skin texture. Hyaluronic acid fillers are the main non-surgical tools used to recover the volume loss, since, besides filling, they act as skin remodeling.

Objective: To describe a new facial rejuvenation technique with hyaluronic acid: delta V lifting. Through this technique, we seek not only to fill in areas with volume deficits but mainly to stimulate tissue regeneration through the interaction between hyaluronic acid and superficial subcutaneous tissue, the main application plan.

Methods: A retrospective observational study assessing 200 patients treated with 2 ml of hyaluronic acid at a concentration of 23 mg/ml in a single therapy session with the delta V lifting technique.

Results: 87% of patients rated the result as "great improvement" and 13% as "good improvement" according to the Global Aesthetic Improvement Scale. Also, they all reported progressive improvement of the result until the moment of return within one month after the procedure.

Conclusions: The delta V lifting technique was effective in bringing satisfactory aesthetic results with a minimal amount of hyaluronic acid. The interaction between hyaluronic acid and adipose tissue is believed to be involved in optimizing results.

Keywords: Hyaluronic acid; Rejuvenation; Techniques

RESUMO

Introdução: *O envelhecimento facial ocorre devido à perda de volume facial e à alteração da textura da pele. Os preenchedores de ácido hialurônico são as principais ferramentas não cirúrgicas utilizadas para recuperar a perda de volume, uma vez que, além de preencher, atuam como remodelador cutâneo.*

Objetivo: *Descrever uma nova técnica de rejuvenescimento facial com ácido hialurônico: delta V lifting. Por meio dessa técnica, buscamos não apenas preencher áreas com déficit de volume, mas principalmente estimular a regeneração tecidual pela interação entre o ácido hialurônico e o subcutâneo superficial, principal plano de aplicação.*

Métodos: *Estudo observacional retrospectivo que avaliou 200 pacientes tratados com 2ml de ácido hialurônico de concentração 23mg/ml em uma única sessão terapêutica com a técnica delta V lifting.*

Resultados: *87% dos pacientes classificaram o resultado como "muita melhora" e 13% como "boa melhora", segundo a Escala de Melhoria Estética Global. Além disso, todos afirmaram perceber a melhora progressiva do resultado até o momento do retorno em um mês após o procedimento.*

Conclusões: *A técnica delta V lifting mostrou-se eficaz em trazer resultados estéticos satisfatórios com quantidade mínima de ácido hialurônico. Acredita-se que a interação entre ácido hialurônico e tecido adiposo esteja envolvida na otimização dos resultados.*

Palavras-chave: *Ácido hialurônico; Rejuvenescimento; Técnicas*

INTRODUCION

Facial aging is characterized by different phenomena that occur at about the same time: variable skin atrophy and wrinkle formation caused by genetic, actinic and environmental factors; loss of bone volume; loss of facial fat, and sagging skin.[1] Thus, facial aging consists of a dynamic and complex interaction of several factors involving three-dimensional changes that occur in the skeleton, as well as in soft tissue structure, associated with superficial skin changes.[2,3]

The drooping appearance associated with aging is due to both facial volume loss and skin texture change.4 Thus, flattening of the concavities of the forehead, eyebrow, glabella and temporal region of the upper face, drooping of the nasal tip, flattening of the cheek in the middle third and retraction of the chin, loss of lip volume, and drooping of the oral commissure in the lower face characterize the aged face.[5]

Hyaluronic acid fillers are the main non-surgical tools used to recover the lost volume. In the past, fillers were mostly used for surface treatments, but nowadays, they have been widely used in volumizing, prioritizing in-depth application plans, and not just superficial skin. By promoting volumization, fillers help limit the impact of sagging and ensure a lifting effect. [6]

There are several filling techniques with hyaluronic acid, such as serial puncture, linear threading, fanning, cross-hatching, and tower technique. An excellent technique depends on the filling agent, the target area to be corrected, and the physician's preference. Their use seeks the best aesthetic results for each case.[7]

The main objective for rejuvenating the face as a whole should be to restructure the lost volume and treat sagging skin. The areas of resorption should be selected and individualized according to each person's characteristics. Thus, we seek to promote rejuvenation with hyaluronic acid through a new technique: delta V lifting. This technique consists of identifying areas with sagging and/or loss of volume and marking them individually in the shape of a triangle (delta). The base of the triangle is the region that presents the highest tissue resorption and, therefore, should receive the most substantial filler volume, while the apex (delta tip) receives the least amount of hyaluronic acid. Also, the triangle represents support vectors (V) (traction movement effect) to perform the lifting effect of the region to be treated.

This new technique can be safely used in various regions of the face, as it should be performed with the use of a cannula (preferably 22G) to prevent the involvement of facial blood vessels. Thus, we seek to perform facial restructuring by identifying areas of volume loss and distribution of hyaluronic acid in triangle-shaped support vectors, promoting more harmony and naturalness to the aged face.

METHODS

Retrospective, observational study that assessed 200 patients treated at a private clinic in the city of São José do Rio Preto, SP, Brazil, from January to December 2018. We included patients over 20 years old, men and women, who did not perform any other treatments than the one proposed in this study. The Research Ethics Committee of the São José do Rio Preto Medical School, SP, approved this study.

All patients were treated with hyaluronic acid 2ml at a concentration of 23 mg/ml in a single therapeutic session. The areas to be treated were marked in triangles (deltas) individually, assessing the areas of volume loss and support in each patient. The triangles size triangles and the number of deltas marked in the patients were specific to each individual according to their needs. However, the primary identified regions to be filled in were: temporal region, supraciliary region, zygomatic region, mandibular region, nasojugal groove region, nasolabial fold region, labiomental groove region, and labial region.

After identifying the treatment areas and the support vectors of each region, the deltas were designed with the base corresponding to the area with the highest support loss. Thus, the direction of the sustaining vectors moves from the triangle apex to its base (Figure 1). For each triangle to be filled, anesthesia was administered about 0.5 cm from the apex with lidocaine hydrochloride 2.0% associated with norepinephrine hemitartrate (1:50,000 in norepinephrine).

After performing the anesthetic button, we used a 21G needle to make the cannula insertion hole. We inserted the 22G cannula at the apex of the triangle, applying hyaluronic acid in the subcutaneous plane through retro-injection with a larger amount of filler at the base of the triangle. We administered three to four retro-injection lines in each triangle. The application plan is in the superficial dermis, just below the dermis, except for the nasojugal groove region, where it is applied in the periosteum plane, and in the lip, where it is performed in the muscle.

After the procedure, the patients returned within one month for medical evaluation, photography, and satisfaction questionnaire. Two physicians not involved in the research evaluated the photographs to rank the results according to the Global Aesthetic Improvement Scale:8 great improvement (excellent cosmetic result), good improvement (marked improvement in appearance, but not entirely optimal), regular improvement (obvious improvement of the appearance, but a touch-up or a new treatment is advised), unaltered (the appearance is es-

Figure 1: Support vectors of the regions to be treated

sentially the same compared with the original condition) and worsening (the appearance is worse compared with the original condition).

RESULTS

Of the 200 patients assessed, 18 (9%) were 20 to 30 years old, 55 (27.5%) were 31 to 40 years old, 50 (25%) were 41 to 50 years old, 56 (28%) were 51 to 60 years old, and 21 (10.5%) were 60 to 70 years old. Most of the evaluated patients were women: 184 female patients and 16 male patients.

According to the physicians' assessment, 58% of patients were rated as presenting "great improvement" according to the Global Aesthetic Improvement Scale, 30% were rated as "good improvement", and 12% were rated as presenting "regular improvement" (Figures 2, 3, 4, 5).

According to the patient satisfaction questionnaire, 87% rated the result as "great improvement" and 13% as "good improvement" according to the Global Aesthetic Improvement Scale. All were satisfied with the treatment and would indicate the procedure for a family member or friend. All patients answered positively when asked if they would like to perform the procedure in the future. Also, all patients reported realizing the progressive improvement of the result until the time of return within one month after the procedure.

Regarding pain, most patients reported mild pain during the procedure (58%), some reported no pain (39%), and only six patients reported moderate pain. The only adverse event observed was mild hematoma in 35% of patients. Patients were followed for three months after treatment, and no other adverse event occurred.

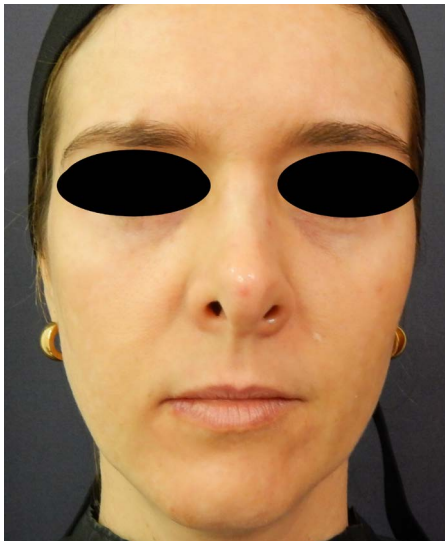

Figure 2: Patient before treatment

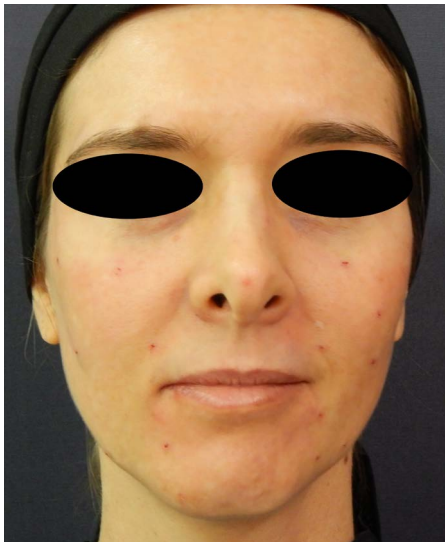

Figure 3: Patient immediately after treatment

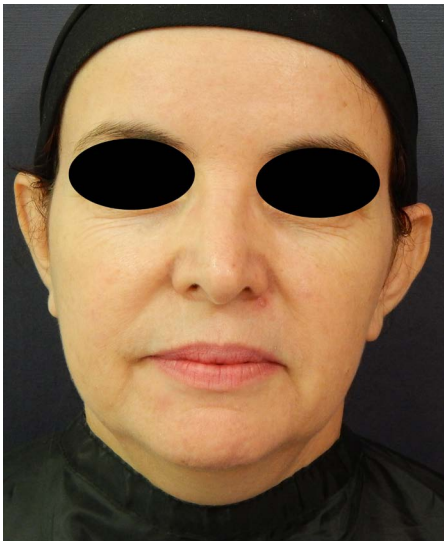

Figure 4: Patient before treatment

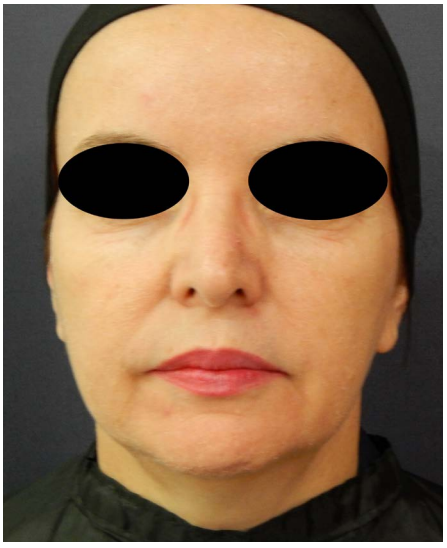

Figure 5: Patient one month after treatment

DISCUSSION

Hyaluronic acid (HA) is widely used for aesthetic treatments due to its efficacy, safety, low allergen potential, and versatility. In addition to replenishing volume, hyaluronic acid acts as a skin remodeling thanks to the observation of the filling effect persistence for a much longer time than the filler bioavailability. Studies have shown that HA can induce increased collagen and elastic fiber production, restoring extracellular matrix by direct stimulation and/or mechanical stretching of fibroblasts.[9]

The location of the filler on the skin is one of the determinants of the cosmetic result.10 Dermal localization is not required for excellent results, as studies show that the vast majority of dermal fillers are predominantly subcutaneous, regardless of the various application techniques.[10, 11, 12, 13] On the other hand, when fillers are placed on a deeper plane (deep subcutaneous or periosteum), more product is needed to achieve the desired effect.[14] In the present study, by injecting hyaluronic acid into the superficial subcutaneous, it was possible to obtain excellent results of volume restoration, sustaining and improvement of facial flaccidity with a small amount of the product (hyaluronic acid 2ml at a concentration of 23mg/ml) and high safety.

An interaction between hyaluronic acid and the subcutaneous tissue where the filler is placed is believed to occur. By increasing the concentration of hyaluronic acid in the adipose tissue, adipocyte expansion occurs in a non-rigid environment, causing a mechanical stress reaction in adipose tissue. Mechanical stress is one of the known factors that induce differentiation of fat-derived stem cells. By injecting hyaluronic acid, mesenchymal stem cells derived from adipose tissue find a microenvironment optimized for expansion and differentiation in connective tissue and endothelial cells, a regenerative pathway resulting in lower filler volume required for facial rejuvenation.[15, 16, 17]

It is also known that subcutaneous adipocytes control the activity of dermal fibroblasts by cytokine secretion. Human dermal fibroblasts express genes that encode receptors for adiponectin and leptin, cytokines that increase the production of hyaluronic acid in fibroblasts.[17, 18] Thus, subcutaneous hyaluronic acid also treats the adjacent dermis, improving sagging skin quality.

Through this new facial rejuvenation technique with hyaluronic acid, we seek not only to fill in areas of volume deficit but mainly to stimulate tissue regeneration through the interaction of hyaluronic acid with the superficial dermis. We thus seek to optimize results with the least amount of hyaluronic acid required for facial remodeling.

The present study demonstrated a high satisfaction rate of the treated patients, minimal adverse events, and positive assessment by the evaluating physicians. Further studies are needed to investigate the exact mechanisms of interaction between hyaluronic acid and subcutaneous acid using this facial rejuvenation technique. Also, the use of a cannula for the hyaluronic acid injection and the delta retro-injection technique brings us certainty regarding the possibility of vascular involvement.

CONCLUSION

The delta V lifting facial rejuvenation technique is effective in providing satisfactory aesthetic results with a minimal amount of hyaluronic acid. It is believed that the interaction between hyaluronic acid and adipose tissue is involved in optimizing the results.●

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Comparative assessment of microneedling with or without drug delivery in melasma treatment

Avaliação comparativa do tratamento de melasma com microagulhamento associado ou não ao drug delivery

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ABSTRACT

Introduction: Melasma is an acquired pathology secondary to hypermelanosis, recurrent, and often refractory to therapy, despite several treatment options. Microneedling is mainly indicated for refractory cases since it is an invasive method with the mechanism of action not yet fully understood for this indication.
Objective: To compare the response to melasma treatment between a group that received only microneedling and another treated with microneedling combined with drug delivery.
Methods: Twenty patients participated in the study: seven received only microneedling and 13 received microneedling followed by drug delivery of lightening serum in three sessions, with monthly intervals. The results between the groups were compared regarding improvement of the Melasma Area and Severity Index (MASI), texture and reduction of skin pore diameter; presence of erythema, crusting and peeling; improvement of melasma extension and tone.
Results: The group that received microneedling combined with drug delivery had the most favorable results in improving texture, decreasing skin pore diameter, and improving melasma extension and tone. MASI improvement occurred in both groups, in similar percentages.
Conclusions: According to the present study, both therapies are promising for melasma treatment.
Keywords: Comparative study; Therapeutic approachs; Treatment outcome; Evaluation of results of therapeutic interventions

RESUMO

Introdução: *O melasma é patologia adquirida, secundária à hipermelanose, com caráter recidivante e, muitas vezes, refratária à terapêutica, apesar das diversas opções para tratamento. O microagulhamento é principalmente indicado para os casos recalcitrantes, visto que é um método invasivo com mecanismo de ação ainda não totalmente esclarecido para essa indicação.*
Objetivo: *Comparar a resposta do tratamento do melasma entre um grupo que recebeu somente microagulhamento e outro no qual foi feita associação entre microagulhamento e drug delivery.*
Métodos: *Participaram do estudo 20 pacientes: sete receberam apenas microagulhamento e 13, microagulhamento seguido de drug delivery de sérum clareador em três sessões, com intervalos mensais. Os resultados entre os grupos foram comparados em relação a: melhora do Melasma Area and Severity Index (MASI), da textura e da diminuição do diâmetro dos poros da pele; presença de eritema, crostas e descamação; melhora da extensão e tonalidade do melasma.*
Resultados: *O grupo no qual foi feito microagulhamento com drug delivery apresentou resultado mais favorável na melhora da textura, diminuição do diâmetro dos poros da pele e melhora da extensão e tonalidade do melasma. A melhora do MASI ocorreu em ambos os grupos, em porcentagens semelhantes.*
Conclusões: *De acordo com o presente estudo, ambas as terapêuticas são promissoras para tratamento do melasma.*
Palavras-chave: *Estudo comparativo; Condutas terapêuticas; Resultado do tratamento; Avaliação de resultado de intervenções terapêuticas*

INTRODUCTION

Melasma is an acquired chronic condition secondary to hypermelanosis. It is characterized by brownish macules, with well-defined and irregular borders in photoexposed areas of the skin, such as the malar and frontal regions. It affects both sexes, with a predominance of women of childbearing age. Also, it affects all races, most often Asian and Hispanic, and is more prevalent in intermediate phototypes.[1] Studies show that its pathophysiology has involvement with sun exposure, genetic alteration, hormonal and vascular disorders, pregnancy, use of oral and topical cosmetic medications. However, it is known that further research is still needed to elucidate its etiopathogenesis fully.1 Ultraviolet radiation is the main factor in the genesis and maintenance of melasma. It causes lipids peroxidation of basal cell membrane, leading to free radicals release, with consequent stimulation of melanocytes.2 It can be treated only clinically and/or with a combination of cometic procedures.

