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Intense Pulsed Light: review of clinical indications

Luz intensa pulsada: revisão das indicações clínicas

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ABSTRACT

Intense pulsed light is a device that emits high intensity, polychromatic, non-coherent and not collimated light. IPL versatility allows combining parameters to treat a variety of skin vascular and melanocytic lesions, epilation and non ablative photorejuvenation. This article describes classic and innovative indications for intense pulsed light use based on medical literature.

Keywords: intense pulsed light therapy; skin diseases; cosmetic techniques

RESUMO

A luz intensa pulsada é um dispositivo que emite luz de alta intensidade, policromática, não coerente e não colimada. Sua versatilidade permite combinar parâmetros e tratar vários tipos de lesões cutâneas vasculares e melanocíticas, além da realização da epilação e do fotorrejuvenescimento não ablativo. Embasado na literatura médica, o presente artigo descreve indicações clássicas e inovadoras do uso da luz intensa pulsada.

Palavras-chave: *terapia de luz pulsada intensa; dermatopatias; técnicas cosméticas*

INTRODUCTION

Intense pulsed light (IPL) is a device that emits high-intensity, polychromatic, non-coherent and uncollimated light, whose beams have wavelengths ranging from 400nm to 1,200nm, and pulse duration of 2ms to 200ms. Current IPL devices consist of a chamber containing xenon gas, which is crossed by an electric current that releases pulses of energy in the form of luminous energy via a sapphire or quartz tip.[1] With the assistance of filters – also called cut offs – it is possible to choose the desired wavelength range: only wavelengths above those blocked by the used filter pass through and reach the cutaneous surface.[2] Wavelengths above 950nm should not be used for they have more affinity with water, entailing they contribute to heat the epidermis, which is not desirable.[3] More modern IPL devices emit a square wave with each shot. This wave is fragmented into multiple emission pulses, allowing the energy to be efficiently delivered to the target chromophore, avoiding damage to adjacent structures.[1]

The mechanism of action of IPL is based on the capture of energy by certain target tissues – the chromophores – through the principle of selective photothermolysis. The three main human skin chromophores are hemoglobin, melanin, and water;

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each of which has a specific light absorption peak.[2]

Thus, the versatility of IPL allows the combination of parameters, aiming at treating the several vascular and melanocytic skin lesions, as well as perform epilation and photorejuvenation treatments, with a high skin coverage rate due to the large size of the spot.[2] This is a useful alternative when patients are not willing to tolerate the adverse effects of other procedures that require longer recovery time. Thus, IPL has an excellent cost / benefit ratio.

METHODOLOGY

The literature search was carried out using the expression *intense pulsed light,* on major databases, including Pubmed, Medline-Cochrane and Lilacs-Scielo. The authors of the present article selected 43 papers based on their titles and abstracts, and only articles relating to human studies were included.

Indications

Vascular lesions

Intense pulsed light based treatment of vascular lesions has the advantage of not causing purpura after the procedure, as compared to pulsed dye laser. This is due to the fact that the laser's very short pulse duration and narrow wavelength range are absorbed by the more superficial portions of the vessels, which rupture and lead to purpura. On the other hand, the spectrum of wavelengths emitted by the IPL allows to heat the vessel completely, and coagulation takes place with less purpura.[4] Immediately after the application of IPL, a blue-grayish coloration of the vessels is expected in the treated area.[3] Intense pulse light heats the vessel's inner side causing their coagulation, with subsequent replacement by fibrous material. In addition, since IPL is polychromatic, it can target the oxyhemoglobin present in lesions red in color, the deoxygenated hemoglobin present in bluish lesions, and the methaehemoglobin, which in normal individuals represents 1%-2% of the total hemoglobin. These hemoglobins' peaks are 418nm, 542nm and 577nm, respectively.[2] Longer wavelengths (515nm to 600nm) allow that deeper vessels be reached.[1]

The ideal clinical response is vasoconstriction associated with mild erythema and/or edema. The vessel's rupture is not desired, since this leads to hemosiderin deposition and possible cutaneous hyperpigmentation.

The pulse duration is variable according to the vessel's diameter, and should be shorter than the thermal relaxation time in order to avoid damage to adjacent tissues.[2]

Rosacea

It is a chronic condition, with periods of exacerbation and remission, being prompted by a great number of triggers. Therapeutic options include topical and systemic treatments, and the use of lasers and other light sources, such as IPL. One of the advantages of IPL is that it allows that the parameters be flexibilized, meaning that it is possible to act in superficial or deep vessels according to the chosen parameters and, in addition, to focus on the caliber of the vessels that will be treated. Another advantage of IPL is its tip's size: for being larger than the laser devices' tips, it allows the treatment of the area with fewer shots, which results in greater swiftness in the application.[5]

Intense pulsed light is the treatment of choice for the erythematous-telangiectasic stage, for it acts on the vascular hyperreactivity to which rosacea is related. The treatment allows reduction of the blood flow, superficial telangiectasias and erythema intensity. Response to IPL is effective, and because of rosacea's chronicity, maintenance is suggested. The condition's adverse effects profiles, which are usually subtle, also favors IPL based treatment. The combination of IPL with the topical and systemic treatments available is interesting for it allows the synergism of the therapeutic effects, optimizing outcomes.[5]

Telangiectasias

Telangiectasias result from the dilatation of capillary micro vessels, most commonly from post-capillary venules. Intense pulse light, as well as lasers, can be used for the management of this condition. The IPL's mechanism of action in the treatment of telangiectasias is based on the photothermolysis – or thermal damage – the vessels, inducing intravascular coagulation.[4] Although pulsed dye laser has shown results that are superior to those of IPL, the absence of purpuric lesions after IPL causes many patients to choose this therapeutic modality.[6]

Intense pulsed light is very effective in telangiectasias, which, however, when located in the nasal alae, are more resistant to treatment and usually recurrent.

In general, the reduction in the spot size requires increased energy (higher fluence) and vice versa.

Poikiloderma of Civatte

It is clinically characterized by the triad atrophy, telangiectasias and hyper and hypopigmented reticulated pigmentation. Intense pulsed light is the treatment of choice for it affects both pigment and vessels, and promotes collagen stimulation.