Due to its relapsing and refractory characteristics, the association is often necessary to obtain a satisfactory response. Topical agents commonly used are hydroquinone-based skin-lightening products, such as the triple formula composed of the combination of this substance with tretinoin and corticosteroids. It is the established therapeutic option, usually indicated early in treatment, associated with intensive photoprotection. Other lightening substances are also effective, such as azelaic, retinoic, ascorbic, tranexamic, and kojic acids, corticosteroids, resorcinol, arbutin, and belides, which act directly and indirectly in the melanogenesis stages. Regarding the procedure options, we can mention chemical and physical peels and laser applications (QSwitched, Nd:YAG 1064, CO2, Erbium YAG 2940), intense pulsed light, and microneedling.[3]

Microneedling consists of multiple perforations of the epidermis and dermis with the aid of microneedle devices. Its use is established for the treatment of skin laxity, as it stimulates neocollagenesis by activating fibroblasts. However, recently, this technique has also been attributed to a whitening action. It is usually indicated in recalcitrant cases of melasma, although its mechanism of action in this condition is not yet fully understood. Nonetheless, studies show that its use alone or in combination with drug delivery of lightening substances has shown satisfactory results.4 As microneedling has lately been introduced in medical practice, there is a scarcity of scientific work on the subject, mainly in the scope of assessing its effectiveness as a lightening method. Thus, this study aimed to compare the response of melasma treatment between the group that received microneedling alone and the group that received the same procedure associated with drug delivery with serum composed mainly of lightening substances.

METHODS

A randomized clinical trial was conducted with patients from the Dermatology Outpatient Clinic of the Faculdade de Medicina do ABC, after approval by the Research Ethics Committee of this institution (CAAE: 93551518.7.0000.0082). For initial selection of participants, we considered the following inclusion criteria: characteristic clinical presentation of facial melasma; men and women aged over 18 years old; be without the following melasma-specific treatments for at least six months: topical use of hydroquinone-based skin-lightening products and their derivatives, performing procedures such as chemical peels, lasers (QSwitched, Nd:YAG 1064, CO2, Erbium YAG 2940) and intense pulsed light. The exclusion criteria adopted were: ongoing pregnancy; hypersensitivity to any component of the applied lightening formula; presence of facial scars or active facial dermatoses at the time the microneedling sessions were performed. The patients signed the informed consent form, which detailed the risks, and consequences of the procedures, such as pain, skin infection, blister formation, facial erythema and paradoxical worsening of the pigmentation. They also signed a document authorizing to make photographic records throughout the study.

Participants were randomly divided into groups A and B. Group A received microneedling on the entire face with a 7x7mm gold-plated microneedle device, of the Solon® (*LMG - Laser Medical Group* Ltda; Guaxupé, MG - Brazil) platform, with the following programming: radiofrequency: zero W, pulse duration: 80ms, needle depth: 1.5mm. The needle tips were discarded at each session. Three sessions were held, with an interval of 30 days between them. One hour before each procedure, a topical local anesthetic (lidocaine and tetracaine Cream 7%/7%) was applied to the entire face. Group B received microneedling identical to group A, both regarding the device used and its programming, and the number of sessions, interval between them, and time of topical anesthetic use of before the procedure. However, in group B participants, the whole-face drug delivery method was associated immediately after the microneedling, consisting of the topical application of 0.8 ml of industrialized lightening product *Md: complex melanoceuticals*®, which combines kojic acid, tranexamic acid, azeloglycine, arbutin, glycolic acid, ascorbic acid, citric acid, and glutathione in undisclosed concentrations (*Md: ceuticals*, imported by Importderm Ltda; Rio de Janeiro, RJ - Brazil). The patients were instructed to apply a high sun protector factor sunscreen (SPF 60) daily, starting 24 hours after the procedure, and to avoid sun exposure throughout the entire treatment period.

The results were obtained by a pooled analysis of the data from the self-assessment questionnaire (Chart 1) designed by the project organizers and applied to the patients after three months of the last session of the procedure. In addition to these evaluations, the Melasma Area and Severity Index (MASI) was calculated for each patient before the procedures and three months after the end of treatment. This score was conducted by three dermatologist examiners using the photographic analyzes of the patients. All photographic records were standardized, performed by a skilled technician with a professional camera, and under conventional light. The information collected from all questionnaires were compared between groups A and B. For statistical analysis, the chi-square test, Stata 11.0 program, with a significance level of 5% was used.

RESULTS

Of the 55 patients selected, 35 were lost to follow-up. Therefore, the total number of participants who completed the study was 20. Group A (microneedling alone) consisted of seven patients and group B (microneedling with drug-delivery) of 13 patients. Table 1 describes the comparative analyzes. Of the participants in group A, only one mentioned scabbing, none reported scaling or scarring, and there were fewer cases of rash after the procedure regarding the other group. Group B reported the highest number of improved melasma extension and tone, decreased pore diameter - open channels during microneedling - and improved skin texture, and no mention of scabbing. Only one patient reported facial scarring with the treatment. Regarding the comparative evaluation of MASI, there was a reduction in the score for both groups in a similar percentage, with a slight advantage for the one that received microneedling alone. The analyses showed no statistically significant differences between the two groups.

DISCUSSION

Melasma is a chronic condition, often resistant to treatment and stigmatizing. Despite the various therapeutic options, it is still a challenge to fully control the condition and maintain it in remission for long periods. Regarding the topical treatment modalities, there are several lightening substances, as shown in chart 2. The combined use of these substances is known to increase the chance of treatment success.[3,5]D Different cometic procedures can assist in therapy, such as peelings, dermabrasion, lasers, intense pulsed light, and mesotherapy. Microneedling has been reported as a promising technique for recalcitrant melasma, but its mechanism of action as a lightener is not yet fully elucidated.[6,7] Frabbocini *et al.*[5] conducted a study with 20 patients with melasma, in which all participants received microneedling followed by drug delivery with lightening serum (rucinol and Sophora-alpha) in one hemiface, while in the other hemiface only the serum was applied. Two sessions were performed, with monthly intervals between them. In the hemifaces that received microneedling followed by drug delivery, there was a mean reduction in MASI from 19.1 to 9.2, while in hemifaces receiving only the topical lightening serum, the mean reduction in MASI was from 20.4 to 13.3. Budamaklunda *et al.*[6] performed a comparative study with patients diagnosed with facial melasma, divided into two groups with 30 participants in each. One group received treatment with mesotherapy with tranexamic acid, and the other received microneedling with drug delivery of tranexamic acid. There were three monthly sessions. In the mesotherapy group, there was an improvement of 35.72% in the MASI compared to an improvement of 44.41% in the microneedling group associated with drug delivery. Lima[8] conducted a study of 22 patients with recalcitrant melasma: all of them underwent a microneedling session and were instructed to use the Kligman formula (retinoic acid 0.05% + hydroquinone 4% + fluocinolone acetonide 1%) every night, for one month, associated with sunscreen SPF 60 with color during the day. The author

Chart 1: Questionnaire applied to patients

1. Assessment of the procedure in the first 24h	**Present**	**Absent**
Redness		
2. Assessment until 4 weeks after the procedure	**Present**	**Absent**
Scabbing		
Peeling		
Scarring		
3. Late evaluation (after 3 months) of the treatment regarding melasma pigmentation	**Yes**	**No**
Extension Improvement		
Tone improvement		
4. Late evaluation (after 3 months) of the treatment regarding improved skin quality	**Yes**	**No**
Texture		
Pore Diameter Decrease		

Table 1: Results of comparative analyzes between groups A and B

Variables	Group A (n; %)	Group B (n; %)	p-value
Erythema	4; 57,14	11; 84,62	0,176
Scabbing	1; 14,29	0	0,162
Peeling	0	2; 15,38	0,274
Scarring	0	1; 7,69	0,452
Texture improvement	4; 54,14	9; 69,23	0,589
Pore diameter reduction	4; 57,14	9; 69,23	0,589
Extension improvement	4; 57,14	8; 61,54	0,746
Tone improvement	4; 57,14	9; 69,23	0,778
MASI reduction	6; 85,71	11; 84,62	0,948

Chart 2: Mechanism of action of topical lightening (adapted from Steiner D, et al. 2009)[3]

Mechanism of action	Substance
Tyrosinase inhibition	Hydroquinone / Belides / Azelaic Acid / Kojic Acid / Retinoic Acid / Resorcinol / Arbutin
Non-selective suppression of melanogenesis	Corticoids
Inhibition of reactive oxygen species	Azelaic Acid / Belides
Melanogenesis copper chelator	Ascorbic acid
Melanosome transfer blockade	Retinoic Acid / Belides
Anti-inflammatory and antiangiogenic	Tranexamic Acid / Belides
Melanin keratinocyte removal	*Chemical peels*

reported improvement of MASI in all patients and a 24-month follow-up without melasma worsening in half of the group. Saraiva *et al*.[9] selected 17 women to treat the melasma with robotic microneedling associated with drug delivery of tranexamic acid. There were four biweekly sessions. Regarding MASI, there was a mean reduction from 21.33% to 11.19%.

In the present study, the reduction in MASI occurred at a high and practically similar percentage between the two groups. There was a more significant benefit from the association with drug delivery concerning the absence of scabbing, improved texture, and decreased skin pore diameter, extension and tone of melasma. In contrast, there were more cases of peeling and erythema after the procedure, probably due to the presence of the acids of the lightening serum formula. Although these study results are promising, it has some limitations, such as the withdrawal of part of the patients for unclear reasons and the fact that it was performed in the summer in a tropical country (higher rate of ultraviolet radiation). One should also question the concentration of compounds present in the drug delivery product, which is not disclosed by the manufacturer. However, the findings of this study are similar to those of the literature cited, showing that microneedling, associated or not with the drug delivery, promotes melasma lightening. There is a need for a better understanding of the pathophysiology of this disease and prospective randomized studies comparing the efficacy of conventional therapies regarding the currently promising ones.

CONCLUSION

There was no statistical difference in MASI improvement between the group receiving melasma treatment with microneedling alone compared to the group that performed the same procedure associated with drug delivery. Therefore, according to the present study, both therapies are promising for the treatment of this condition.●

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Botulinum toxin for Raynaud's phenomenon: an useffull but seldom reminded therapy for severe cases

Toxina botulínica e Fenômeno de Raynaud: terapia útil mas pouco lembrada para casos severos

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ABSTRACT

Introduction: Raynaud's phenomenon (RP) is an exaggerated physiological response of the ex- tremity vessels, mainly to cold and stress. Patients refractory to clinical treatment or intolerant to its adverse events may be treated with local injection of botulinum toxin (BTX).

Objective: To describe the experience of botulinum toxin use in severe cases of RP.

Methods: Observational, descriptive, retrospective, and unicenter study of case series of severe RP treated with BTX-A, from 2011 to 2015. Parameters of pain, numbness, color, and stiffness were scored by visual analogical scale (VAS) and tabulated and compared before and after the treatment.

Results: Total pain improvement in 71.4% of cases and partial improvement in 28.6%. Numbness disappeared in 57.1% of cases and improvement in 42.9%. There was a total regression of stiffness in 57.1% of cases and partial improvement in 28.6%. The color was completely reversed in 57.1% of the patients. There was ulceration healing in the only case in with they were present. Ischemic attacks were reduced in 85,7% of cases. No complications occurred.

Conclusions: This study suggests that the use of BTX-A in patients with severe RP is a promising therapeutic option.

Keywords: Raynaud disease; Botulinum toxins; Botulinum toxins, type A

RESUMO

Introdução: *O fenômeno de Raynaud (FR) é uma resposta fisiológica exagerada dos vasos das extremidades, principalmente ao frio e ao estresse. Pacientes refratários ao tratamento clínico ou intolerantes aos seus efeitos colaterais podem ser tratados com injeção local de toxina botulínica.*

Objetivo: *Descrever a experiência do uso da toxina botulínica em casos severos de FR.*

Métodos: *Estudo observacional, descritivo, retrospectivo e unicentrico de série de casos de FR graves tratados com toxina botulínica-A, no período de 2011 a 2015. Parâmetros de dor, dormência, cor e rigidez foram pontuados por escala visual analogica e comparados antes e depois do tratamento.*

Resultados: *Melhora total da dor em 71,4% dos casos e parcial em 28,6%. A dormência desapareceu em 57,1% dos casos e melhorou em 42,9%. Houve regressão total da rigidez em 57,1% dos casos e melhora parcial em 28,6%. A cor foi completamente re- vertida em 57,1% dos pacientes. Houve cicatrização das ulcerações no único caso em que estavam presentes. Houve redução dos ataques isquêmicos em 85,7% dos casos. Não ocorreram complicações.*

Conclusões: *Este estudo sugere que o uso da toxina botulínica A em pacientes com fenômeno de Raynaud grave é opção terapêutica promissora.*

Palavras-Chave: *Doença de Raynaud; Toxinas botulínicas; Toxinas botulínicas tipo A*

Original Article

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INTRODUCTION

Raynaud's phenomenon (RP) is an exaggerated physiological response of the extremity vessels, especially to cold and emotional stress.[1] Traditionally, three phases characterizes it: pallor (vasoconstriction), cyanosis (due to blood deoxygenation), and redness (reactive hyperemia).[2]

Most cases of RP are classified as primary or idiopathic and are not associated with other conditions. Less often, RP is classified as secondary and is associated with conditions such as connective tissue diseases, especially systemic scleroderma (SSc).[3,4]

The pathogenesis of primary RP is related to the exacerbated stimulation of alpha-adrenergic receptors present in vascular smooth muscle, causing its vasoconstriction. Primary RP can be controlled with preventive measures, keeping the patient away from triggering factors such as cold exposure, stress, caffeine, vasoconstrictor medications, and smoking.[1,4] On the other hand, in secondary RP, the presence of structural vasculopathies characteristic of associated diseases potentiates the reduction of vessel caliber and makes such patients more prone to develop pain, numbness, and ischemic complications, such as functional limitation, digital ulcers, and partial digit amputations, promoting strong impact on quality of life.[4]

In the presence of RP signs and symptoms, despite the adoption of preventive measures, pharmacological treatment is required to regulate vasodilation/ vasoconstriction. Several drug classes are available, such as antiplatelet agents, cilostazol, sarpogrelate, intravenous and oral prostanoids, phosphodiesterase type 5 inhibitors (PDE5), endothelin receptor antagonists (ERA), and bosentan. However, calcium channel blockers remain the therapy of choice in treating this condition.[5] When patients are refractory to clinical treatment or cannot tolerate the adverse events, there are few alternative therapies, including surgical treatment (periarterial sympathectomy), and, more recently, the use of local botulinum toxin injection (BTX).[6]

Botulinum toxin is a polypeptide composed of a light chain (50kDa) and a heavy chain (100kDa) joined by disulfide bond. It is produced by the gram-negative bacterium *Clostridium botulinum* and was discovered in 1897 by Emile van Ermengen, in Belgium. In 1949, Arnold Burgen described the first elucidation of its mechanism of action as an inhibitor of acetylcholine release in neuromuscular junctions.[7]

Of the seven existing types of BTX (A-G), two (BTX-A and BTX-B) have been successfully used in both dermatological and cometic therapy, and in recent years they have been cited as a therapeutic option for symptomatic RP cases refractory to clinical treatment. This is because they act on the various pathogenesis of the disease, inhibiting adrenergic or cholinergic sympathetic vasoconstriction and acting on various pain-related neurotransmitters, such as norepinephrine, substance P, glutamate, and calcitonin gene-related peptide (CGRP).[2,8-11]

Such use was first reported in 2004 by Sycha *et al.* in two patients with severe and intractable Raynaud's phenomenon. These patients showed improvement in stiffness and numbness as well as increased digital perfusion.[12]

In 2007, Vanbeek *et al.* described a series of 11 patients with Raynaud's phenomenon secondary to connective tissue disease. In this study, the injections were performed only on the affected fingers, with early recurrence on the uninjected fingers, which justified a change in the treatment protocol for all fingers. All patients received a total dose of 100 U/hand and showed pain relief within two days (pain score decrease from 9-10 to 0-2). Nine out of 11 patients had ulcer healing and two underwent successful grafts.[3]

Then, Fregene *et al.* sought to standardize the injection technique in a series of 26 patients. However, statistical evaluation did not define a specific injection site with superior results.[1]

Most botulinum toxin publications in RP show the experiences of countries in North America (USA and Canada), Europe (France, Austria and England), Asia (Japan and China), and South America (represented by Colombia only). However, so far, national research on the subject has not been found.

OBJECTIVE

To describe the experience of using botulinum toxin type A in patients with severe Raynaud's phenomenon.

METHODS

Observational, descriptive, retrospective, single-center, case series study conducted following the ethical principles of the Declaration of Helsinki, the Americas document, following the guidelines of Good Clinical Practice (GCP) and local laws of Brazil where it was developed. It was submitted and approved by the institution's Research Ethics Committee (REC) under number 3.510.407.

Patients older than 18 years of age, treated at the Collagenosis Outpatient Clinic of the Dermatological Clinic of the Hospital do Servidor Público Municipal de São Paulo (HSPM), from June 2011 to July 2015, were selected. The inclusion criteria were previous diagnosis of clinically evident RP refractory to clinical treatment; application of botulinum toxin to treat RP in the period mentioned; follow-up for at least four months after the application, and signature of the Informed Consent Form (ICF).

Patient data such as gender, age, associated disease and respective treatments, type of toxin, dose and mode of application, as well as the treated hand were evaluated. Information on pain, numbness, color, and stiffness were scored and evaluated using the visual analog scale (VAS) applied before and after the treatment. Episodes numbers, ulceration regression, follow-up time, and BTX adverse events were also recorded. All information was collected from the HSPM medical records and transcribed into a data collection table designed by the researchers.

RESULTS

We found seven women (100%) with a mean age of 45 years, ranging from 31 to 56 years. All had been treated with BTX-A injections on the lateral and medial surfaces of the finger bases, as shown in Figure 1.

The doses applied were 10 UI/finger in one case (14.3%) and 5 UI/finger in six cases (85.7%). All seven patients had RP

secondary to collagenosis (100%), one had dermatomyositis (14.3%), one had systemic lupus erythematosus (14.3%), two had systemic scleroderma (28.55%), two had mixed connective tissue disease (28.55%), and one had Sjögren's syndrome (14.3%). Table 1 presents the demographic data.