In 2012, a study by Scattone et al. evaluated 14 patients who underwent 3 monthly sessions with IPL.7 Two passes were performed in each session: the first with a 570nm filter and the second with a 540nm filter. Clinical results were positive in 13 (92.9%) patients, and the histological analysis demonstrated thickening of the collagen fibers, which were more compact in 12 patients. In addition, basal layer melanin redistribution occurred in 85.7% of the cases, which was consistent with the clinical improvement observed in the pigmentary component. Regarding the vascular component, the histological analysis showed a reduction in vessel diameter in only 35.7% of the cases, however there was superior clinical improvement. The authors' hypothesis for the improvement of the vascular component is that the increase in the amount of the collagen fibers adjacent to the vessels made them less visible.[7]

Stretch marks

Striae occur due to changes in the reticular collagen after rapid cutaneous stretching, caused by physical or hormonal causes. Many treatments can be used, among them the topical methods, such as retinoids that result in the removal of more superficial layers of the skin, in addition to stimulating neocol-

lagenesis, and the use of lasers and light sources.[8] Intense pulsed light can act in the initial erythematous-purpuric phase, when there is dilation of dermal capillaries, in addition to thinning and retraction of elastic fibers and collagen. Through dermal heating, IPL stimulates the fibroblasts to produce collagen fibers and reorganize them in the stroma.[8] In 2013, a study by Al-Dhalimi and Abo Nasyria compared the use of IPL with a 590nm and a 650nm filter. The 590nm filter yielded better results in the treatment of stretch marks, however it also led to a greater number of adverse effects.[8] Other studies also show that IPL can reduce stretch marks in number and length.[9]

Hypertrophic scars and keloids

They occur in a percentage that varies from 30% to 90% of the patients and can lead to physical, psychological and social damage, with an important impact on the quality of life.[10]

The mechanism of action IPL on these conditions is not fully understood, nevertheless it is likely to target vascular proliferation, which is crucial for the excessive proliferation of collagen and its resulting effect on pigmentation.[11]

The longer wavelengths of the IPL spectrum (close to 1,200nm), have affinity with water, stimulating dermal neocollagenesis. Meanwhile, wavelengths ranging from 400nm to 600nm, heat dermal collagen fibers and promote their contraction, leading to an improvement in the texture of the scars. Finally, the IPL's effect on the inhibition of vasculature yields a reduction in the lesion's thickness and elevation, inhibiting its growth.[12]

Erol et al. prospectively evaluated the safety and efficacy of IPL in hypertrophic scars in 109 patients whose lesions were secondary to trauma, surgery, burn or acne.[11] The patients received an average of 8 sessions in intervals ranging from 2 to 4 weeks. The treatment was evaluated using digital photographs, regarding the improvement in the clinical appearance, the decrease in height, erythema and the firmness. The majority of patients (92.5%) had clinical improvement of the parameters evaluated: the outcome was excellent in 31.2% of patients, good in 25.7% and minimum in 9.1%. The study also included a group in which IPL was used to prevent hypertrophic scarring after surgery in 17 patients predisposed to hypertrophic scar formation. The sessions occurred between 3 and 8 weeks after a aesthetic surgery (abdominoplasty and mammary reduction), while the surgical scar was still in the active growth phase. Although 13 patients did not complete the treatment, the improvement was clearly visible at the moment of the measurement, with 65% having experienced good to excellent improvement in the clinical appearance. The study proposes the use of IPL as a preventive treatment in patients with a tendency to hypertrophic and keloid scarring.

In 2014, a study by Meymand evaluated the use of IPL associated with intralesional corticosteroids in the treatment of 86 patients with hypertrophic and keloid scars. Eight sessions were carried out with intervals of 3 weeks. According to the study, the association of treatments accelerated the results without presenting significant adverse effects, with the degree of clinical improvement considered excellent in 73% of the cases.[13]

Intense pulsed light has also been used in combination with "microbotox" and corticoid in hypertrophic and keloid scars – the so called triple therapy.[14] In the "microbotox", the botulinum toxin injection is very diluted, and is applied intradermally or subdermally. The triple therapy combines IPL (540nm filter) (which reduces erythema and vascularization), intralesional triamcinolone (which flattens the lesion), and "microbotox" (to induce apoptosis, as well as to reduce the binding tension of actin and myosin between the lesion's edges, thus reducing recurrence. Initially, the IPL is applied with a 540nm filter, then the microbotox is injected into the keloid and the perilesional skin, and finally the triamcinolone is injected up until the point at which the keloid whitens. The toxin would have a synergistic effect with triamcinolone, reducing the dose of corticoid and the recurrence of keloid.[15]

Angiokeratomas

Angiokeratomas are characterized by violaceous papules, resulting from ectasic and congested vessels in the superficial dermis, with hyperkeratosis of the suprajacent epidermis. Treatment with ablative lasers is described as a therapeutic option, nonetheless the risk of unaesthetic scar should be considered. Intense pulsed light and long pulse Nd:YAG laser are the most indicated systems due to the greater penetration of light into the lesion. The use of IPL presents a variable response, since the keratotic component and the greater depth of the vessels hamper the action of light.

In 2013, Ichikawa et al. reported the use of IPL with 500nm to 635nm filters, which lengths were more closely related to oxyhemoglobin for the treatment of Fordyce angiokeratomas. Four sessions were performed with intervals of two or three weeks between them. There was a partial reduction of the lesions.[16]

Hemangioma

Intense pulsed light is considered a safe and effective option for the treatment of hemangiomas. Its tip, which is larger in size than those of the lasers, allows the procedure to be performed in a shorter time and makes it more tolerable, which is extremely important for pediatric patients. In addition, IPL penetrates deeper than pulsed dye laser by changing the filters used.[17]

Intense pulsed light is more effective in superficial lesions with thin and medium caliber vessels. Hemangiomas with deep dermal or subcutaneous involvement may show whitening of the superficial portion.[17] Old lesions may present hypertrophy of the structures and formation of nodules on the lesion.

A 2011 study by Caucanas et al. presented a series of 14 cases of infantile hemangiomas treated with IPL filters 550 and 590nm during the proliferative phase. Patients had an average of 4.8 months of age and underwent on average 3 IPL sessions. All patients presented regression of the lesion 1 month after the last session. Only 1 had adverse effects: bleeding, ulceration and crusting after the first 2 sessions.[18]

Port wine stain

The port wine stain is a vascular malformation resulting from an increase in the number and diameter of blood vessels, being present since birth. The lesion is initially reddish and flat, however nodosities emerge over the years, due to tissue hypertrophy. Pulsed dye laser is the treatment of choice, nevertheless IPL and Nd:YAG laser are therapeutic options.[17] Intense pulsed light is an alternative when lasers are not available, and when the patient desires to undergo a treatment that does not result in purpura in the post-procedure.[19]

Due to the IPL's variety of pulse durations and fluences, it is possible to reach vessels of different depths and diameters. Dermoscopic examination shows a change in the coloration of vessels from reddish to bluish, immediately after the application of IPL.[12]

Grillo et al. evaluated the histological effects of IPL on port wine stain type capillary malformations, concluding that those red in color present the best results with the treatment. The purpuric ones – especially in high phototypes – should undergo intense epidermal cooling during the treatment and present high risk of burns. Those pink in color are the most resistant, meaning that other therapeutic methods should be tried.[20]

Ochre dermatitis

It involves a pigmentary alteration secondary to venous stasis and an increase in intravascular pressure, in which there is extravasation of erythrocytes and deposition of hemosiderin and melanocytes in the skin. It yields good results to the treatment with IPL, however literature data are scarce. In 2008, Pimentel et al. published a case report using IPL with 570nm filter in a patient with ocher dermatitis. Three monthly sessions were conducted with excellent outcomes. The authors report that lesions initially became darkened, with subsequent whitening.[21]

Pyogenic granuloma

The lesion clinically corresponds to a red-purplish papule with a peripheral desquamation ring. The treatments described include surgical excision, chemical cauterization, cryotherapy, electrocoagulation and laser therapy. The use of IPL in the management of these lesions is described by Paradela et al. in 2007 and later on by Scalvenzi et al. in 2013. Paradela et al. describe the treatment of a pyogenic granuloma that developed with adjacent lesions and was previously removed with CO_2 laser therapy. The treatment was performed with 2 sessions of IPL with 570nm filter, resulting in the total regression of the lesion. On the other hand, Scalvenzi et al. emphasized the benefit of non-surgical therapies for recurrent pyogenic granuloma lesions – in special IPL – since it targets dermal hemoglobin, reducing hypervascularization, but keeping the epidermis untouched.[22,23]

Melanocytic lesions

Several benign melanocytic lesions can be treated with IPL. The best outcomes are observed in those with more superficial pigment.[24]

The treatment of hyperchromic lesions is effected via the rapid differentiation of keratinocytes, induced by the IPL's photothermal phenomenon, which promotes the removal of melanosomes with necrotic keratinocytes through the cutaneous surface, when it is possible to see micro crusts eliminated on the days following the treatment.[1,2] In general 3 to 6 sessions, with intervals of 3 to 4 weeks, are necessary. The expected immediate result of IPL application is the darkening of the treated melanoses, with formation of crusts within 24 to 48 hours, which will be eliminated during the first 7 subsequent days.[2] Melanocytic lesions in extrafacial areas treated with IPL may become topped by micro crusts during a period ranging from 15 to 20 days.

Solar Melanoses

Intense pulsed light has the advantage of allowing localized treatment, reducing the risk of complications in the extrafacial areas, especially in the dorsum of the hands. The lesions with the best therapeutic response are those with greater amount of melanin pigment and more intense color. In 2015, Tanaka et al. evaluated the use of 500nm and 635nm IPL in the treatment of face, neck and hand melanoses of 40 Japanese patients (phototypes III and V), with a single IPL session using a well located tip. Satisfaction with the outcomes was observed in 90% of the patients. Clinical analysis with photographs revealed improvement of lesions in all treated patients.[25]

Ephelides

Intense pulsed light is indicated, however most patients tend to experience recurrence of the lesions.[24] Filters between 500nm and 600nm are the most indicated.[17] Photoprotection is extremely important for the maintenance of the results obtained with IPL.

***Café-au-lait* spots**

Café-au-lait spots are well-delimited hyperpigmented lesions of epidermal origin that can measure from 1cm to 30cm in diameter and are often located in the trunk. Intense pulsed light is an alternative that requires many sessions, and whitening may be only partial. The best choice is Q-switched lasers, however responses are varied, and there may be recurrence in half of the cases.

Nevus of Ota

Q-switched lasers are the most indicated.[17] Due to the fact that melanin pigment is located in the dermis, deeper wavelengths that reach deep planes without epidermal damage are necessary. Intense pulsed light has a variable response, with incomplete whitening and recurrence being common. Residual hypochromia may occur in response to treatment with IPL, and represents a negative outcome.

Infraorbital hyperpigmentation (dark circles)

Intense pulsed light may be beneficial in dark circles with exogenous or melanin pigmentary component – hyperpigmentation induced by penicillamine and bimatoprost – and also with vascular component. Outcomes are considerably variable, and patients with predominance of the vascular component respond

better. Dark circles of hereditary origin present a partial or very mild response to IPL. Higher phototypes require the use of longer wavelength filters, lower fluences, and longer pulse durations, for epidermal protection. In addition, the use of smaller tips facilitates application in this region, also reaching greater depths. Patients need an average of 3 sessions to achieve results. Erythema occurs after the procedure and lasts from some hours to 3 days. In addition, crust formation may occur in hyperchromic areas. A 10% overlap between passes is recommended aimed at avoiding untreated areas.[26]

Post-inflammatory hyperpigmentation (PIH)

Intense pulsed light is most indicated in epidermal PIH. In patients with high phototypes it is necessary to avoid burns and secondary hypochromia. In dermal PIH, treatments are limited and Q-switched lasers are the best option.

Melasma

The treatment of melasma with IPL is controversial, with variable outcomes and risk of exacerbation after application. Skin preparation with whitening agents and performing IPL with long pulse duration and low energy are necessary to reduce this risk.