The mean follow-up was 11.4 months, ranging from 4 to 18 months. Pain improved by 100% in five of the seven cases (71.4%). In the remaining two cases (28.6%), this improvement was over 70%. Numbness disappeared after treatment in four of seven cases (57.1%) and improved 70% or more in three cases (42.9%). Regarding finger stiffness, there was total regression in four of seven patients (57.1%), partial improvement greater than 50% in two cases (28.6%), and no change in one patient (14.3%). The color, which was related to perfusion, was reversed entirely from purple to normal in four of seven cases (57.1%), and in three cases (42.9%), there was no change.

In the only case where ulcerations were present, complete healing occurred within 90 days post-toxin. Regarding the frequency of ischemic attacks, in six women (85.7%) the reduction ranged from 50% to 100%, and in only one case (14.3%) it did not change. No early or late postoperative complications were described in any of the seven patients.

DISCUSSION

Since the first description in 2004 by Sycha *et al.*, several authors have been reporting promising results in the use of botulinum toxin for refractory RP cases.[1,3,5,8,11]

In our study, we used BTX-A to treat RP in 100% of patients, following the literature trend due to its already validated indications. Only one study used serotype B.[2,13] According to Kranz *et al.*, in 2010 there would be no difference in efficacy between these serotypes, and only their pharmacokinetics would be different. BTX-A would have the advantage of presenting a longer duration of action (>1 year), reducing the frequency of injections.[14]

Several studies describe botulinum toxin use, but most use heterogeneous populations, including patients with primary RP (which by definition is not associated with an underlying connective tissue disease) or with RP secondary to other connective tissue diseases.[1,3,4,7,8,12,15-17] Only five studies specifically focus on RP secondary to scleroderma,[2,13,18-20] limiting the interpretation of the evidence for this patient population.[19]

In our study, we used a heterogeneous group of patients with RP secondary to five different types of collagenosis. Only one of these patients, who had more severe sclerosis, responded less well to treatment, as in a single case series suggesting that individuals with sclerosis may be less responsive to BTX-A injections compared to other patients with RP.[8] This may be because in scleroderma there is an association of vasospasm with the sclerotic mechanical component of the arterial wall that could theoretically make this group more prone to severe symptoms, frequent ischemia, and complications, as well as reducing its response to toxin.[4,21,22]

All other patients in our study, including the less severe case of scleroderma, presented a good response to BTX, suggesting that this treatment is also effective in RP secondary to scleroderma [2,14,18-22] and the other collagenoses.[1,3,4,12,17,18,23] Regarding toxin application, there is no consensus on dilutions, injection sites, and doses, which vary according to the authors.[1-3,5] The doses used in our study follow the literature trend of 50U to 100U BTX-A per hand described by Van Beek and Neumeister.[3,8]

Fregene *et al.* tried to standardize injection sites by separating patients into three application categories based on their symptoms: interdigital neurovascular bundles; distal superficial palmar arch; and proximal phalanges, adjacent to the radial and ulnar arteries in the wrist. However, the statistical evaluation was unable to find a better injection pattern.[1,5]

Thus, as distal digital injections can be equally effective, there is currently a tendency to avoid toxin application in the palmar region, as it is associated with muscle weakness, even without statistical significance. This adverse event, found in the literature, is related to neuromodulator diffusion to the intrinsic hand musculature.[1,2,5] In our study, injections were limited to the lateral and medial sides of the digits. Thus, we didn't observe muscle weakness in our cases.

A previous study reporting cases of early recurrence in non-treated fingers when injections were restricted to the affected fingers only justified the choice of applying the toxin to the base of all fingers (affected or not) in both hands.[3,5]

Regarding the clinical presentation of RP, BTX-A injections showed promising results in improving pain, numbness, stiffness, number of seizures, ulcerations, and cold sensitivity.[1,3,5,8,12]

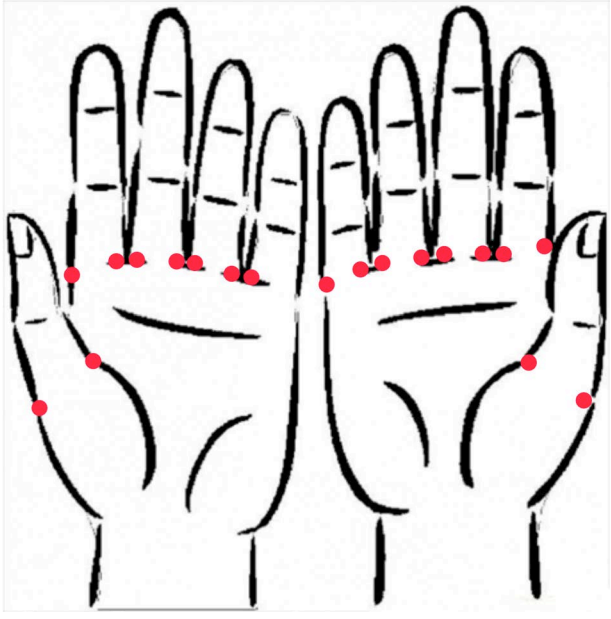

Figure 1: BTX-A Application Points

Table 1: Case report table

Case	Sex / Age (years)	Associated systemic disease	Botulinum toxin used	BTX dose applied	BTX Application mode	Hand treated	Pain (0-10 points)		Numbness(0-10 points)		N crises / week		Coloring(normal)/ pale/ red/ purple)		Stiffness(0-10 points)		Ulcers(Yes/ No)		Follow-up time	Complications	Medications in use
							A	D	A	D	A	D	A	D	A	D	A	D			
1ABM	F 51	DM	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	8	0	6	0	Daily	0	Purple	nl	4	0	N	N	18 months	Absent	MTX DC AAS-Nifedipine Cilostazol
2SMG	F 56	ES	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	7	0	10	0	Daily	2	Purple	nl	4	4	N	N	13 months	Absent	Colchicine Diltiazen Simvastatin
3ABS	F 50	SJ	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	10	0	8	2	3x	1x	Purple	nl	7	0	N	N	13 months	Absent	Prednisone MTX AINH
4LSS	F 32	DMTC	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	5	9	10	3	Daily	3x	Purple	Purple	2	0	N	N	11 months	Absent	DC MTXPentoxifylline
5LBLC	F 39	DMTC	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	9	2	10	2	Daily	3x	Purple	Purple	10	3	N	N	10 months	Absent	Prednisone MTXPentoxifylline
6LGA	F 31	LES	BTX-A	5U/Finger 50u/Hand	Interdigital	Both	7	0	8	0	Daily	1x	Purple	nl	9	0	N	N	11 months	Absent	HCQ AINH
7CPC	F 54	ES	BTX-A	10U/Finger 100u/ Hand	Interdigital	Both	7	2	4	0	3x	3x	Purple	Purple	9	4	S	N	4 months	Absent	Bosentan Omeprazol Pentoxifilina Sidenafil

Scale: 0-no symptoms; 10-o m

Abbreviations: B - Before botulinum toxin; A - After botulinum toxin; Y - presence of ulcers; N - absence of ulcers; BTX- Botulinum toxin; DM- Dermatomyositis; MCTD - Mixed connective tissue disease; SC- Systemic scleroderma; F- Female; SLE- Systemic lupus erythematosus; MTX-Methotrexate; HCQ: Hydroxychloroquine; CD-Chloroquine diphosphate; ASA-Acetylsalicylic acid; nl: Normal

Decreased muscle contraction can explain the reduction of stiffness symptoms. When the toxin undergoes endocytosis in the presynaptic nerve ending, it binds to synaptosome nerve-associated protein 25 (SNAP-25 of the SNARE complex), inhibiting it and preventing the mobilization and exocytosis of acetylcholine vesicles in the nerve terminal membrane. Without cholinergic stimulation, muscle cells do not contract, contributing to the treatment of stiffness observed in patients.[2,23,11] Our results showed improvement of this symptom, with total regression in 57.1% of patients, and partial regression in 28.6% of them, is consistent with the literature.[2,11,12,17,23]

Cholinergic neuromuscular action can also explain pain and numbness reduction, since vascular smooth muscle cells are also inhibited, promoting vasodilation and reperfusion. However, some authors question whether there would be other mechanisms involved. This is because the effect of the toxin on pain and numbness modulation is immediate and could not be explained only by the anticholinergic action, which would require a longer time to cause muscle paralysis and, consequently, flow restoration. BTX-A also acts by blocking several neurotransmitters related to C-fiber depolarization that propagate chronic pain, such as norepinephrine, substance P, glutamate, and calcitonin gene-related peptide.[2,11,23]

Another possible mechanism of action is the inhibition of alpha-2 adrenergic receptor expression both in the peripheral nerve walls chronically irritated by ischemia or trauma and in the vessel walls, suppressing cold-induced noradrenergic vasoconstriction. Also, it has been reported that, in vitro, the toxin would reduce the intracellular accumulation of reactive oxygen species (ROS) produced in response to cooling, which is responsible for enhancing surface expression of adrenergic receptors. Finally, BTX-A could further reduce pain by inhibiting ectopic sodium channels expressed chronically in nerves irritated or injured by chronic ischemia in patients with RP.[20]

Two case series reported pain and numbness improvement with the use of BTX-A was reported, which described a decrease in both symptoms in all patients evaluated.[12,18] Other 16 studies have shown pain reduction in 75% to 100% of cases, but with no evaluation of numbness.[1-3,6-8,11,13,16,18-21,23-25] In our study, total pain regression occurred in 71.4% of cases and partial improvement in the remaining 28.6%. Numbness disappeared in 57.1% of patients and partially decreased in 42.9%.

The normalization of the finger color using BTX-A is also described by some authors.[1,11,20,24] The vasodilation provided by the neuromodulator leads to the blood flow restoration and fingers reperfusion. Thus, the fingers resume their pink color. In our study, 57.1% of the patients had a complete change from purple to pink, as shown in Figure 2.

A similar mechanism of action justifies the beneficial effects of BTX-A on the healing of digital ulcers secondary to RP.5 By acting to prevent disregulation between vasoconstriction and vasodilation in RP, the toxin disrupts the vicious cycle of ischemia-reperfusion (I/R). Blood reperfusion would lead to infiltration of inflammatory cells and production of pro-inflammatory cytokines in previously ischemic tissue, resulting in damage to vascular endothelium, edema, capillary narrowing, apoptosis, and tissue necrosis.[20,26,27]

An experimental study showed that BTX-A injection prevented the formation of skin ulcers after I/R induction in a murine model. The toxin reduced the area of hypoxic tissue and protected it from oxidative stress and cell apoptosis.[28] Another 10 publications have reported human cases of healing of digital ulcer secondary to RP with BTX-A.[2,3,8,13,16-21,23,25] In the only case of our study where ulcers were present, there was complete lesion closure within 90 days post-toxin (Figure 3), following the findings in the literature.

Regarding the frequency of ischemic attacks, our results showed a reduction in the number of episodes and were similar to those found in three other studies.[3,18,20] Although the mechanism of action is not well established, it is believed that the toxin would act by reducing the expression of alpha-2-adrenergic receptors on vessel surfaces. Thus, patients would become less responsive to sympathetic discharges triggered by cold and stress,7 stimuli considered the main provokers of vasoconstriction and ischemic attacks in RP.[1]

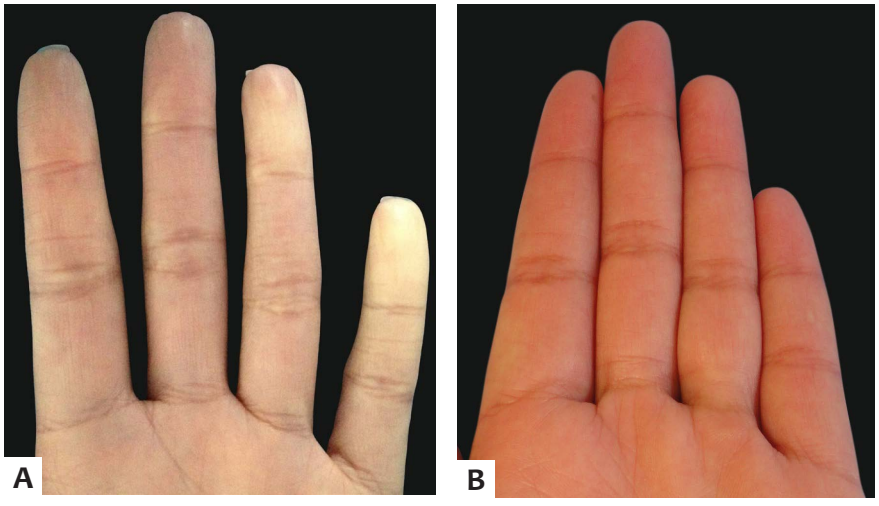

Figure 2:
A: RP ischemic phase in the 4th and 5th fingers of the left hand. **B:** Improved finger color

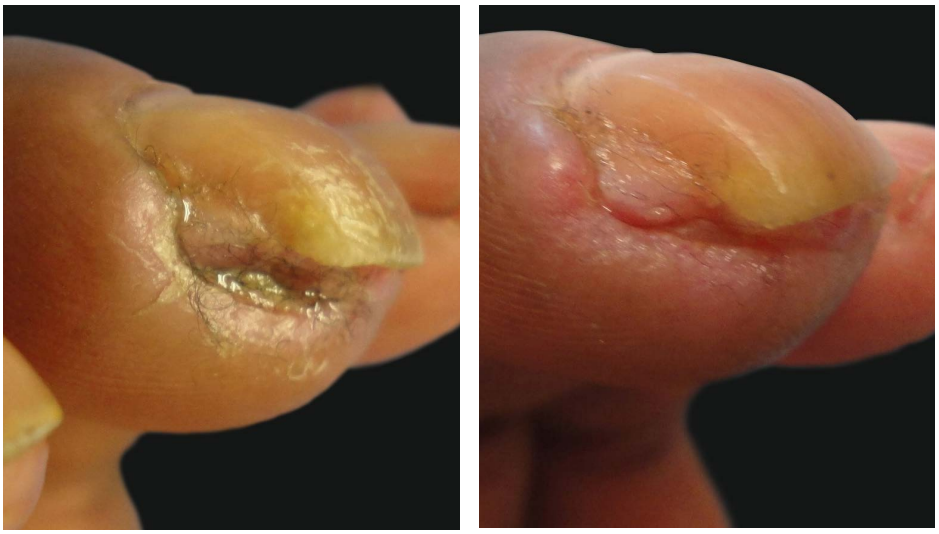

Figure 3:
Ulceration healing 3 months after BTX-A injection

CONCLUSION

Further research is still needed to build consensus on BTX-A doses, dilutions, and injection sites. Despite the small sample size, the beneficial and fast toxin results seen in our case series suggest this medication may be a promising therapeutic option in refractory RP cases.

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Original Article

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Quality of life assessment of patients with hidradenitis supurativa using adalimumab: a pilot study

Avaliação da qualidade de vida de pacientes com hidradenite supurativa em uso de adalimumabe: estudo-piloto

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ABSTRACT

Introduction: Hidradenitis supurativa (HS) is a chronic skin disease whose mechanism is not yet fully understood. It has a direct impact on the quality of life of affected patients, but there is no well-established therapy for its treatment.

Objective: To assess the quality of life of patients diagnosed with HS on adalimumab using the Dermatology Life Quality Index (DLQI) questionnaire.

Methods: Information was collected from patients with HS on adalimumab and standard DLQI questionnaires were applied before the beginning of treatment and at least 12 weeks after.

Results: Of the three patients included, two presented decreased DLQI. Of these two, one showed significant improvement after treatment with adalimumab. The third patient showed worsening of this index.

Conclusions: The impact of hidradenitis supurativa on the quality of life of affected patients is significant and is related to factors other than adequate therapy. Life habits such as smoking and alcoholism, as well as the presence of other comorbidities, probably impact these indices. Affected patients should be assessed globally to determine the actual impact on the quality of life related to the disease in question. Thus, we suggest further studies with a larger number of patients.

Keywords: Hidradenitis suppurativa; Quality of life; Indicators of quality of life

RESUMO

Introdução: *A hidradenite supurativa (HS) é uma doença de pele crônica, cujo mecanismo ainda não está totalmente esclarecido. Exerce impacto direto na qualidade de vida dos pacientes acometidos, mas não há uma terapia bem estabelecida para seu tratamento.*

Objetivo: *Avaliar a qualidade de vida dos pacientes com diagnóstico de HS em uso de adalimumabe por meio do questionário Dermatology Life Quality Index (DLQI).*

Métodos: *Foram coletadas informações de pacientes portadores de HS em uso de adalimumabe, e utilizados questionários- padrão do DLQI, aplicados antes do início do tratamento e no mínimo 12 semanas após.*

Resultados: *Dos três pacientes inclusos, dois apresentaram diminuição do DLQI. Dos dois, um apresentou melhora importante após o tratamento com o adalimumabe. O terceiro paciente demonstrou piora desse índice.*

Conclusões: *O impacto da hidradenite supurativa na qualidade de vida dos pacientes acometidos é importante e está relacionado a outros fatores além da terapêutica adequada. Hábitos de vida, como tabagismo e etilismo, além da presença de outras comorbidades, provavelmente exercem impacto nesses índices. Os pacientes acometidos devem ser avaliados de forma global, a fim de se determinar o real impacto na qualidade de vida relacionado à doença em questão. Para isso, sugerimos novos estudos com um número maior de pacientes.*

Palavras-Chave: *Hidradenite supurativa; Qualidade de vida; Indicadores de qualidade de vida*

INTRODUCTION

Hidradenitis suppurativa (HS), or "acne inversa", is a chronic, inflammatory, recurrent and debilitating skin disease that affects the hair follicle. Most of the time, the disease presents after puberty, with painful, deep, and inflamed lesions in areas with the representativeness of apocrine glands, mainly armpits, inguinal and anogenital region.[1,2]

The precise inflammatory mechanism that leads to HS lesions is not yet fully known. The central pathogenic event is considered to be the occlusion of the upper parts of the hair follicle, leading to a perifollicular lymphohistiocytic inflammation. Stimulation of inflammatory cells by microbial products that activate TLR2 may be an essential triggering factor in the chronic inflammatory process. The pro-inflammatory role of cytokines IL-12, IL-23, and IL-17 are also reported.[1,2]

Primary criteria for the diagnosis of HS include recurrent, painful, or suppurative lesions more than twice in six months. They are characterized by nodules, sinus tracts, underarm abscesses, or scars in the armpits, genitofemoral area, perineum, buttocks, and inframammary region.. Secondary criteria include positive family history and healthy skin microbiota in affected areas.[1,2]

There is no well-established and universally accepted therapy for the treatment of HS. Current therapeutic options include antibiotics, retinoids, immunosuppressive treatment, surgery, and, more recently, biological agents such as adalimumab and infliximab.[2]

Determining treatment response can be challenging due to the limitations of currently available methods for assessing disease activity.[3] Several criteria have already been proposed for classifying and assessing the severity of HS. Hurley's classification separates patients into three groups with different severity levels, but only makes a qualitative classification of lesions, and it is not suitable for evaluating the efficacy of clinical trial interventions. The Sartorius score, in turn, assesses the severity of HS in a more detailed and dynamic way but may fail in severe cases where initially separated lesions become confluent. Also, it includes lesions that may not be sensitive to clinical treatment, and it is not ideal for analyzing therapeutic efficacy. The Physician Global Assessment (PGA) divides the disease into six different stages and has been the most frequently used criterion for assessing improvement in clinical trials. The Hidradenitis Suppurativa Clinical Response (HiSCR) was developed to address the problems mentioned above, considering improvements in disease activity, simplifying the scoring process, and increasing the sensitivity to identify specific HS lesions.[3]

Furthermore, a parameter widely used in various skin conditions can evaluate the influence of HS on the quality of life of affected patients thoroughly: the Dermatology Life Quality Index (DLQI). This questionnaire aims to measure how much skin involvement influenced daily activities and interpersonal relationships in the last week. Combined with the questionnaires mentioned above, it can be a useful tool for patient follow-up in clinical practice as well as but also in assessing patients in clinical trials.[4,5]

METHODS

Information was collected from patients with HS on adalimumab followed at the Dermatology Outpatient Clinic of a referral hospital, aged 18 to 60 years, of both sexes, classified as Hurley II or III, or with lesions refractory to three months of antibiotic therapy or isotretinoin target dose therapy. Patients using isotretinoin had not been released or had contraindications to the use of acitretin. Standard DLQI questionnaires were applied before the start of adalimumab treatment and at least 12 weeks after the start of the treatment. Weight, body mass index (BMI), presence of comorbidities, and lifestyle habits were also assessed (smoking, alcoholism, physical inactivity).