Becker's nevus

Intense pulse light can be used initially to remove hairs and subsequently to treat the pigment component.[12]

Seborrheic keratosis

It can be treated with IPL, which acts on the melanin component. Dermoscopic evaluation immediately after IPL changes in the lesion's color from brown to gray.[12]

Epilation

Intense pulse light is aimed at reaching and thermally destructing the melanin present in the hairs' roots, which are located in the deep dermis. In addition, epidermal melanin should be spared to avoid damage to the skin's surface.[1] In order for this to occur, pulse duration should be longer than the epidermis' thermal relaxation time (3ms to 10ms) and approximately similar to that of the hair follicle (30ms to 100ms). Hairs in the anagen phase are the most responsive to IPL-based epilation, as it is at this stage that they contain the greatest amount of melanin.[2] Thus, darker and larger diameter hairs – rather than fair and thin hairs – tend to absorb more energy and respond better to IPL-based photoepilation.[2] The permanent removal of the hair occurs when the capillary bulb cells and those located close to the hair erecting muscle's insertion are destroyed.[1] The ideal wavelength to selectively act on the follicles' dense melanin deposits without causing epidermal damage ranges from 590nm to 900nm.[1]

It should not be performed on phototypes higher than III or in tanned patients due to the risk of epidermal damage.[27] It is important that an adequate level of energy be used in order to prevent complications such as hyper or hypopigmentation and paradoxical hypertrichosis.[2,3] The risk of paradoxical hypertrichosis should be quoted in the Term of Consent. It occurs by activation of inactive follicles in areas located near to the treated area due to the use of subtherapeutic doses.[3]

Non-ablative photorejuvenation

Intense pulsed light has proven effective in photorejuvenation, acting not only on the vascular and pigmentary components, but also influencing neocollagenesis, improving the cutaneous texture.[28,29] The principle of the use of IPL for this purpose is based on the theory that heating dermal collagen fibers with high intensity energy would cause their contraction, reducing skin looseness. In addition, heat stimulates fibroblasts that synthesize extracellular matrix proteins.[1] The final pathway of this stimulus is the production of collagen type I and type III, and elastin.[2]

Intense pulse light can be used for rejuvenation in extra facial areas, such as the hands. A study by Cignachi et al. compared the use of 2,940nm fractional laser with isolated non-ablative 1,340nm laser or associated with IPL with 540nm filter. The study observed that the group treated with the combination of the 1,340nm tip and IPL achieved the best results in terms of overall rejuvenation.30 Another study compared the use of isolated long pulse 1,064nm Nd:YAG with the same laser associated with IPL with 580nm filter (also for rejuvenating the dorsum of the hands) concluding that the combination treatment is more effective.[31]

Longer IPL wavelengths – above 515nm – have more affinity with water and for this reason can activate the dermis more effectively for the stimulation of collagen. On the other hand, shorter wavelengths have a greater affinity for melanin and hemoglobin, which allows improving the dyschromias and telangiectasias resulting from the aging process. Thus, it can be seen that IPL can act on the various elements of aging with minimal adverse effects.[1]

In IPL-based extrafacial rejuvenation, some of the recommendations aimed at achieving positive results and avoiding complications are: to consider risks, weigh parameters, opt for a less aggressive treatment and a greater number of sessions. The fluence in extrafacial treatments should be 10% lower than that used in the face.

With IPL, therefore, it is possible to treat all the visible elements of aging (fine wrinkles, sagging, telangiectasia, irregular pigmentation) with a low rate of adverse effects and rapid recovery.

Other Uses

Acne

Two mechanisms of action of IPL promote improvement of active acne: the first is the photodynamic effect caused by the visible light's and UV's spectrum, which are absorbed by the porphyrins produced by the *Propinonibacterium acnes*, culminating with the formation of oxygen free radicals responsible for the bactericidal effect. The second mechanism is based on the selective photothermolysis of blood vessels that nourish the sebaceous gland: by reducing the blood flow, the gland's rate of

secretion decreases.[3,32]

Although it is not the first line treatment of mild to moderate inflammatory acne, IPL is an option in patients who present contraindications to the available treatments and can be associated with topical treatments.[1]

A 2014 study by El-Latif et al. compared the treatment of 50 patients bearing mild to moderate inflammatory acne using 5% benzoyl peroxide at night daily versus the application of 530nm IPL in weekly sessions for five weeks. At the end of the study, both groups achieved similar results, with a reduction of inflammatory lesions of 61.56% in the IPL group and of 69.4% in the benzoyl peroxide group (the difference was not statistically significant).[32]

Intense pulsed light has also been cited as an option in the treatment of acne scars, especially if erythematous and hypertrophic, with an effect similar to that of pulsed dye laser, with the advantage of the absence of purpura and a larger treated area. Notwithstanding, it is considered more painful.[33]

Photodynamic Therapy

Intense pulsed light can be used associated with 5-δ-aminolevulinic acid (ALA) for the treatment of photoaging associated with non-hyperkeratotic actinic keratoses and acne. There is an improvement in fine wrinkles, texture, telangiectasias and solar melanoses, possibly due to the photosensitizer's strengthening effect on the IPL's photothermolysis capacity. Its use has also been described by Kalil et al. in the treatment of recalcitrant periungual viral warts. The 560nm filter was used, and IPL was proven to destroy the proliferative vascular component, while the photosensitizing active principle allows it to reach deeper planes, leading to more effectiveness in the treatment.[34] Intense pulsed light is adequate for the activation of ALA, since the highest absorption peaks include 410nm, 504nm, 538nm, 576nm and 630nm, all within the IPL's spectrum.[3]

Drug delivery

In IPL, the transdermal delivery of drugs occurs through the photothermal effect, which increases the permeability of the stratum corneum without affecting the viability of the skin. Intense pulsed light facilitates the permeation of macromolecules and formulations, such as nanoencapsulated and liposomes, with modified permeation systems. Based on the type of damage caused – in special photothermal damage – there is a decrease in the skin's barrier function, leading to increased penetration of the active principles for a short period of time (15 to 30 minutes).[35] Vehicles used to optimize drug delivery must be fluid, not contain propylene glycol, and contain chemical permeators.[35]