Individuals younger than 18 years old and older than 60 years, pregnant women or women planning to get pregnant in the next four months, and patients using adalimumab in different regimens than that described in the package insert for HS treatment (160mg on D1; or two 40mg injections per day for two consecutive days - D1 and D2, followed by 80mg on D15 and D29, followed by a 40mg dose per week), were excluded from this pilot study. We also excluded patients who did not agree to participate in the study or did not sign the informed consent form (ICF).

RESULTS

Of the 14 patients diagnosed with HS under regular follow-up at the Dermatology Outpatient Clinic of a referral hospital, four were selected for adalimumab use. One of these patients was excluded from the study because he did not take the induction dose as proposed.

After exclusion, three patients using adalimumab for HS treatment were evaluated. Two patients were staged as Hurley 3 and one as Hurley 2. One patient had inguinal and perineal lesions, one had inguinal and axillary lesions, and the last one had lesions in the inguinal, axillary, and retroauricular regions. Two patients were female and one male, all aged 37 to 38 years. One patient had adequate weight for height, one was overweight, and another presented grade I obesity. Two patients were smokers and none had a history of alcoholism. Only one patient had other comorbidities (osteoarthritis). All had DLQI greater than 10 before the beginning of the treatment: one patient presented a decrease of 16 points after 20 weeks of treatment, one, a reduction of one point after 32 weeks of treatment, and another a decrease of seven points after 48 weeks of treatment (Table 1).

DISCUSSION

In the assessed patients, HS had a significant impact on all DLQI subdomains. Still, it is noteworthy the value attributed to symptoms and feelings and the intervention in daily activities.[5,6] This impact seems to be more critical than that present in patients with other skin diseases commonly related to poor quality of life, such as chronic urticaria, psoriasis, atopic dermatitis, and neurofibromatosis.6 This is because all patients presented DLQI greater than 10, which means a great effect of the skin condition on quality of life. Still compared to other skin diseases in which the use of immunobiologicals may lead to complete remission, thus raising the level of quality of life to zero DLQI, patients

Table 1: Representation of demographic data and Dermatology Life Quality Index (DLQI) indexes before and after adalimumab use

	DLQI before	DLQI after	Types of lesion	Site	Hurley	Age	Sex	BMI	Comorbidities	Alcoholism	Smoking
Patient 1	28	12	Nodules, fistulas and scars	Armpits and groin	3	38	F	31.83	None	No	No
Patient 2	24	23	Fistulas, beams and scars	Vulva and perineum	3	37	F	29.29	None	No	Yes
Patient 3	18	25	Nodules, fistulas and scars	Groin	2	38	M	24.22	Osteoarthritis	No	Yes

with HS on adalimumab didn't present this level of intervention, maintaining rates higher than 10 throughout the treatment, even with some improvement in quality of life.

Although not objectively assessed, we observed the feeling of frustration in those patients who did not show a significant improvement in the quality of life. The same was observed in those patients whose response to treatment did not match the expectation initially created.

Another matter observed was the difficulty of understanding the applied questionnaire. In the case that the patient did not understand very well what was questioned, using the DLQI as a response parameter may not have been adequate, thus to consider that this index worsened in one of the evaluated subjects can be a bias.

As expected, the impact of HS on quality of life correlated with the severity of skin involvement,[7,8] worsening the DLQI of the patient with lesions in more exposed regions, and with a history of smoking, being the only non-smoking patient who presented the most significant response after the adalimumab use.

CONCLUSIONS

The skin plays a crucial role in interpersonal relationships, self-esteem, and perception of self-image and public image, as it is the most significant and most visible part of the human body.[5,9] Therefore, due to the character of the disease, many patients with HS have to deal with depression and embarrassment. Also, pain (commonly reported), fever, and fatigue may prevent individuals from performing everyday tasks.[1]

Collecting baseline data regarding the personal impact of hydradenitis suppurativa is a necessary first step in determining the extent to which adopted interventions improve the quality of life of patients with the disease.[4] Patient expectations regarding the treatment should be managed.

The choice of using adalimumab to treat severe or refractory lesions should consider the risks and cautions involved in using an immunobiological. Also, this line is often viewed by patients as the last opportunity for treatment, which can increase frustration and worsen the quality of life in cases that do not respond as expected or considerably improve the quality of life of those who present a good response.

Thus, the information obtained in this research can undoubtedly contribute to broadening the knowledge about the subject, allowing a better structuring of the approach, considering better care for patients with this disease, with an impact mainly on social inclusion and improved quality of life of these patients. We expect further studies, including more patients, to be conducted in the future to determine the real influence of adalimumab use on the quality of life of patients with HS.

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"Ruin appearance" in nail free margin dermoscopy - a diagnostic clue for onychomycosis

"Aspecto em ruína" na dermatoscopia da borda livre ungueal - uma pista diagnóstica para onicomicose

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ABSTRACT

Onychomycosis is the nail disease responsible for 50% of onychopathies. The most common clinical form is distal and lateral onychomycosis. The dermoscopic finding of subungual hyperkeratosis in "ruin appearance" in the nail free margin is a relevant diagnostic clue and, when present, suggests the diagnosis of onychomycosis.

Keywords: Dermoscopy; Nail diseases; Onychomycosis

RESUMO

A onicomicose é a doença ungueal responsável por 50% das onicopatias. A forma clínica mais comum é a onicomicose distal e lateral. O achado dermatoscópico de hiperqueratose subungueal em "ruína" na borda livre ungueal é pista diagnóstica relevante e, quando presente, sugere o diagnóstico de onicomicose.

Palavras-Chave: *Dermoscopia; Doenças da unha; Onicomicose*

Nail dermoscopy or onychoscopy is a fundamental tool for better visualization of clinical findings and may be a key to the diagnosis of some nail pathologies. Nail free margin dermoscopy is complementary to plate examination, providing information on nail thickness, presence and pattern of subungual hyperkeratosis, and characteristic findings of nail pathologies.

Onychomycosis is the prevalent nail disease, and it is responsible for approximately 50% of onychopathies.[1] The similarity between some onychopathies tends to make it challenging to obtain a definitive clinical diagnosis. Direct mycological examinations and fungal culture or nail plate biopsy (periodic Schiff staining [PAS] staining) should confirm the diagnosis. However, these tests may show false-negative results in more than 35% of cases.[1] The most common clinical form is distal and lateral onychomycosis, representing over 85% of cases.[2] In this clinical form, the fungal invasion occurs from the infected skin, passing through the hyponychium or lateral fold, reaching the nail bed and, finally, the ventral surface of the nail plate. As a consequence, subungual hyperkeratosis and onycholysis occur. When examining the free margins with the dermoscope, keratotic debris creates a unique appearance under the free edge of the nail that De Crignis *et al*. called a "ruin appearance" (Figure

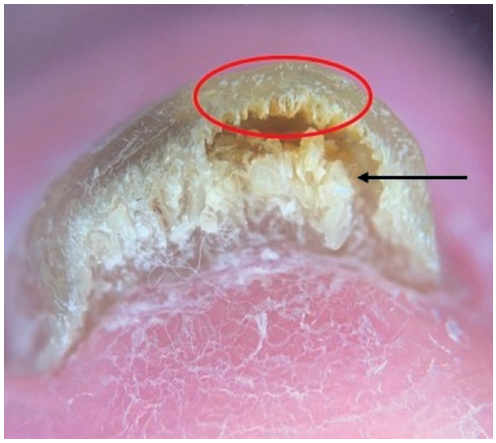

Figure 1: Nail free margin dermoscopy of onychomycosis. Arrow: "ruin appearance" of subungual keratosis. Circle: irregular indented shape of the ventral region of the nail plate (x10)

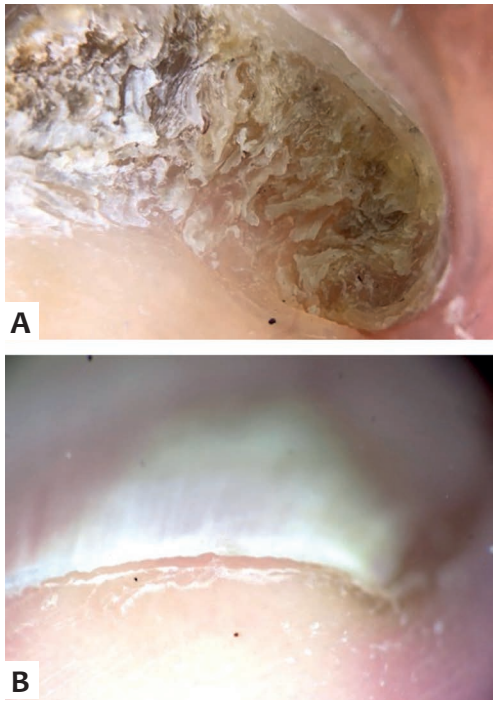

Figure 2: Comparison between nail free margin dermoscopy of onychomycosis **(A)** and traumatic onycholysis **(B)** (x10)

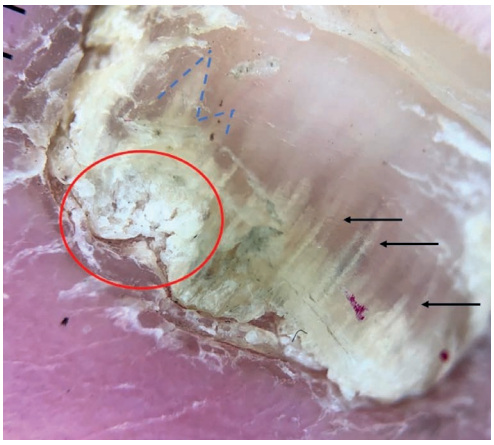

Figure 3: Dermoscopy of the onychomycosis plate: onycholysis proximal edge "jagged" and "indented" (dotted); longitudinal striations (arrow) and visualization of the "ruin appearance" of subungual keratosis (circle) (x10)

1).[3] The formation of this type of subungual hyperkeratosis is due to the exacerbation of the irregular indented shape of the ventral region of the nail plate (Figure 1) associated with the accumulation of debris resulting from fungal invasion. This finding can also be observed in total dystrophic onychomycosis. The absence of the "ruin appearance" in dermoscopy, common in traumatic onycholysis (Figure 2), does not necessarily exclude the diagnosis of onychomycosis. However, its presence strongly indicates the diagnosis, mainly when associated with dermoscopic findings in the nail plate (Figure 3).[2] For definitive diagnosis, direct mycological examinations, nail plate culture or histology (nail clipping) should be performed.[1] Nail free margin dermoscopy is a noninvasive exam that should be routinely used to assess suspected cases of onychomycosis. The dermoscopic finding of subungual hyperkeratosis showing a "ruin" pattern is a relevant detection and, when present, suggests the diagnosis of onychomycosis.

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Jigsaw puzzle advancement flap: an unusual surgical technique for nasal alar reconstruction

Retalho jigsaw puzzle: uma técnica cirúrgica inusitada de reconstrução da asa nasal

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ABSTRACT

Nasal surgical defects resulting from the removal of non-melanoma skin cancer represent a challenge for the surgeon due to the anatomical complexity and the high functional and aesthetic relevance of the region. The purpose of this paper is to demonstrate the *jigsaw puzzle* advancement flap. Resection of basal cell carcinoma was performed in the patient's perialar region, followed by the reconstruction with the *jigsaw puzzle* advancement flap, with excellent aesthetic and functional results. The presented technique is useful and not yet widespread, and it should be part of the dermatological surgeon's arsenal in the reconstruction of surgical defects located in the nasal ala-perialar region.

Keywords: Nose; Reconstructive surgical Procedures; Surgical flaps

RESUMO

Defeitos cirúrgicos nasais provenientes da retirada de câncer de pele não melanoma representam um desafio para o cirurgião devido à complexidade anatômica e à alta relevância funcional e estética da região. O objetivo deste trabalho é demonstrar o retalho de avanço jigsaw puzzle. Foi realizada ressecção de carcinoma basocelular na região perialar do paciente, seguida de reconstrução com retalho jigsaw puzzle, com excelente resultado estético e funcional. A técnica apresentada é útil e pouco difundida, devendo fazer parte do arsenal do cirurgião dermatológico na reconstrução de defeitos cirúrgicos localizados nas regiões alar e perialar do nariz.

Palavras-chave: *Nariz; Procedimentos cirúrgicos reconstrutivos; Retalhos cirúrgicos*

INTRODUCTION

Non-melanoma skin cancer (NMSC) is mainly located on the face, accounting for 75% of cases; of these, 30-35% are located in the nose.[1] These tumors are homogeneously distributed in the nose, being more frequent in the wings (nasal ala), followed by the dorsum and tip of the nose.[2]

The treatment of NMSC is mostly surgical, aiming at complete removal of the lesion and minimal functional and aesthetic damage. Surgical defects located in the nasal ala are challenging to reconstruct since the integrity of this region is very important for maintaining the aesthetics and function of the nose.[3] Because it is a prominent and central structure, the nose has considerable aesthetic relevance where minimal distortion may compromise facial harmony.

Several methods are described for the closure of surgical defects of the alar region. Minor defects may heal by secondary closure.[3] Superficial defects, in turn, can be repaired with full-thickness skin grafts, often with substantial aesthetic results. Rarely, some defects in the nasal ala may be repaired by direct closure.

Although they are more difficult to perform than grafts, the flaps have aesthetic advantages since they use adjacent skin similar to that of the surgical defect, thus minimizing the problems related to contour, color, and texture.[3] There are several types of flaps described for closing the alar region,[4] and the surgeon should indicate which technique best suits the patient considering factors such as site, size, depth, and personal experience. New flaps have been described to compose the set of therapeutic options in the nasal reconstruction of surgical defects. Goldberg *et al.*, in 2005, described the jigsaw puzzle advancement flap with good results.[4] This paper aims to illustrate and disseminate this technique that, although still little known, is reproducible and useful in the reconstruction of surgical defects located in the nasal alar and perialar regions.

METHODS

Description of the surgical technique

The lesion was excised, resulting in a 13 mm deep surgical defect in the perialar region. An advancement flap was drawn with the offset tissue triangles inferiorly along the nasolabial fold and superiorly along the boundary between the nasal and malar anatomical units (Figure 1). The flap was incised, and the compensation triangles were removed. The flap had a random pedicle and lateral base. The underlying fat was removed from the flap to give it the thickness of the surgical defect. Secondary defects resulting from the excision of compensation triangles were closed with absorbable subcutaneous sutures. Anchorage points were made by attaching part of the flap to the periosteum of the maxillary bone and the piriform foramen. The closure was completed by performing skin sutures using nylon thread (Figure 2).

RESULTS

A 72-year-old woman, phototype III, presented a lesion located in the left perialar region (Figures 3 and 4), characterized by an 8mm papule with perlaceous borders and typical dermoscopy. The pathological examination confirmed the diagnosis of basal cell carcinoma.

After total resection of the lesion, which resulted in a 13 mm deep surgical defect in the largest diameter (Figures 1 and 2), the nasal ala was reconstructed with a jigsaw puzzle advancement flap using the tissue located between the nasal and malar anatomical units.

The immediate postoperative period was uneventful, without flap distress, hematoma, seroma, or surgical site infection.