Sarcoidosis

Although there is absence of randomized clinical trials on IPL and sarcoidosis in the literature, many published articles report lasers and other light systems, including IPL, as therapeutic alternatives in cases resistant to other treatments. The mechanism of action is probably based on the destruction of the lesions' nourishing vessels, which deliver the proinflammatory cytokines to the skin. This anti-inflammatory and anti-proliferative action ends up destroying the granuloma in formation.1 In 2012, Rodende et al. describes the treatment of lupus pernio – the most common form of presentation of cutaneous sarcoidosis – with IPL associated with 1,064nm Nd:YAG laser with an excellent response.[36]

Onychomycosis

Although not considered the first choice, the use of lasers and other light sources for the treatment of onychomycosis has been shown to be effective for this purpose. A 2015 study by Vieira Machado Vila et al. evaluated the fungicidal effect of 1,064nm Nd:YAG laser and 420nm IPL for Candida and Fusarium, demonstrating a reduction in fungal cell viability with the two proposed treatments.[37]

Pilonidal cyst

It is a foreign body reaction with chronic inflammation, which occurs most commonly in the sacrococcygeal region.

It is believed that hair fragments in the cyst area create a granulomatous foreign body reaction. Surgical intervention remains the treatment of choice, however this is an invasive method with a risk of recurrence ranging from 30% to 40%.[38] The use of IPL in recurrences or in patients already operated to prevent recurrences has been receiving attention.[38] The mechanism of action of IPL consists of reducing hairs in the area adjacent to the cyst in order to prevent recurrences. Shafigh et al. treated 30 patients with 6 sessions of 590nm IPL in intervals of 4 to 6 weeks, up until the removal of the hairs. These patients were reassessed 2.5 years after, with recurrence rates of 13.3%.[38]

In addition, the IPL's anti-inflammatory mechanism also acts to prevent recurrences.[12]

Hidradenitis suppurativa

Suppurative hidradenitis has an etiopathogenesis similar to that of active acne, which is why IPL is effective in treating this dermatosis. It is speculated that the mechanism of action is linked to the antibacterial and anti-inflammatory effects, and selective vascular photothermolysis, in addition to the destruction of the follicle with resulting epilation.[39,40] Intense pulsed light can be used in isolation or associated with photodynamic therapy.

Other uses already described include: pigmented actinic lichen planus, recalcitrant warts, atopic dermatitis, and plaque and ungual psoriases.[41]

Final considerations

Patient selection is critical to successful treatment. Patients who are tanned, have high phototypes and are not willing to avoid exposure to the sunlight are not good candidates for treatment with IPL.[1,20] Patients should be advised to avoid exposure to the sun for up to 8 weeks in the treated area.[3]

Criteria that contraindicate undergoing IPL are: pregnancy, use of systemic retinoids and drugs fotossensibilizantes.[3] Patients with herpes simplex history in the region to be treated should receive prophylaxis antiviral.[3]

The cooling of the epidermis is extremely important as it increases the effectiveness of the treatment, and reduces complications and discomfort during the procedure. Topical anesthetics can be used.[3] Proper eye protection is of utmost importance for the iris has a high concentration of melanin, which absorbs the IPL's energy, possibly resulting in iritis with permanent eye damage. External or intraocular eye shields can be used.[3] Any pigments and/or makeup present on the skin surface must be carefully removed in order to prevent burns.

The correct coupling of the spot across the entire cutaneous surface is also important to prevent burns. The application should be performed carefully, with minimum overlapping of the spot, aimed at preventing that any area is left untreated.

It is crucial to observe the immediate or short-term tissue reactions to the application, which are a reliable and safe guide to the appropriate treatment. This is much more important than following guidelines or "recipes", and crucial for the setting of parameters, for both increasing the effectiveness of the treatment and avoiding side effects.[42,43]

It is important to bear in mind that extrafacial areas have few pilosebaceous follicles as compared to the face; therefore healing in the first is not as fast as it is in the latter. This factor should be remembered when the parameters are being set.[6]

The patients must sign a Term of Informed Consent contemplating possible adverse effects, including hypo- or hyperpigmentation, atrophy, blisters, hypertrophic scars and keloids. They should also be properly photographed.[3,27]

CONCLUSION

Intense pulsed light is already part of the therapeutic armamentarium of dermatologist physicians for a variety of lesions, due to its ability to act in different chromophores. Its versatility and cost effectiveness are attractive both from the patient's the dermatologist physician's points of view. The combination of technologies using IPL, lasers and chemical peels can and should be kept in mind, according to the therapeutic objective. The combination of techniques results in greater convenience, with fewer sessions required.

Dermatologist physicians should deepen their expertise in IPL for optimizing the their application techniques. ●

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Androgenetic alopecia treatment: associating 1550nm erbium-glass laser with drug injections of active principles

Tratamento da alopecia androgenética: associação de laser Erbium Glass 1550nm e infiltração de ativos

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ABSTRACT

Introduction*:* Introduction: Androgenetic alopecia is the most common type of hair loss in men and women. Nowadays, medication based treatments are the most frequently used nevertheless they yield poor results. More recently, the use of lasers has been proposed to treat this condition. At the same time, the infiltration of medications in the scalp has also been growing as a therapeutic option, although there are few scientific studies on this treatment modality.

Objective*:* To evaluate the results of using 1,550nm Erbium-Glass laser associated with the injection of active principles (minoxidil, finasteride, growth factors and a vitamin complex) for the treatment of male and female androgenetic alopecia.

Methods: A retrospective study was carried out with patients with androgenetic alopecia diagnosis, who underwent monthly sessions of the proposed combination therapy. The results were evaluated by means of comparative photographs taken before and after the treatment period and the assessment of the patients' opinion.

Results*:* Sixty-two patients were treated with 3 to 14 sessions; 48.39% of patients had mild improvement, and 46.77% had significant improvement. The vast majority (96.77%) was satisfied with the treatment. The patients who were very satisfied with the outcomes underwent a greater number of sessions (more than six, on average).

Conclusions: The association of 1,550nm Erbium-Glass laser therapy with the injection of active principles in the scalp is an effective and safe option for the treatment of androgenetic alopecia.