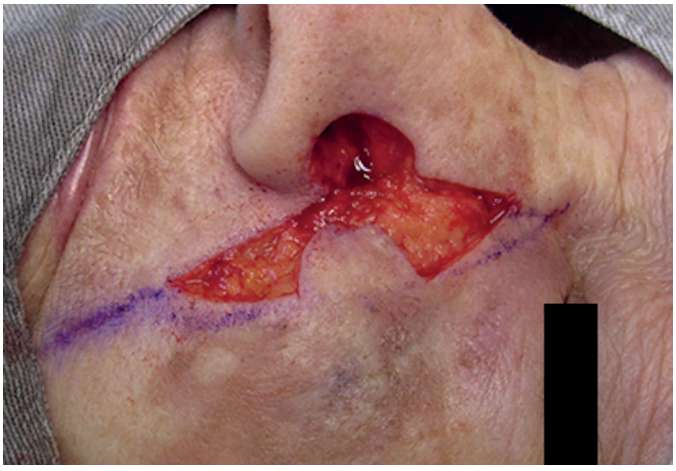

Figure 1: Clinical appearance after incision of jigsaw puzzle advancement flap and resection of both compensation triangles

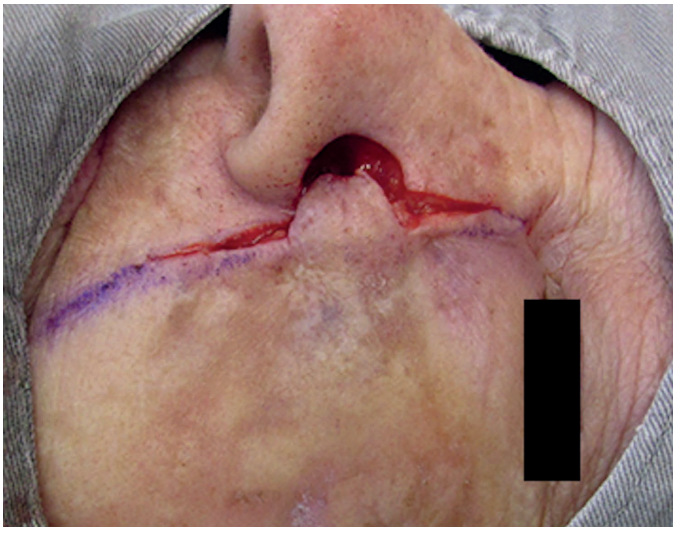

Figure 2: Clinical aspect of jigsaw puzzle advancement flap after fixation of anchor points in the periosteum with absorbable thread. Note the reduction in surgical defect with no tension in the flap or alar skin. In the next step, absorbable dermal internal sutures were performed followed by simple 5-0 and 6-0 nylon sutures

The aesthetic result was very satisfactory, without loss of nasogenian sulcus or nasal ala contour, or distortion of free margins. In the six-month postoperative period, the treated region maintained excellent aesthetic and functional results (Figure 5).

DISCUSSION

The nasal region is a common area for NMSC, and total surgical resection of the lesion is the method of choice for its treatment.[5] The functional needs, anatomical characteristics, and aesthetic relevance of the nasal alar and perialar regions are often a challenge to the dermatologic surgeon in reconstructing surgical defects in this area.

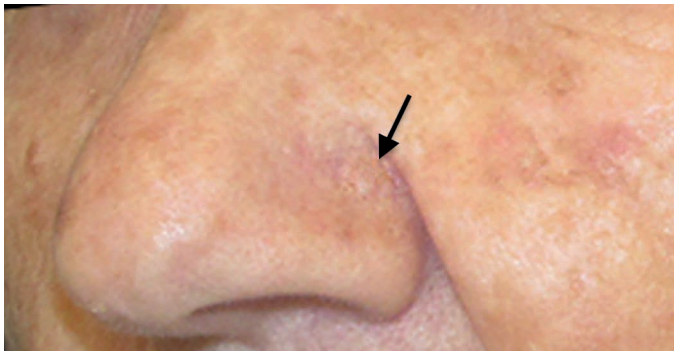

Figure 3: Clinical aspect of the lesion located in the left perialar region, characterized by 8mm normochromic papule with well-defined pearly borders

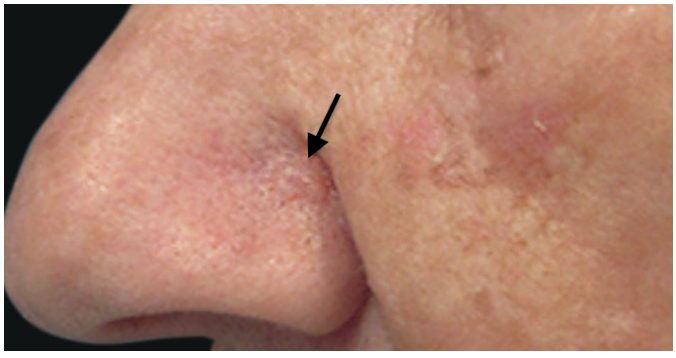

Figure 4: Postoperative clinical aspect. Six months postoperative with excellent aesthetic and functional results

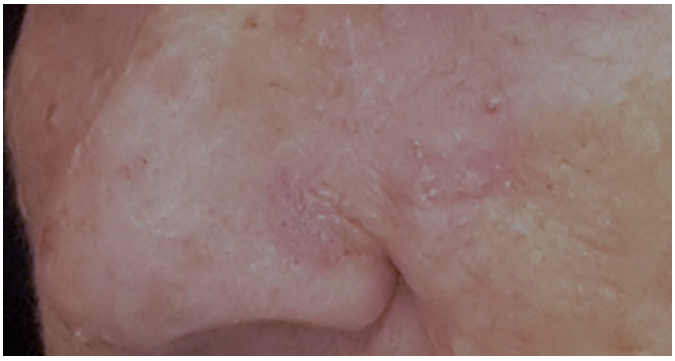

Figure 5: Postoperative clinical appearance. Six months postoperative with excellent aesthetic and functional results

Studies show that there is no statistically significant difference regarding complications when comparing flap and total skin grafts.[6] Regarding the aesthetic results, it is consensual the superiority of the flaps when well executed, since they present similarity of the texture and color of the local skin and tend to preserve the anatomical contour,[3] mainly in deep defects characteristic of the nasal region.

Several flap options are available for the reconstruction of the alar region, such as:V-Y advancement flap, bilobed flaps, and nasolabial interpolation flaps, among others.[7,8] The jigsaw puzzle advancement flap, although unconventional, allows the nasal ala reconstruction while maintaining the contour and structural integrity,[4] with great cosmetic result, as showed in our patient. Several authors have used flaps obtained from the nasogenian region and malar area for the reconstruction of nasal alar defects due to good compatibility between the tissues of these different anatomical zones.[8]

Regarding the choice of the best flap region, the melolabial tissue, which is located between the nasal and malar anatomical units, is an excellent option for nasal and malar region reconstruction.[9] Melolabial tissue was considered superior for nasal reconstruction due to its better texture correspondence and absence of noticeable scar when compared to the paramedian forehead flap.[10]

The advantages of the jigsaw puzzle advancement flap include: 1) excellent aesthetic result due to the similarity of texture and color of the flap skin; 2) incision lines located at the boundary between the nasal, perioral and malar anatomical units, leading to a good scar camouflage; 3) suture anchorage to the periosteum, essential for recreating the alar sulcus and the boundary between the nasal and maxillary anatomical units, also removing the tension of the surgical defect, avoiding the secondary movement of the nasal ala; 4) performance in a single operation.

One of the limitations of this technique is that in order to perform it, the malar region must present sagging skin. It also has the disadvantage of removing healthy skin from both compensation triangles.

Nasal ala amputation may be required for complete tumor removal, leading to extensive and full-thickness surgical defect. In such cases, the jigsaw puzzle advancement flap should be associated with techniques that restore nasal mucosa and cartilage. When performed in isolation, this flap is indicated for the correction of defects that reach the thickness of the dermis as it provides soft tissue thickness but does not provide structural support.[4]

CONCLUSION

Surgical defects located in the nasal alar region are frequent since the incidence of basal and squamous cell carcinomas in this region is high. Due to the anatomical characteristics of

the alar region, defects located in this area are challenging to reconstruct, involving high aesthetic and functional relevance. The jigsaw puzzle advancement flap is a reproducible, useful, easy-to-perform technique that has excellent aesthetic results. Thus, it should be part of the dermatologic surgeon's arsenal for the reconstruction of surgical defects located in the nasal ala-perialar region.

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Botulinum toxin in the treatment of sequelae of facial palsy: dermatologist's practice

Toxina botulínica no tratamento de sequelas da paralisia facial: área de atuação do dermatologista

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ABSTRACT

The application of botulinum toxin to patients with sequelae of Bell's palsy is a beneficial adjuvant therapy for the reduction of synkinesia and facial asymmetries. Bell's palsy is the most common cause of facial nerve paralysis. After the paralysis phase of the facial muscles, the condition may evolve with facial asymmetry and synkinesia. In the treatment of synkinesia, punctual injections into the orbicularis and platysma muscles relieve the spasms. Selective application to the unaffected hemiface aims to reduce facial asymmetry and its negative social impact, with improved quality of life.

Keywords: Facial paralysis; Bell palsy; Botulinum toxins, type A; Rehabilitation; Quality of life

RESUMO

A aplicação de toxina botulínica nos pacientes com sequela de paralisia de Bell é uma terapia auxiliar de extrema valia para a redução da sincinesia e de assimetrias faciais. A paralisia de Bell é a causa mais comum de paralisia do neurônio motor facial. Após a fase de paralisia dos músculos da face, o quadro pode evoluir com assimetria facial e sincinesia. No tratamento da sincinesia, as injeções pontuais no músculo orbicular e platisma aliviam os espasmos. A aplicação seletiva na hemiface não acometida objetiva reduzir a assimetria facial e seu impacto social negativo, com melhora da qualidade de vida.

Palavras-chave: *Paralisia facial; Paralisia de Bell; Toxinas botulínicas tipo A; Terapêutica; Qualidade de vida; Reabilitação*

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INTRODUCTION

Bell's palsy has a sudden onset and is unilateral, with facial paralysis associated with retroauricular pain, dysgeusia, paraesthesia, and hyperacusis. The maximum symptomatology occurs within the first 48-72 hours.[1] The severity of paralysis correlates with the duration of facial distension, the extent of facial recovery, and the impairment of quality of life.[1]

Some patients have incomplete recovery and develop hypertonia, synkinesis, or hyperkinesis. Physical therapy associated with botulinum toxin is an option in the treatment of synkinesis.

METHODS

In this study, we report the case of a patient with an excellent therapeutic response to the use of botulinum toxin to correct facial asymmetry. The review of the specialized literature, conducted between May and July 2018, used selected scientific articles by searching the Pubmed database. The keywords employed were Bell's palsy, facial palsy, and botulinum toxin.

The inclusion criteria for the studies found were the therapeutic approach of the use of botulinum toxin in the treatment of synkinesis and facial asymmetry after facial paralysis, with emphasis on cases of Bell's palsy. We excluded studies that reported the use of botulinum toxin in other facial asymmetry etiologies.

Soon after, we sought to study and compare the number of patients involved in each study (n), the botulinum toxin used, the average dose used, the application interval, the duration of the effect, and the follow-up time.

CASE REPORT

A 54-year-old woman reported that, during the summer of 1999, when moving from one refrigerated area to another with room temperature, she presented paralysis and paresthesia in the left hemiface. Bell's palsy was diagnosed, and she started the treatment with systemic corticosteroid therapy and physiotherapy (cryo and electrostimulation). She had a history of herpes episodes in the same area affected by the paralysis, the last one occurring four months ago. The patient maintained sequelae of left hemifacial paralysis and oro-ocular synkinesis, closing her left eye when smiling (Figure 1). When recruiting the facial muscles of the unaffected side (to contract (Figure 2) or raise the right forehead (Figure 3), as well as to close or move the oral cavity (Figure 4) laterally), the left eye also closes. There is ipsilateral platysma band contracture, causing pain in the region (Figure 5). She is having annual applications of botulinum toxin (she has performed approximately 16 sessions), reducing asym-

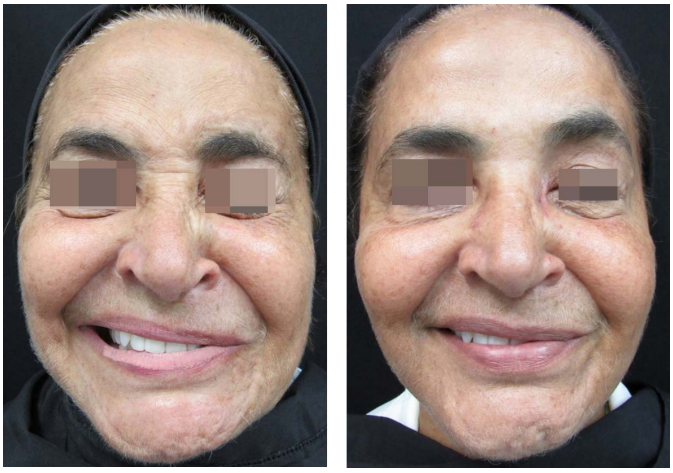

Figure 1: Oral ocular synkinesis, with left eye closing when the patient smiles, before and after botulinum toxin application

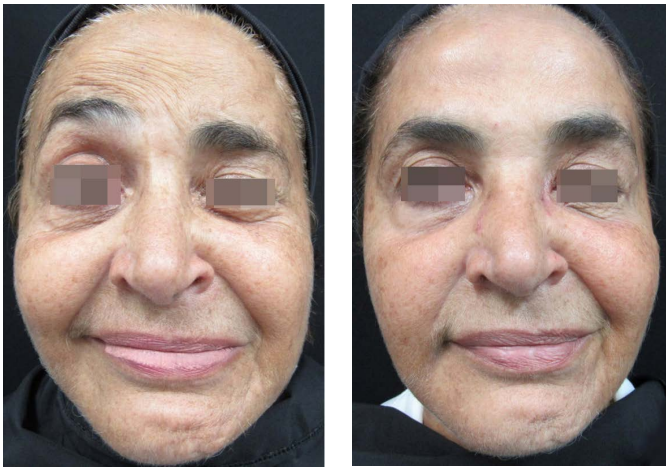

Figure 3: Closing of the left eye when the patient recruits the facial muscle of the unaffected side to elevate the forehead, before and after botulinum toxin application

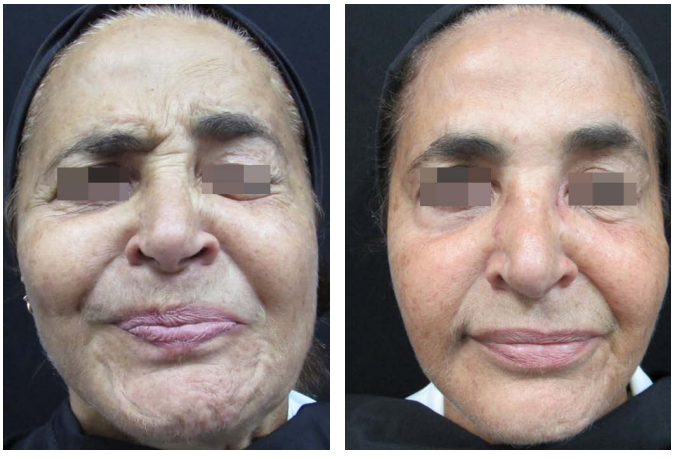

Figure 2: Closing of the left eye when the patient recruits the facial mimic muscles of the unaffected side to contract the forehead, before and after botulinum toxin application

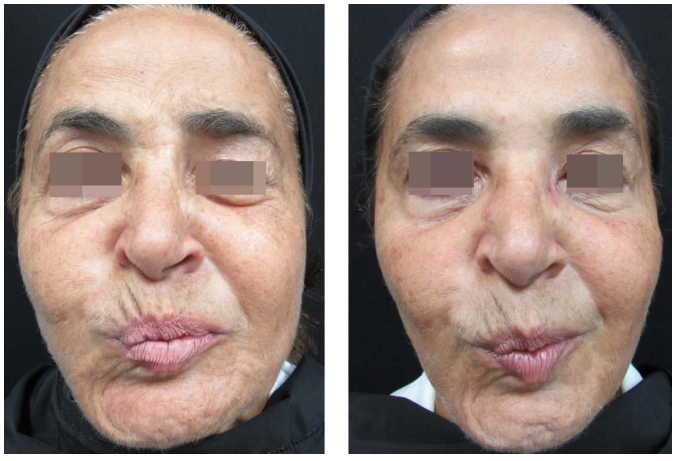

Figure 4: Closing of the left eye when the patient recruited the facial muscle of the unaffected side for the lateral movement of the oral cavity, before and after botulinum toxin application

metry, painful contractions, and synkinesis. Otolaryngologist, neurologist, dermatologist, and physiotherapist are following her multi-disciplinarily. It was decided to apply onabotulinum toxin A (totaling 85 U - Figure 6 and Table 1), using anesthetic cream before the procedure and syringe with a 30G needle in order to reduce the pain of the injection. In the left (affected) hemiface, injections of 1U of botulinum toxin were applied at three points in the orbicularis oculi muscle and of 2U at each of the four points in the platysma muscle to relieve the spasms. The corrugator supercilii muscle was also approached, and injections of 3Us were applied at one point in order to reduce hypertonia. The selective application to the right (unaffected) hemiface, forehead, glabella, orbicularis oculi, orbicularis oris, depressor anguli oris muscle, as well as to the masseter, mental, nasal and platysma muscles was guided in an attempt to improve facial asymmetry and correct some wrinkles, according to Table 1. The functional and aesthetic results were considered satisfactory by the patient in the review 20 days after the procedure.