Keywords: alopecia; lasers; therapeutics

RESUMO

Introdução: *A alopecia androgenética é a forma mais comum de perda de cabelos em homens e mulheres. As opções de tratamento com medicações são as mais utilizadas atualmente, embora tragam poucos resultados. Recentemente o uso do laser tem sido sugerido para tratar essa entidade. A infiltração de medicação no couro cabeludo também vem crescendo como opção terapêutica, apesar de existirem poucos trabalhos científicos sobre esse tratamento.*

Objetivo: *Avaliar o resultado do uso do laser de Erbium Glass 1550nm associado à infiltração de ativos (minoxidil, finasterida, fatores de crescimento e complexo vitamínico) para tratamento da alopecia androgenética masculina e feminina.*

Métodos: *Estudo retrospectivo de pacientes com esse diagnóstico, submetidos a sessões mensais da associação terapêutica proposta. Os resultados foram avaliados por meio de fotografias comparativas realizadas antes e após o período de tratamento e de pesquisa de opinião dos pacientes.*

Resultados: *Foram tratados 62 pacientes, com sessões, cujo número variou de três a 14; 48,39% dos pacientes apresentaram melhora discreta, e 46,77% melhora importante. A maioria (96,77%) ficou satisfeita com o tratamento. Os pacientes muito satisfeitos realizaram maior número de sessões, em média mais de seis.*

Conclusões: *A associação de laserterapia com Erbium Glass 1550nm e infiltração de ativos no couro cabeludo é opção eficaz e segura para o tratamento da alopecia androgenética.*

Palavras-chave: *alopecia; lasers; terapêutica*

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INTRODUCTION

Androgenetic alopecia is the most common type of hair loss in men and women, affecting 50% of men at 50 years of age and 50% of women at 80 years of age.[1,2] It is a genetic condition caused by the action of circulating androgens. In addition, its multifactorial etiopathogenesis also involves hormonal factors. The clinical picture of hair loss is the result of the genetically determined distribution of hair follicles with specific sensitivity to the androgens and their own sensitized end-receptors.[3]

The involvement of the follicles leads to a reduction in follicular epithelial proliferation and progressive miniaturization of the scalp's terminal hairs.[2] The terminal follicles are reduced in size and diameter and, have their cycles progressively shortened over time, entailing a reduction in the growth period of the anagen hairs.[4] The result is a reduction in hair density and miniaturization, predominantly in the frontolateral and vertex regions in men, and along the frontoparietal region, with diffuse pattern, in women.[5]

The only drugs currently approved by the FDA for treatment of androgenetic alopecia are finasteride and minoxidil. However, due to the fact it is a very common condition, several types of treatment have been sought, with only a few leading to satisfactory results. Laser therapy has become an alternative treatment both to prevent hair loss and to stimulate its growth in male and female androgenetic alopecia.[6]

Two types of devices already have FDA clearance for this purpose, due to the minimal level of associated risks – namely the Hair Max Laser Comb (Lexington Int. LLT, Boca Raton, FL, USA) and the TOPHAT 655 (Aspira Science Inc., Boca Raton, FL, USA), both with 655nm wavelength.[7]

The exact mechanism of this action on the hair is not well defined. Possibly, there is activation of the telogen hairs and reversion into the anagen phase, increasing the cycle's duration and the growth rate during this phase, preventing its advancement into the regression stage (catagen phase).[8]

Kim et al. evaluated the effects of fractional 1,550nm laser on male androgenetic alopecia and observed increased hair density and growth. It is known that fractional photothermolysis caused by this wavelength stimulates collagen regeneration. In that study, the histological analysis has evidenced the conversion of follicles from the telogen into the anagen phase.[9]

Another treatment option for androgenetic alopecia is the application of intradermal injections into the scalp aimed at stimulating hair growth. Although there are few scientific studies on this method, this type of treatment has been growing as a therapeutic option.[10-12]

The most studied topical substances aimed at stimulating hair follicles, such as minoxidil, finasteride, dutasteride, biotin, vitamins and organic silicon, have also been employed for intradermal use.

The present study's objective was to evaluate the association of laser therapy with injection of active principles in the scalp using mesotherapy, aimed at treating androgenetic alopecia. In light of the positive results obtained both with laser treatment and mesotherapy in androgenetic alopecia, it was hypothesized that the association of these techniques could lead to optimized results. The dermal stimulus and fractionation columns created by the laser's action might strengthen the absorption and action of the injected active principles. In this manner, the authors of the present study sought a new and effective therapeutic option for androgenetic alopecia.

METHODS

A retrospective observational study was carried out including male and female patients older than 18, with clinical diagnosis of androgenetic alopecia, who had undergone at least three sessions of 1,550nm Erbium:Glass (Fraxel Laser Dual®, Solta Medical, Hayward, CA, USA) laser therapy associated to the injection of active principles (minoxidil, finasteride, growth factors and vitamin complex), from January 2015 to July 2016, at a private practice in the city of São José do Rio Preto, São Paulo State, Brazil. The sessions were performed at intervals of one month. Patients with other types of alopecia were excluded from the study. Women at childbearing age underwent oral hormonal contraceptive use prior to the beginning of the treatment due to the presence of finasteride among the injection's active principles. The study was approved by the Research Ethics Committee of the Faculdade de Medicina de São José do Rio Preto (SP), Brazil.

The patients initially underwent injectable anesthesia on the scalp with 2% lidocaine with vasoconstrictor by means of anesthetic points in the region to be treated, in the frontoparietal direction. Subsequently, 1,550nm Erbium:Glass laser was applied with the following settings: energy = 6mj, treatment level = 3, and six passes (three in the vertical direction, followed by three in the horizontal direction). Next, intradermal injection with the following active principles was performed: 1ml 0.05% finasteride, 2ml 0.5% minoxidil, 2 ml of a vitamin combination (25mg L-methionine, 50mg L-taurine, 10mg L-proline, 10mg biotin, 5mg vitamin B, 10mg vitamin B3, 10mg vitamin B6, 10mg D-panthenol), and 2ml of growth factors (1% copper peptide, 1% IGF, 1% VEGF, 40mg D-panthenol and 10mg biotin). Patients were instructed to wash the scalp two hours after the intradermal injections.