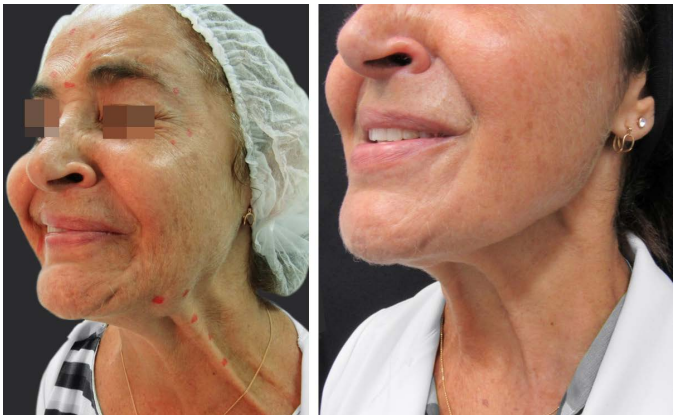

Figure 5: Botulinum toxin application points in platysma to relieve spasms

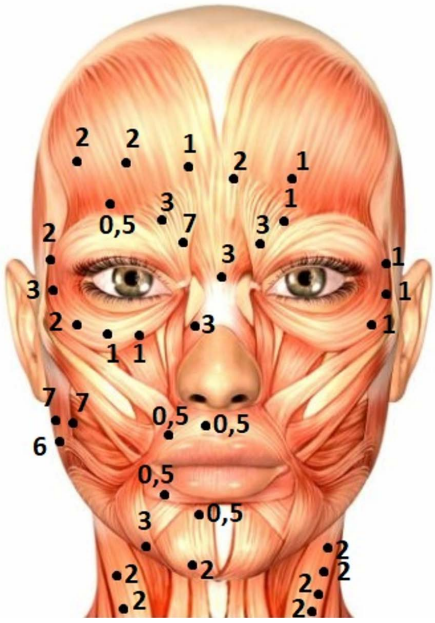

Figure 6: Scheme showing the botulinum toxin application points in the left (affected) hemiface, into the orbicularis oculi and platysma muscles, in order to relieve spasms and correct synkinesis. Selective application to the right hemiface (unaffected) in an attempt to improve facial asymmetry and correct some wrinkles

DISCUSSION

Bell's palsy is the most common cause of paralysis of facial motor neurons and affects motor, sensory, and parasympathetic fibers. It was first described in 1830 by Charles Bell and presents an incidence rate of 15 to 40 per 100,000 patients.[2] According to Eviston TJ et al[1], there is no preference for gender, but it tends to occur more frequently in older age groups.

The pathogenesis is still controversial and is related to herpesvirus type 1 infection, nerve compression (ischemic mechanisms) and autoimmunity. Herpesvirus HSV-1, HSV-2 EVZV subtypes are known to latently establish in multiple cranial ganglia, dorsal root and autonomic ganglion following mucocutaneous exposure.[3] Intra-axonal degradation and activation of apoptotic pathways in response to the virus, associated with a susceptible phenotype, are believed to contribute to the episode of facial paralysis.[1]

Combined treatment with acyclovir and corticosteroids for classical Bell's palsy in the acute phase remains controversial.[4] Some authors suggest the use of systemic corticosteroids only.

Botulinum toxin is a neurotoxin produced by the anaerobic bacteria *Clostridium botulinum*.[5] It acts on the presynaptic membrane of the neuromuscular junction, inhibiting acetylcholine release and causing a dose-dependent reduction in the muscle contraction.

After the paralysis phase of the facial muscles, there is a tendency for hypertonia. The toxin performs chemodenervation, weakening the hypertonic muscles, and contributing to the correction of facial asymmetry and synkinesis.

Synkinesis corresponds to involuntary abnormal muscle contraction during voluntary movements, attributed to aberrant reinnervation after nerve injury. It may be oro-ocular when the patient closes the eye while smiling or eating, or ocular-oral, when the patient twitches the lip while closing the eye. Activation of the platysmal bands to the movement of the contralateral hemiface also occurs.[1] In addition to the platysmal bands, the patient presented oro-ocular synkinesis. In the synkinesis treat-

Table 1: Dose applied according to muscle group

Muscle Group	Dose used on non-paralyzed side	Total units used
Frontalis	5 points, 0.5-2U	7.5U
Glabella-procerus	2 points, 3-7 U	10U
Nasalis	1 point, 3U	3U
Masseter	3 points, 6-7U	19U
Orbicularis oris	4 points, 0,5U	2U
Depressor anguli oris	1 point, 3U	3U
Mentalis	1 point,2U	2U
Platysma	2 points,2U	4U

Table 2: Literature review

AUTHOR	n	WITH BP	LOCAL	TOXIN USED	DOSE/ AVERAGE DOSE USED	APPLICATION INTERVAL	DURATION OF THE EFFECT	FOLLOW-UP
Chua CN *et al*, 2004[8]	5	3	England	Abobotulin toxin A	40 - 120U	3 months	2 - 3 months	*
Finn JC, 2004[9]	2	1	USA	*	*	*	*	*
Bulstrode NW *et al*, 2005[2]	23	23	England	Abobotulin toxin A	*	1 month	*	37 months
Borodic G *et al*, 2005[10]	30	20	USA	*	*	*	*	*
Ito H *et al*, 2007[11]	11	7	Japan	Onabotulinum toxin A	5,76U (4-18,75U)	14,5 weeks	*	43 months
De Maio *et al*, 2007[12]	18	*	Brazil	Abobotulin toxin A	112U	*	3 - 6 months	180 days
Toffola ED *et al*, 2009[13]	30	11	Italy	Onabotulinum toxin A	15,7U (7,5-27,5U)	*	4 months	*
Álvaro MLN *et al*, 2010[14]	48	48	Spain	Onabotulinum toxin A	*	4 months	*	18 months
Terzis JK *et al*, 2012[15]	18	18	USA	*	45U	3-4 months	3-4 months	at least 18 months
Sadiq SA *et al*, 2012[16]	14	1	England	Abobotulin toxin A	30U (10-80U)	*	média de 13 semanas (7 a 24 sem.)	*
Filipo *et al*, 2012[17]	41	28	Italy	Onabotulinum toxin A	17-36U	singles application	2-3 months	2 years and 3 months
Choi KH *et al*, 2013[18]	42	24	South Korea	Onabotulinum toxin A	on the paralyzed side: 10 to 26U; on the non paralyzed side: 35 to 72U	*	*	2 years
Monini *et al*, 2013[19]	20	0	Italy	Onabotulinum toxin A	10 a 40U	*	*	2 years
Kim J *et al*, 2013[20]	18	9	South Korea	Onabotulinum toxin A	47,5±8,4U (32-68U)	singles application	6 months	2 years
Mendonça MCC *et al*, 2014[21]	12	2	Brazil	Onabotulinum toxin A	8,2-51U	90 - 120 days	*	2 years and 11 months
Pourmomeny AA *et al*, 2015[22]	34	34	Iran	Abobotulin toxin A	*	singles application	*	4 months
Risoud M *et al*, 2015[23]	30	0	France	Onabotulinum toxin A	on the paralyzed side: 10.4U; on the non paralyzed side: 9.8U	4-6 months	*	average 2.3 anos
Salles AG *et al*, 2015[24]	353	79	Brazil	Onabotulinum and Abobotulin toxin A	17,3U-38,5U (2-106U)	196 days	*	11 days
Remigio AFN *et al*, 2015[25]	55	*	Brazil	Onabotulinum and Abobotulin toxin A	Onabotulinum toxin A 15-70 U or Abobotulin toxin A 16-64 U	*	6 months	6 months
Mandrini S *et al*, 2016[26]	27	13	Italy	Onabotulinum toxin A	5.9U-18.6U	average 7.7 months	5 months	*
Bennis Y *et al*, 2016[27]	50	*	France	*	21-37U	*	*	*
Sahan *et al*, 2017[28]	1	0	Turkey	Botulinum toxin type A + hyaluronic acid	20,5U	*	*	4 months
Neville *et al*, 2017[29]	51	*	England	*	0,5 a 5U a cada ponto. Dose total não informada	4 meses	3-4 meses	18 meses

Dose administered according to muscle group (BP: Bell's palsy, * not reported)

ment, the botulinum toxin punctual injections into the orbicularis and platysma muscle relieve the spasms and should be associated with physiotherapy, with a particular focus on biostimulation exercises.[6] Selective application to the unaffected hemiface, forehead, and depressor anguli oris muscle may be considered in an attempt to improve facial asymmetry, as performed in the reported patient. It is essential to highlight that the application to the paresthetic zygomatic muscle or affected by synkinesis is not recommended to prevent loss of its smile function.[1]

According to Jowett *et al*.[7], the recommended starting dose for correction of contralateral eyebrow weakness is 9U of toxin into the frontal muscle, distributed in three zones, following a triangular pattern, always 1.5 cm above the eyebrow to prevent eyelid ptosis. The starting dose for the platysma muscle would be 20U distributed in four zones (rectangular pattern), 2 cm below the mentum.

Some patients require three to four annual applications, while others do not benefit from the treatment. The reported patient has already undergone about 16 annual applications without loss of efficacy. She denies adverse events and is undergoing adjunctive physiotherapy.

The literature review (Table 2) showed that the number of patients involved in each study on facial paralysis and treated with botulinum toxin ranged from one to 353, and the botulinum toxin used was onabotulinum toxin A and abobotulinum toxin A. The average dose used in each patient ranged from 2U to 120U, the application interval ranged from single application to 7.7 months, with duration of effect from two to six months and follow-up from one month to 11 years.

CONCLUSION

Botulinum toxin application in the treatment of patients with sequelae of Bell's palsy (approximately 16% of cases)[2] is an adjunctive therapy for reducing synkinesis and facial asymmetries. Often performed by other medical specialties, it is also an area of expertise for dermatologists, requiring the study and mastery of the technique for patient safety and obtaining satisfactory results.

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To the patients of the Cosmiatrics and Corrective Outpatient Clinic of the Pedro Ernesto University Hospital/ Universidade do Estado do Rio de Janeiro.

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Case Report

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Nevus lipomatosus cutaneous superficialis: unusual presentation

Nevo lipomatoso cutâneo superficial: apresentação incomum

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ABSTRACT

Nevus lipomatosus cutaneous superficialis is an uncommon dermatosis in which the adipose tissue is present ectopically in the dermis. This condition is clinically divided into two variants: classical and solitary. The first is characterized by soft, pedunculated, cerebriform, skin-colored or yellowish papules or nodules, mainly involving the pelvic region. The latter is observed as a solitary or sessile papule. Treatment with surgical excision is usually enough. Nevus lipomatosus cutaneous superficialis may be associated with other conditions such as multiple lipomas, as in our case.

Keywords: Nevus; Dermis; Adipocytes; Lipoma

RESUMO

O nevo lipomatoso cutâneo superficial é uma dermatose pouco frequente, na qual o tecido adiposo está presente de forma ectópica na derme. Esta condição é clinicamente dividida em duas variantes: clássica e solitária. A primeira caracteriza-se por pápulas ou nódulos macios, pedunculados, cerebriformes, do tom da pele ou amarelados, envolvendo principalmente a região pélvica. A última é observada como uma pápula solitária ou séssil. O tratamento com excisão cirúrgica é geralmente suficiente. O nevo lipomatoso cutâneo superficial pode estar associado a outras condições como, no nosso caso, a múltiplos lipomas.

Palavras-chave: *Adipócitos; Derme; Lipoma; Nevo*

INTRODUCTION

Nevus lipomatosus cutaneous superficialis (NLCS) is a rare and benign hamartomatous condition characterized by the presence of mature dermal adipocytes. NLCS is usually found at birth or arises within the first two decades of life. There are no reports of gender predilection or genetic predisposition. Clinically, it is classified into two variants. Asymptomatic clusters of soft, pedunculated, cerebriform, skin-colored or yellowish papules or nodules characterize the classical type. Lesions may coalesce into smooth, wrinkled, or *peau d'orange* textured plaques. This form is usually found in the pelvic girdle, especially in the gluteal, lumbosacral, and upper third of the thighs. The solitary type of NLCS manifests as a solitary or sessile papule. This form usually develops during adulthood and has been described in different locations: lower trunk, knee, armpit, arm, ear, and scalp. NLCS is treated with simple surgical excision. Because the condition is benign, it is removed for aesthetic reasons.[1-7]

Some lesions, such as angiokeratoma of Fordyce, *café-au-lait* or vitiligo-like macules, hemangioma, basal cell carcinoma (BCC), nevoid hypertrichosis, comedone-like lesions, and

lipoma were described concomitantly with the NLCS.[2-6] The rarity of the association of NLCS with lipomas in the literature and the exuberance in the presentation of our patient motivated us to publish it.

LITERATURE REVIEW

NLCS is characterized by the presence of ectopic mature dermal adipocytes. Clusters of soft, yellowish or skin-colored nodules, or papules that do not cross the midline and may follow Blaschko's lines characterize the classical type, described by Hoffmann and Zurhelle in 1921. They may already be present at birth or, more commonly, appear by the second decade of life. The most frequent locations are the pelvic girdle, lumbosacral region, buttocks and thighs.[2,3,4,8]

The solitary type, described by Nikolowsky in 1950, consists of a single nodular lesion with later onset, usually occurring after the third decade of life.[9] Its location varies greatly, with lesions on the lower trunk, clitoris, knee, armpit, arm, ear and scalp being described. This type is also referred to as a pedunculated lipofibroma. There are no reports of family history or gender preference in any of the clinical variants.[10-12]

In some cases, NLCS has been described to occur concurrently with some lesions such as angiokeratoma of Fordyce, café-au-lait or vitiligo-like macules, hemangioma, basal cell carcinoma (BCC), nevoid hypertrichosis, and comedone-like lesions.[2-5] However, only one Spanish study has reported the association of nevus lipomatosus with lipomas. In this study, a female patient presented, at the age of 34, the onset of soft nodules in the popliteal fossa, the central lesion corresponding to nevus lipomatosus and the peripheral lesions corresponding to lipomas.[13]

Histologically, nevus lipomatosus cutaneous superficialis is characterized by the accumulation of ectopic mature dermal adipocytes. When they are scarce, they present perivascular distribution with lymphomonocytic infiltrate. When they are abundant, this relationship is not so clear, and the boundary between dermis and hypodermis becomes blurred. Dermal collagen fibers are unchanged and may be disorganized, or with increased density. Elastic fibers may be normal, increased, reduced or even absent. An increase in mucin has also been reported in the papillary and subpapillary dermis. The epidermis is normal or presenting acanthosis and may contain comedonian structures.[13,14] Skin appendages are not replaced. However, some cases of NCLS with hairy abnormalities have been described, such as abortive germinal follicular-like structures, hypertrophic pilosebaceous units, perifollicular fibrosis, fibrofolliculomas, and folliculosebaceous cystic hamartoma.[8]

The pathogenesis of NLCS is not yet determined. Some authors have suggested that it originates from adipocyte precursor cells located around blood vessels.[15] However, in a study with electron microscopy, only mature lipocytes were observed inside the perivascular mononuclear infiltrates, and no lipoblasts or the transition from mesenchymal cells to lipocytes were observed.[16]

The treatment of choice is surgical resection, which is instituted for aesthetic purposes only, given the benignity of the lesion and the possibility of increasing its size. Malignant degeneration and recurrences are extremely rare.[1-7]

CASE REPORT

A 33-year-old man presented with four asymptomatic nodular lesions, distributed in the trunk and limbs for two years, and with one asymptomatic pedunculated tumoral lesion, located in the upper third of the right posterior thigh. The latter had progressive growth, becoming unsightly. He had no family history of similar changes.

Dermatological examination revealed four nodules covered by normal skin, with a soft consistency, measuring 2-6cm in the largest diameter, located in the lumbar region to the left, in the right and left forearms, and in the anterior aspect of the right thigh (Figure 1). It also revealed a skin-colored, lobulated, pedunculated tumoral lesion with fibrous consistency measuring 6.5cm in length and 3cm in diameter, located below the right infragluteal sulcus (Figure 2). Clinically, we hypothesized lipomas for nodular lesions in the trunk and limbs, and solitary type of nevus lipomatosus cutaneous superficialis for the pedunculated lesion located below the right infragluteal sulcus. The pedunculated lesion and the nodules, except the one located on the left forearm (2cm), were surgically removed and confirmed by histopathological examination (Figure 3).

Histopathological examination of the exuberant pedunculated lesion revealed the presence of mature adipose tissue in the reticular dermis extending to the papillary dermis, characterizing the diagnosis of nevus lipomatosus cutaneous superficialis (Figure 4). Histopathological examinations of trunk and limb nodules showed similar characteristics among them, revealing mature adipose tissue interspersed with some congested capillaries, compatible with lipoma (Figure 5).

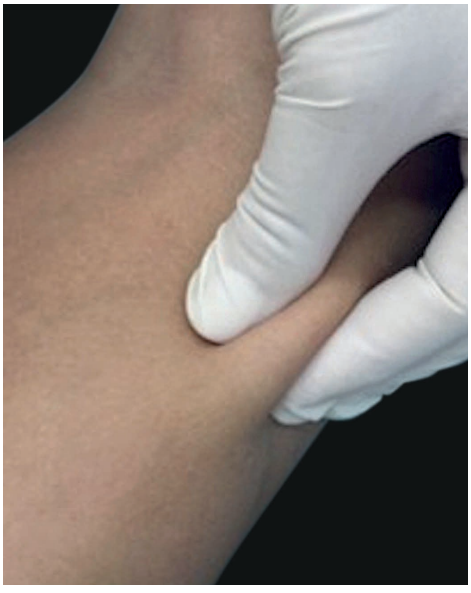

Figure 1: Nodule covered by normal skin, with soft consistency, located in the right forearm (lipoma)

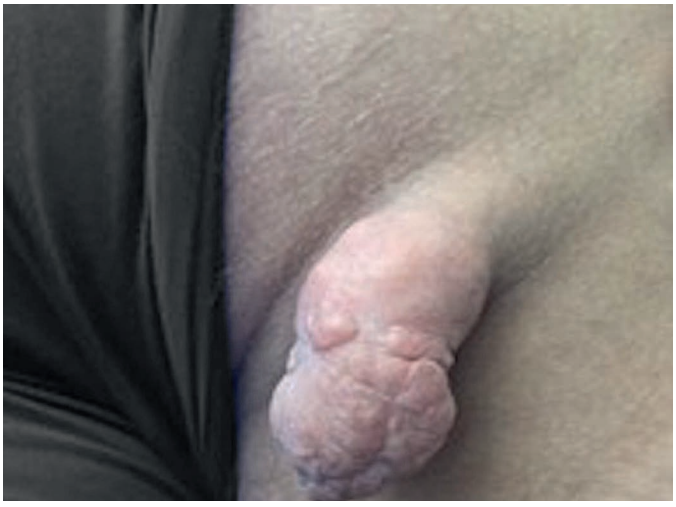

Figure 2: Skin-colored, lobulated, pedunculated tumoral lesion with fibrous consistency measuring 6.5cm in length and 3cm in diameter, located below the right infragluteal sulcus

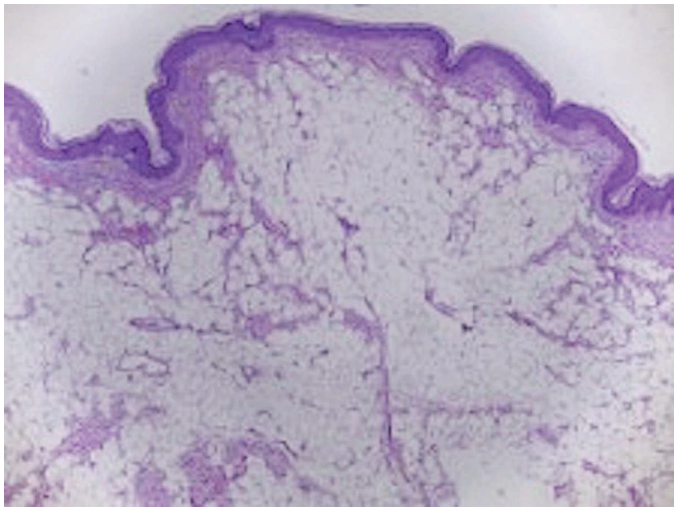

Figure 4: Presence of mature adipose tissue in the reticular dermis extending to the papillary dermis, characterizing the diagnosis of nevus lipomatosus cutaneous superficialis (Hematoxylin & eosin, 40x)

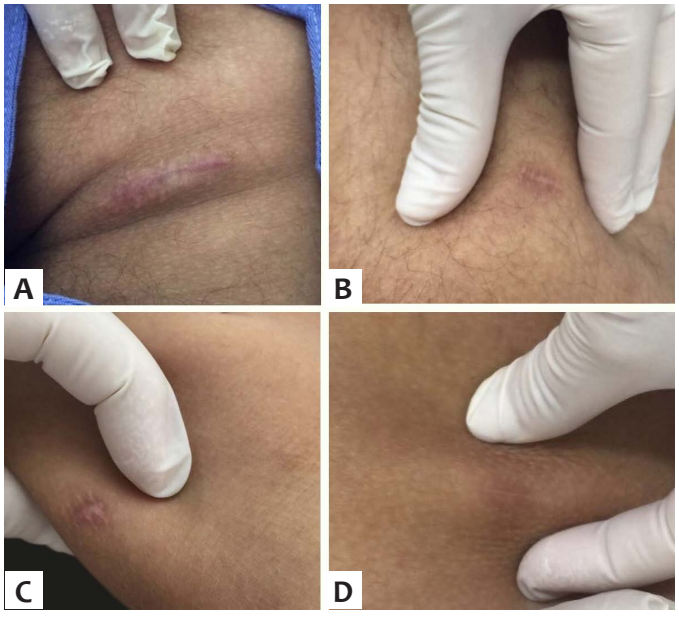

Figure 3: Scars after surgical excision of the lesions. **A.** Nevus lipomatosus cutaneous superficialis; posterior aspect of the right thigh. **B.** Lipoma; anterior aspect of the right thigh. **C.** Lipoma; medial aspect of the left forearm. **D.** Lipoma; dorsal region

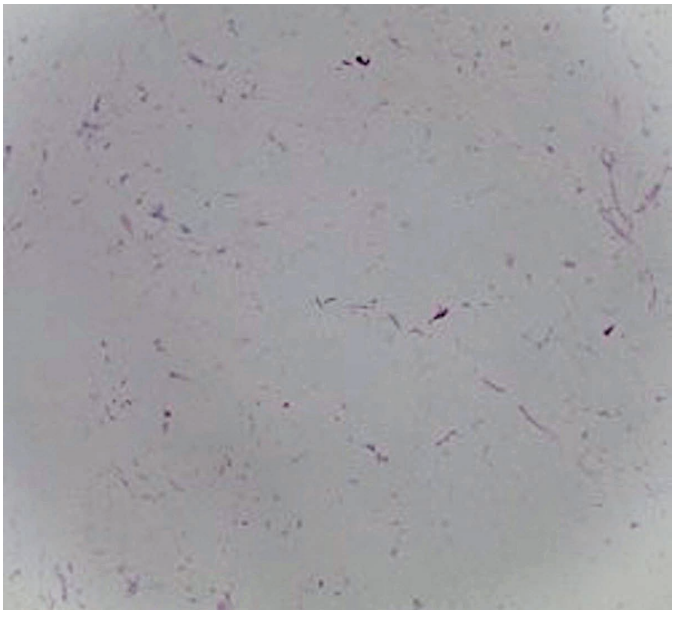

Figure 5: Mature adipose tissue interspersed with some congested capillaries, corroborating the diagnosis of lipoma (Hematoxylin & eosin, 40x)

DISCUSSION

Nevus lipomatosus cutaneous superficialis (NLCS) may be present from birth or may appear after the third decade of life. When present from birth - the classical type - it is typically located in the pelvic region and lower limbs. In its solitary type, which begins after the third decade of life, it appears as a single and pedunculated lesion and has a very diverse location. In the case reported here, the patient presented the solitary type of the nevus lipomatosus cutaneous superficialis; however, it was located in the common area of the classical type. In agreement with the literature, the patient had no family history.[1-7] There are some reports in the literature showing the association of NLCS with other dermatological changes, such as angiokeratoma of Fordyce, café-au-lait or vitiligo-like macules, hemangioma, basal cell carcinoma (BCC), nevoid hypertrichosis, and comedone-like lesions.[2-5] However, little is known about the concomitance of this type of nevus with lipomas. To date, only one case has been reported demonstrating this association.[13] Our report is similar to the case previously described, but it differs in the location of the lesions. Our patient's lipomas and nevus lipomatosus were in distant sites of the body.

Despite its benign character, many patients wish to remove the lesion. In our case, the patient sought the Dermatology

Service of the Universidade Federal Fluminense for the surgical removal of a lesion with an unusual and exuberant presentation. The aesthetic result after surgery was considered very good by the doctors and the patient (Figure 3A).

CONCLUSION

Diagnosis of nevus lipomatosus cutaneous superficialis may be difficult due to its rarity and different presentation forms. There are some reports of associations of NLCS to other dermatological changes. However, concomitance with lipomas was described only in a previous case. We report this case because of its peculiarity and exuberance as well as its association with multiple lipomas.

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Case Report

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Use of island advancement flap (V-Y) in lip reconstruction after Mohs micrographic surgery: report of three cases

Emprego do retalho de avanço em ilha (V-Y) na reconstrução labial após cirurgia micrográfica de Mohs: relato de três casos

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ABSTRACT

Lip reconstruction after tumor excision is challenging because the results must be functional and cosmetic. In this context, Mohs micrographic surgery (MMS) is essential in ensuring maximum tissue preservation, with lower recurrence rates and the possibility of less complicated reconstructions. We report three cases of lip tumors treated with Mohs surgery, whose reconstruction was performed with island advancement flaps (V-Y). The relevance of the correct management of this type of tumor is discussed, highlighting the use of Mohs surgery and V-Y advancement flap, which provide satisfactory aesthetic and functional results.

Keywords: Lip neoplasms; Mohs surgery; Surgical flaps

RESUMO

A reconstrução labial após exérese de tumores é desafiadora, pois os resultados devem ser funcionais e cosméticos. Neste contexto, a cirurgia micrográfica de Mohs (CMM) é importante ao garantir máxima preservação tecidual, com menores taxas de recorrência e possibilidade de reconstruções menos complexas. Relatamos três casos de tumores labiais tratados com cirurgia de Mohs, cuja reconstrução foi realizada com retalhos de avanço em ilha (V-Y). Discute-se a relevância do correto manejo deste tipo de tumor, destacando-se o emprego da cirurgia de Mohs e do retalho de avanço em V-Y, que proporcionam resultados estéticos e funcionais satisfatórios.

Palavras-Chave: *Neoplasias labiais; Cirurgia de Mohs; Retalhos cirúrgicos*

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INTRODUCTION

Lip reconstruction of surgical defects affecting the skin and the vermilion border is challenging considering the impact that may be caused by unfavorable cosmetic and functional results.[1,2,3] The control of surgical margins, obtained through Mohs micrographic surgery (MMS), helps to achieve better results, providing maximum tissue preservation combined with lower recurrence rates and the possibility of less complicated surgical reconstructions.[1,3]

We report three cases of malignant lip neoplasms, whose surgical treatment was performed with MMS and reconstruction used an island advancement flap (V-Y).

CASE REPORT

Case 1: Woman with nodular basal cell carcinoma (BCC) in the center of the upper lip, 0.5cm in diameter, involving the philtrum and the vermilion border (Figure 1A). The repair was performed by anatomical subunits with double V-Y advancement flap (Figures 1B and 2A). The three-month clinical follow-up demonstrates the maintenance of anatomical and functional characteristics (Figure 2B).

Case 2: Woman with nodular and ulcerated BCC in the left portion of the upper lip, 0.8 cm in its largest length, affecting the philtrum and the vermilion border (Figure 3A). After free margins in the second stage of the MMS (Figure 3B), the repair was performed with a skin-mucosa double opposing V-Y advancement flap (Figure 4). The four-month clinical follow-up (Figure 5) demonstrates the preservation of anatomical and functional characteristics.

Case 3: Man with well-differentiated invasive squamous cell carcinoma (SCC) in the central region of the lower lip, with a diameter of 1cm and exclusive involvement of the vermilion border (Figure 6A). After MMS (Figure 6B), the repair was performed with a V-Y advancement flap of the lip mucosa (Figure 7A). The nine-month clinical follow-up (Figure 7B) showed satisfactory cosmetic and functional results.

DISCUSSION

The reconstruction of surgical defects involving the lip region, especially those including the vermilion, is technically complex.[4,5] Due to the region's limited reserve tissue, there is a potential distortion of facial symmetry and losses in speech, eating, and facial expression functions,[1,3,4] what should be considered by the surgeon when planning this type of intervention.

Using MMS in these cases plays an important role. The surgical margin control provided by the technique minimizes the sacrifice of healthy tissues adjacent to the tumor and allows more tissue to be made available for reconstruction.[3] MMS also guarantees excellent long-term cure rates,[3] preventing re-approaches in this critical area.

There are some closure options for surgical defects of the lip region. Primary linear closure may be considered when the operative wound is especially small or in the case of the philtrum when it is less than half of its width.[3,4] Rotation flaps also include small surgical wounds due to potential anatomical changes in this limited area.[3] Full-thickness skin grafts can be used and are suitable for treating large defects, with better results when positioned to occupy a whole cosmetic subunit.[3] Even secondary wound closure may be considered in the concave area of the philtrum; however, the scar contraction of large wounds in this area may evolve with eclabium.[3] As, in general, the surgical defects usually have an intermediate size between the ones

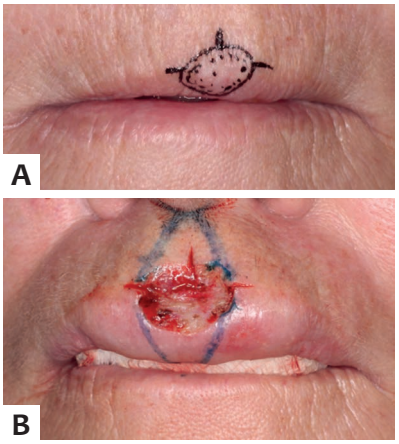

Figure 1: Case 1 – 1A: Basal cell carcinoma marked in the lip region, affecting the cutaneous lip (including philtrum) and lip vermilion. **1B:** Final surgical defect after free margins in MMS with double V-Y flap design

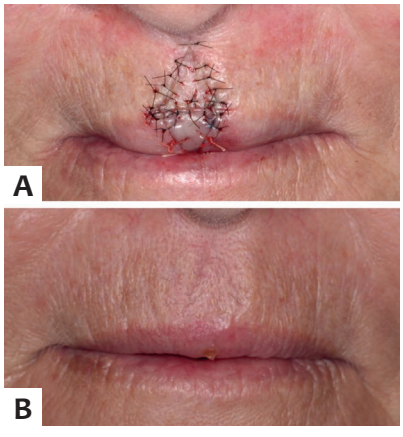

Figure 2: Case 1 – 2A: Flaps positioned and sutured. **2B:** Postoperative aspect in three months

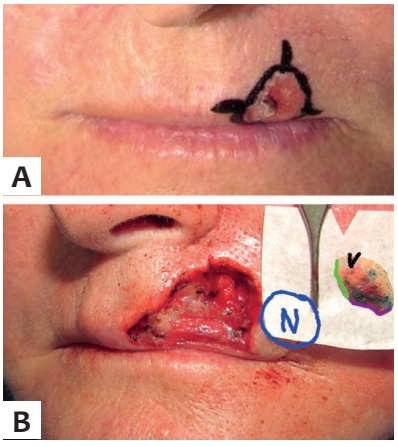

Figure 3: Case 2 – 3A: Basal cell carcinoma in the left portion of the upper lip, affecting the cutaneous lip and the vermilion. **3B:** Surgical defect after free margins in the third stage of MMS

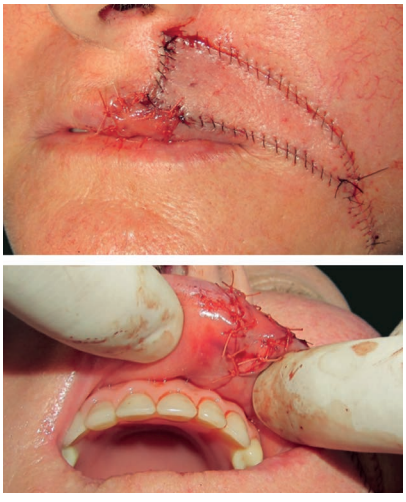

Figure 4: Case 2 – Flaps positioned and sutured

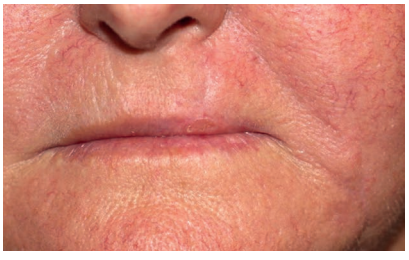

Figure 5: Case 2 – Postoperative aspect in four months

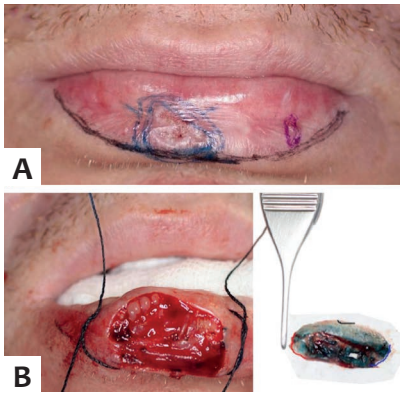

Figure 6: Case 3 – A: Demarcation of the lesion in lip vermilion. **B:** Surgical defect after free margins in MMS

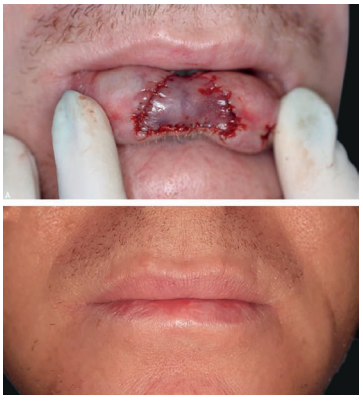

Figure 7: Case 3 – A: Mucosa V-Y advancement flap positioned and sutured. **B:** Nine months postoperative appearance

mentioned in our study, the correction through these techniques can result in microstomy, vermilion reduction and potential alteration of the natural lip contour.[4]

The V-Y advancement flap is an excellent option for treating surgical lip defects as it recruits tissues of very similar texture, thickness, color, and even photodamage,[2,4] also maintaining the pattern of facial cosmetic subunits. Notably, the possibility of correcting upper lip defects involving the philtrum, considered even more complicated due to the Cupid's bow contour characteristics,[6] evidences the applicability of this technique, as observed in the first case. We also highlight the maintenance of the aesthetically relevant lip contour observed in the three cases.

In case 1, the area to be corrected included the central portion of the upper lip and also the philtrum; two island advancement flaps were performed perpendicular to the lip edge - one containing skin and the other containing mucosa. In case 2, the defect in the left portion of the upper lip also included skin and mucosa; its correction required two V-Y advancement flaps: the first, cutaneous, lateral to the lip; the second, a labial mucosa, which was projected perpendicularly and upwards to maintain the anatomical line of the vermilion border. In case 3, in which only the vermilion was affected, a single mucosal advancement was performed. In all cases, clinical follow-up showed satisfactory cosmetic and functional results.

CONCLUSION

The V-Y advancement flap should be remembered when planning surgical repairs that affect the labial region, highlighting the importance of its association with the MMS, which provides safety for margin control, in addition to satisfactory aesthetic and functional results.

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ÚNICO NUTRACÊUTICO QUE COMPROVA:

EFICÁCIA NÃO INFERIOR *VS.* MEDICAMENTO REFERÊNCIA NO TRATAMENTO DAS ALOPECIAS[1]

REFERÊNCIA NUTRACÊUTICA NO REEQUILÍBRIO DO CICLO E DA SAÚDE CAPILAR.

VITAMINAS, MINERAIS E *POOL* DE AMINOÁCIDOS

- REDUZ A QUEDA E MELHORA A DENSIDADE CAPILAR.[1]
- AUMENTA A RESISTÊNCIA, A QUALIDADE E O BRILHO DOS CABELOS.[1]
- MELHORA A ESPESSURA DA DERME E A ANCORAGEM DA HASTE.[2]

EXCLUSIVO

POOL DE AMINOÁCIDOS

19 CONSTITUINTES DA QUERATINA, INCLUINDO A **CISTINA**[3]

- NÃO CONTÉM GLÚTEN[3]
- VITAMINAS E MINERAIS em 100% da IDR[3]
- ZERO KCAL[3]
- RECOMENDAÇÃO DE USO CÔMODA: 1 comprimido, 1x ao dia[3]
- ALTA TOLERÂNCIA GÁSTRICA[1]
- SEM DERIVADOS DE PEIXE[3]

Referências bibliográficas: 1. Addor FAS, Donato LC, Abreu Melo CS. Comparative evaluation between two nutritional supplements in the improvement of telogen effluvium. Clinical, Cosmetic and Investigational Dermatology. 2018;11:431-6. **2.** Addor FAS, Melo CSA, Vieira JC. Efeito de uma associação de nutrientes na papila dérmica folicular humana: estudo in vitro. Surg Cosmet Dermatol. 2018 jul-set;10(3)(3 suppl. 1):9-13. **3.** Rotulagem do produto Exímia Fortalize Kera D.