The assessment of the results was based on photographs taken before and after the treatment, and analysis performed by a dermatologist unrelated to the study, who classified the comparison between the images in: *absence of improvement*, *slight improvement* and *significant improvement* of androgenetic alopecia. The patients' satisfaction was assessed by an opinion survey that rated the answers regarding the treatment as: *dissatisfied*, *satisfied* and *very satisfied*.

RESULTS

Sixty-two patients participated in the study (27 men, 35 women / mean age = 45.27 / age range = 20 to 81).

The patients underwent one session per month (min = 3, max = 14 / average = 6 sessions per month) (Graph 1).

The assessment of the photographs carried out by a physician classified 3 patients (4.84%) with *absence of improvement*, 30 (48.39%) with *slight improvement* and 29 (46.77%) with *significant improvement*. Of the patients who showed *slight improvement*, the majority (96.55%) underwent 3 to 6 sessions. Among those who experienced *significant improvement*, the majority (67.7%) underwent more than 7 sessions (Graph 2).

Regarding the evaluation of the patients' satisfaction, 2 (3.23%) said they were *dissatisfied* with treatment (one of whom underwent 3 sessions, the other 4 sessions), 13 (20.97%) reported being *satisfied*, and 47 (75.80%) said they were *very satisfied* (Graph 3). Those who were *satisfied* underwent on average 3.8 sessions, while those who were *very satisfied* underwent an average of 6.8 sessions (Graph 4).

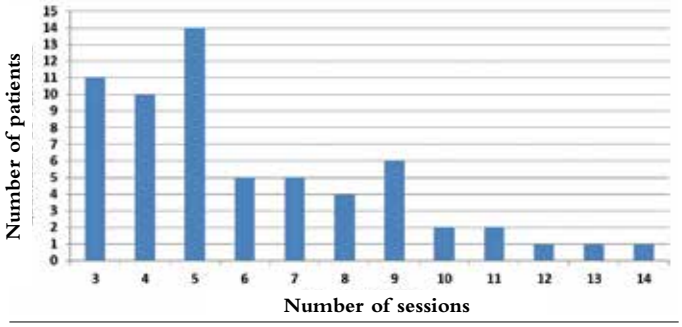
Adverse effects were deemed as mild, with erythema being more common within the first hours after the session, and mild pain on the scalp occurring on the day after the treatment.

DISCUSSION

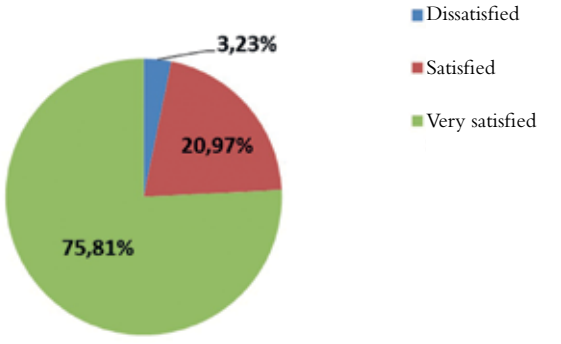
Several studies have demonstrated the use of laser therapy for hair growth, describing an increase in hair density and of anagen hairs in most of them.[1,6-9,13,14] Kim et al. have suggested that the mechanisms of action involved in inducing hair growth using fractional laser includes increased blood flow, induction of cytokines and growth factors associated with hair biology, as well as platelet-derived growth factor, keratinocyte growth factor, insulin-like growth factor and fibroblast growth factor. In addition, there is direct stimulation of stem cells, bulge cells or dermal papilla cells.[9] Moreover, laser radiation acts to reduce the inflammation present in the follicles in cases of alopecia areata.[6,14]

The treatment using the injection of active principles in the scalp aimed at controlling hair loss has increased in recent years.[11] The effects of hair mesotherapy are: increase in the local microcirculation and nutrient supply, delayed hair involution process and stimulation of hair growth due to the trauma in the dermis caused by the needling procedure.[10,15,16] Minoxidil acts as a vasodilator, vitamins are crucial in promoting hair growth, finasteride acts by inhibiting the hormonal action involved in androgenetic alopecia, and growth factors act directly on the development of the hair follicle.[10,17]

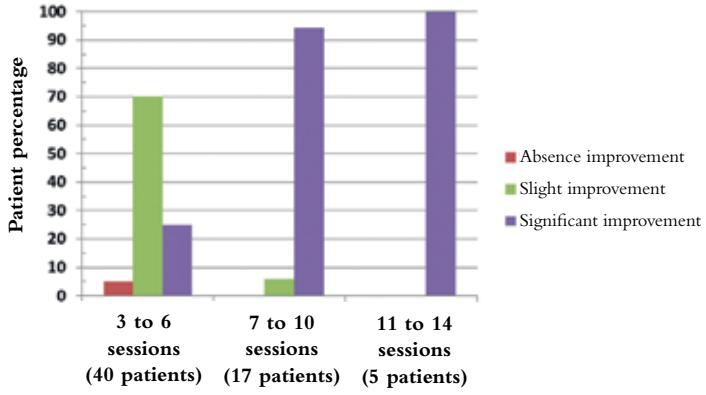
In light of the findings of the present study, it was possible to observe that the improvement in the clinical picture of androgenetic alopecia was proportional to the number of therapeutic



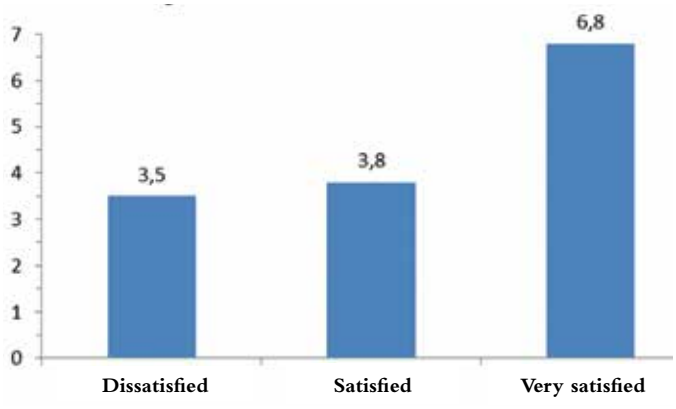
Graph 1: Number of treatment sessions undergone by patients



Graph 3: Patient satisfaction index



Graph 2: Patient improvement in number of treatment sessions



Graph 4: Patient satisfaction index as a function of the average number of sessions

sessions undergone by the patients, since the majority of the patients who underwent more than 7 sessions experienced a significant improvement of the picture, and all patients who underwent more than 11 sessions showed an important improvement of androgenetic alopecia.