Gestantes, nutrizes e crianças até 3 (três) anos somente devem consumir esse produto sob orientação de nutricionista ou médico. Produto dispensado da obrigatoriedade de registro - Resolução RDC 27/2010.

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CONSCIÊNCIA PELA PELE
Uma divisão do FQM GRUPO.

Case Report

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Rejuvenation with cervical lifting and zetaplasty

Rejuvenescimento com lifting da região cervical e zetaplastia

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ABSTRACT

Neck appearance is one of the indicators of a person's biological age. Conventional rhytidoplasty has been the standard treatment for correction of cervical aging. Some patients, especially men, show evident changes in the neck, with excess skin and/or fat in the anterior cervical region, but with little flaccidity of the face. Cervical *facelift*, combined with zetaplasty, is a surgical option for rhytidoplasty and treats excess skin, fat, and platysma bands. It can be performed under local anesthesia, presenting low morbidity, rapid recovery, and high level of satisfaction.

Keywords*: Rhytidoplasty; Rejuvenation; Cervicoplasty; Neck*

RESUMO

A aparência do pescoço é um dos indicadores da idade biológica de uma pessoa. A ritidoplastia convencional tem sido o tratamento padrão para correção do envelhecimento cervical. Alguns pacientes, especialmente homens, apresentam alterações evidentes no pescoço, com excesso de pele e/ou gordura na região cervical anterior, porém com pouca flacidez do rosto. O lifting cervical, associado à zetaplastia, é uma opção cirúrgica à ritidoplastia e trata o excesso de pele, gordura e bandas platismais. Pode ser realizado sob anestesia local, apresentando baixa morbidade, rápida recuperação e alto nível de satisfação.

Palavras-chave: *Ritidoplastia; Rejuvenescimento; Cervicoplastia; Pescoço*

INTRODUCTION

The appearance of the neck is one of the most accurate indicators of a person's biological age. With the aging process, this region loses its natural shape and contour due to the fat accumulation in the sub-segment, formation of platysma bands, laxity, and excess skin.[1]

Treatments aim to restore the neck to a youthful appearance, characterized by a well-defined mandibular border, visible thyroid cartilage, well-demarcated anterior border of the sternocleidomastoid muscle, and a cervical-mentonian angle between 105 and 120 degrees.[1] Non-surgical therapeutic options have gained popularity in the last decade. However, long-term benefits are limited and ineffective for treating excess cervical skin.[2]

Facial and neck lift (rhytidoplasty) with periauricular incision has been the most traditional surgical option for the treatment of aging of the lower third of the face and cervical region.[2] However, this is an invasive surgery with long recovery time and high cost. A growing number of patients, particularly men and

elderly population, have sagging and excess skin more evident in the neck than in the face, a condition called "turkey neck".[3]

Several surgical techniques of neck lift with direct skin excision have been described to treat this condition. The original technique consisted of performing a "T" excision (Figure 1) in the submental region, and it is an option for patients with slight skin and fat excess. For moderate to severe cases, zetaplasty neck lift achieves superior results and is an ideal choice. Zetaplasty increases the cervical-mentonian angle definition due to increased neck constriction and helps to improve the functional and aesthetic outcome of the resulting cervical scar.[4]

Direct excision neck lift and zetaplasty is suitable for patients with sagging neck, with or without submental fat, who do not wish to undergo traditional rhytidoplasty or who are contraindicated for this procedure. It can be performed under local anesthesia, presenting low surgical morbidity, fast recovery and high level of patient and surgeon satisfaction.[4]

SURGICAL TECHNIQUE

With the patient seated, the excess skin is pinched in the anterior neck (Figure 2A), and a vertical ellipse (spindle) is marked in the midline, with the apex in the submental sulcus and the inferior extension covering the entire redundant skin. The ellipse diameter is conservatively marked. Then the level of the new cervical-mentonian angle is marked with a horizontal line approximately at the level of the hyoid bone. If submental liposuction is required, the following limits are marked: lower border of mandible, superiorly; thyroid cartilage or suprasternal notch, inferiorly; anterior border of the sternocleidomastoid muscle, laterally (Figure 2B).

After local antisepsis, subcutaneous infiltration of a tumescent anesthetic solution with 0.9% saline, 1% lipid, and 1:100,000 epinephrine is performed. In individuals with excess cervical fat, preplatysmal fat liposuction (above the platysma) is performed using 3mm diameter cannulas coupled to a 20ml or 60 ml aspirator or syringe.

Subsequently, skin and subcutaneous tissue incisions are made to the platysma muscle. Excess preplatysmal skin/fat is removed "en bloc", exposing the platysma muscle (Figures 3A, B,

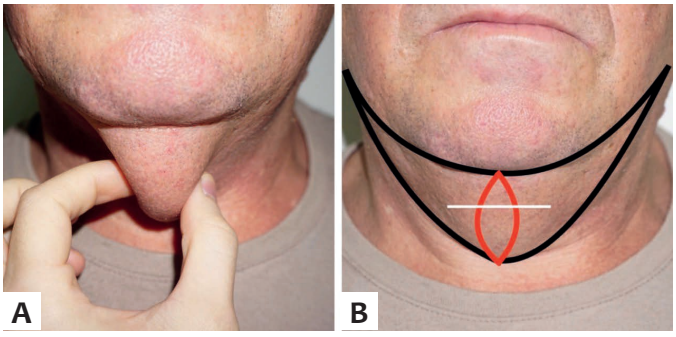

Figure 2: A. Pinching of excess skin in the anterior neck. **B.** Preoperative marking: vertical ellipse (red), new cervical-mentonian angle (white) and liposuction limits (Black)

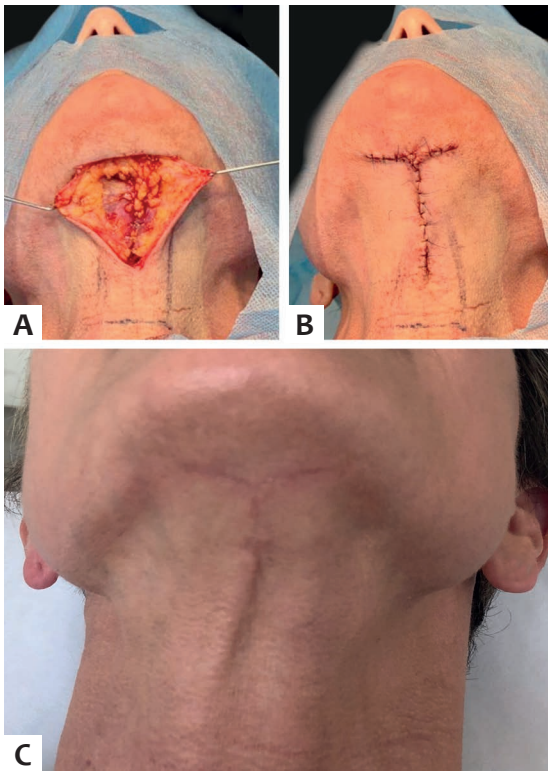

Figure 1: A. Platysma muscle exposure after direct skin excision **B.** Immediate postoperative of neck lift with "T" direct excision

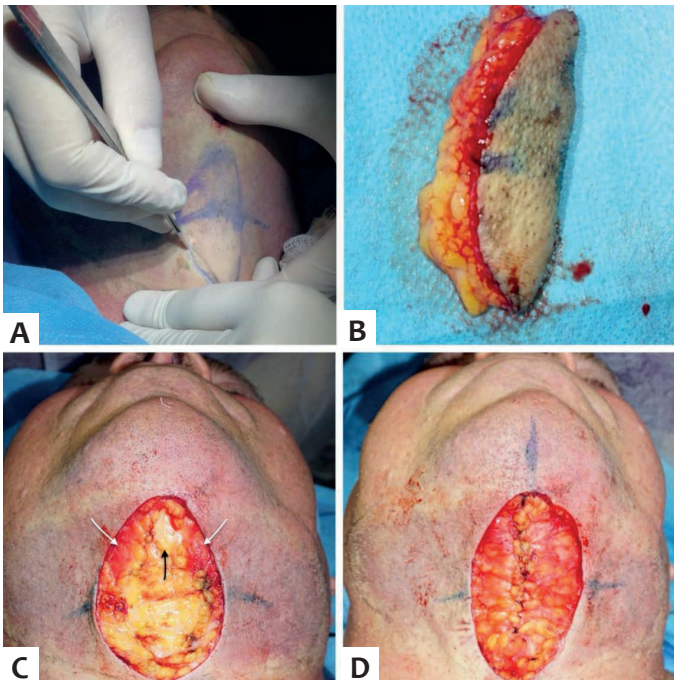

Figure 3: A. Incision to platysma muscle level. **B.** Specimen of pre-platysmal skin and fat removed en bloc. **C.** Surgical defect after excision. Note decussation of the anterior fibers of the platysma muscle (white arrows) and exposure of subplatysmal fat (black arrow). **D.** Platysmaplasty: continuous suture of the medial edges of the muscle with 3-0 mononylon thread

and C). Since liposuction only removes preplatysma fat, when there is extreme adipose tissue accumulation (morbidly obese), direct lipectomy of subplatysmal fat (located between the platysma and the anterior belly of the digastric muscles) may be performed. Removing it, if necessary, will help to improve the contour and shape of the neck, making it more concave. Excessive removal of subplatysmal fat should be avoided as it may cause an unsightly result called "snake neck". Most patients with cervical aging also have flaccidity and/or division of the medial borders of the platysma muscle. Thus, platysmaplasty is usually performed (Figure 3D). It consists of approaching and suturing the medial borders of the muscle with single or continuous stitches and 3-0 mononylon thread. It helps to reverse the platysma laxity and to provide a better tightening effect of the neck. Before border suturing, a platysma portion of the midline can be removed, allowing for a firmer approach.

After completion of the treatment of preplatysmal, platysmal and, if necessary, subplatismal fat, zetaplasty is performed. Initially, the sides of the neck should be detached in the subcutaneous plane. Then the surgical defect is temporarily closed in a vertical line. The marking of the cervical-mentonian angle is again verified and used as the central branch of zetaplasty. Two oblique lines of 2cm and 60 degrees are drawn (Figure 4A). Temporary sutures are removed, and incision and transposition of both flaps are made (Figure 4B).

Finally, the surgical wound is sutured with 4-0 polyglactin 910 intradermal sutures in the deep layers and continuous 5-0 mononylon suture in the superficial layer. The resulting zetaplasty is in the cervical line/ cervical-mentonian angle drawn preoperatively (Figure 4C).

A compressive dressing and bandage are placed to prevent bruising. The patient is reevaluated after 24 hours for dressing change, and the sutures are removed within seven to 10 days.

DISCUSSION

Significant improvement of the cervical region can already be observed in the immediate postoperative period. Three-month postoperative photography exhibits excellent results (Figures 5, 6, 7, and 8). The three assessed patients reported a

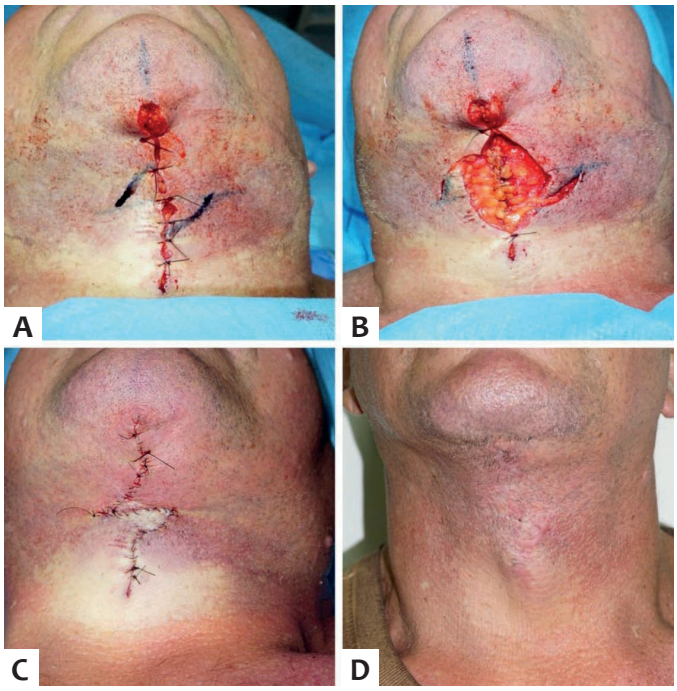

Figure 4: A. Temporary sutures with simple stitches and marking of the two branches of the zetaplasty 60 degrees from the cervical-mentonian angle/ cervical line. **B.** Zetaplasty incisions after removal of temporary sutures. **C.** Immediate postoperative: transposition of the branches of the zetaplasty and continuous suture. **D.** Three-month postoperative with barely visible "Z" scar

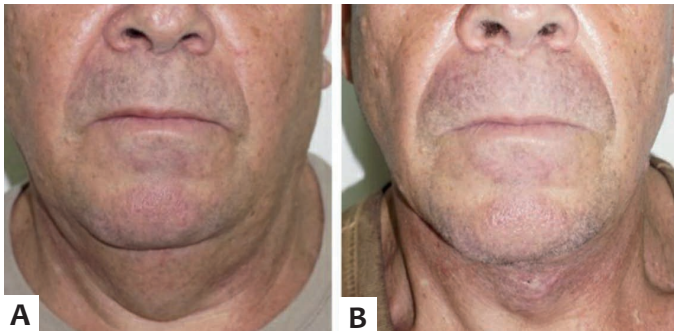

Figure 5: A. Preoperative, male, 53 years old, with excess skin and cervical fat, frontal view. **B.** Postoperative in three months after direct excision neck lift, zetaplasty, platysmaplasty and submental liposuction

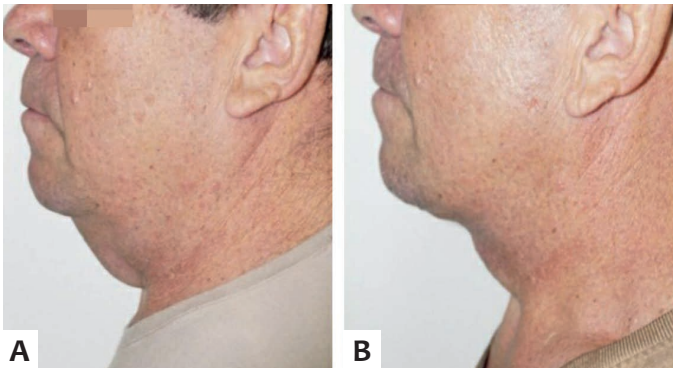

Figure 6: A. Pre and **B.** Postoperative in three months, left lateral view

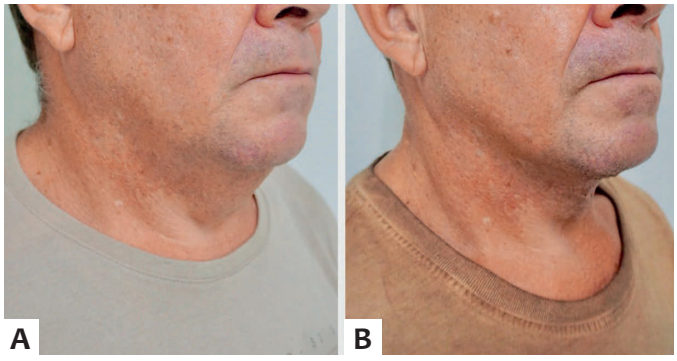

Figure 7: A. Pre and **B.** Postoperative in three months, right oblique view

high level of satisfaction with the results and believed that the aesthetic improvement of the neck exceeds the resulting scar.

Cronin and Biggs originally described the neck lift technique associated with zetaplasty in 1971 for the treatment of men with cervical sagging and "turkey neck" appearance. It has emerged as an alternative to traditional facial lift and can be indicated for any patient, including women, who have excess neck skin, apparent platysma bands, submental fat, and who is willing to accept isolated neck rejuvenation in exchange for a discreet scar in "Z".[3]

The negative aspects of the described technique include the presence of visible scar and little improvement of the jowl, as it only treats the neck. Scars in the anterior cervical region are usually well camouflaged. The upper portion (above the thyroid cartilage) is usually not seen in daily life unless the patient performs a neck extension movement, and the visible lower portion is usually little evident.[4] Hypertrophy may occur, and Miller reported this complication in 12 of 74 patients who underwent this procedure.[5] Erythema improves over time or with intense pulsed light sessions. The zetaplasty allows the resulting vertical scar to be less visible, more camouflaged, and with a lower risk of contracture. Other complications, such as expansive hematoma and necrosis, are rare.[4]

The technique can also be used concomitantly with rhytidoplasty in patients with severe excess cervical skin or with recurrence of sagging after surgery. Although not as comprehensive as a conventional face and neck lift, this technique presents surgery, anesthesia, recovery, and cost markedly lower. As with any surgical procedure, it is necessary to understand the benefits and disadvantages of this technique and to note that it does not apply to all patients but to a specific group of individuals.[3]

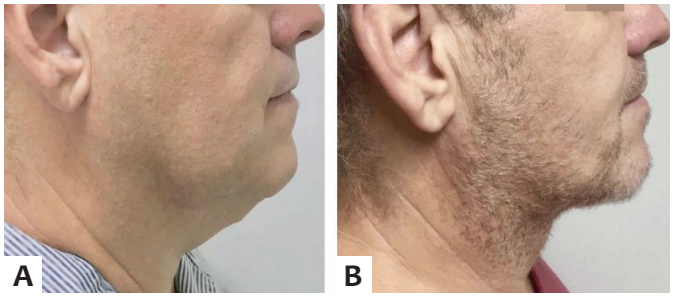

Figure 8: A. Pre and **B.** Postoperative in one month, male patient, 45 years old, with excess cervical skin, right lateral view

CONCLUSION

Neck lift with the direct excision technique and zetaplasty is a procedure that achieves a high level of patient and surgeon satisfaction and may be an alternative to conventional rhytidoplasty.

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