Patient satisfaction was also progressive according to the number of sessions. Overall, the majority of patients (96.77%) were satisfied with the treatment. The majority of patients was significantly satisfied (75.8%) and underwent the greatest number of sessions on average (> 6 sessions).

In face of these data, it is possible to conclude that the combination of two treatments in a single session aimed at treating androgenetic alopecia allowed patients to achieve an important degree of personal satisfaction, since it is a condition of difficult treatment at the present time. In addition, the improvement observed on the photographs analysis, demonstrates the perceptible increase in the hair density obtained with the treatment (Figures 1-3).

Figure 1: A. Patient 1 before the treatment; **B.** After the treatment (6 sessions)

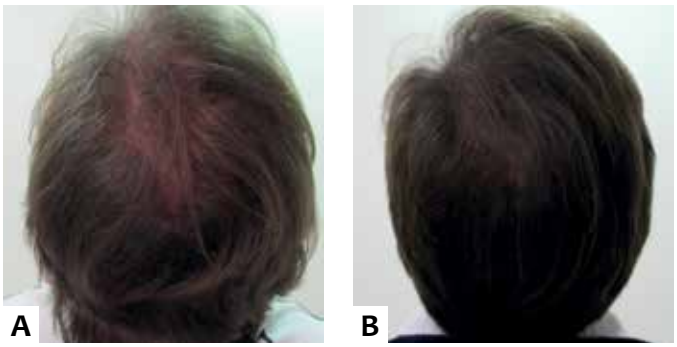


Figure 2: A. Patient 2 before the treatment; **B.** After the treatment (8 sessions)

Figure 3: A. Patient 3 before the treatment; **B.** After the treatment (12 sessions)

CONCLUSION

Androgenetic alopecia is a frequent complaint in dermatological practices, being characterized by poor therapeutic results to date. The present study allows to conclude that the association of 1,550nm Erbium:Glass laser with injections of active principles (minoxidil, finasteride, growth factors and vitamin complex) in the scalp was effective and safe for the treatment of this condition, reinforcing the relevance of this novel treatment option.

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Original Articles

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Lip volumization using botulinum toxin

Aumento do volume labial com o uso de toxina botulínica

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RESUMO

Introdução: A aplicação da toxina botulínica na região perioral é procedimento minimamente invasivo que permite melhora substancial nos sinais de envelhecimento e aumento do volume dos lábios, com pouca documentação ainda na literatura.
Objetivo: Avaliar alterações na forma e volume dos lábios com aplicações de toxina botulínica nas linhas periorais bem como a satisfação do paciente.
Métodos: 19 pacientes submeteram-se a análise, registro fotográfico e medições seguidos de aplicação de toxina botulínica na região perioral. Posteriormente, foram avaliados quanto a alterações labiais e satisfação.
Resultados: A maioria dos pacientes considerou os lábios moderada ou significativamente mais atraentes após a toxina (p = 0,039), e 15 mulheres notaram a mudança do lábio como um dos principais contribuintes para a melhoria global da face.
Conclusões: A aplicação de toxina botulínica na região perioral provoca elevação do lábio superior, levando ao encurtamento do filtro e extensão do vermelhão. Ao aplicar a toxina na borda do vermelhão, permitimos o relaxamento do músculo orbicular, favorecendo maior efeito do tônus muscular dos músculos de elevação do lábio superior. A satisfação das pacientes com a aparência dos lábios avaliada pelas quatro perguntas adicionais (forma, volume, atração e beleza) foi positiva, com efeitos colaterais mínimos.
Palavras-chave: lábio; toxinas botulínicas tipo a; toxinas botulínicas

ABSTRACT

Introduction: *The application of botulinum toxin in the perioral region is a minimally invasive procedure that leads to substantial improvement in the signs of aging in addition to increasing the volume of the lips. However literature on this procedure is still scarce.*
Objective: *To evaluate changes in shape and volume of the lips, as well as the patients' satisfaction after the application of botulinum toxin in perioral lines.*
Methods*: Nineteen patients underwent evaluation, photographic record and measurements following the application of botulinum toxin in the perioral region, being subsequently assessed for changes in the lips and satisfaction.*
Results: *Most of the patients rated their lips as moderately or significantly more attractive after the application of botulinum toxin (p = 0.039). Fifteen women deemed the changes in the lips as a major factor in the overall improvement of their faces.*
Conclusions: *The use of botulinum toxin in the perioral region leads to the elevation of the upper lip, causing the shortening of the philtrum and the extension of the vermilion. The application of botulinum toxin in the vermilion's border leads to the relaxation of the orbicularis muscle, favoring a more intense tonus effect arising from the upper lip lifting muscles. The patients' satisfaction with the appearance of their lips was evaluated by four additional questions (linked to the lip's shape, volume, attraction and beauty), receiving positive answers. Side effects were minimal.*
Keywords: *lip; botulinum toxins, type a; botulinum toxins*

INTRODUCTION

Botulinum toxin is an exotoxin produced by *Clostridium botulinum*, a gram-positive anaerobic bacterium. There are eight bacterial serotypes (A, B, C alpha, C beta, D, E, F and G) that produce seven distinct exotoxins. Type A, B and E are most commonly associated with botulism in humans. The toxin's action's final path is to prevent the release of acetylcholine at the neuromuscular junction of the striated muscles thus producing chemical denervation and resulting muscular paralysis.[1]

In the last three decades, botulinum toxin has been used for therapeutic purposes in a number of conditions. Botulinum toxin type A was first approved in 1989 for use in strabismus, blepharospasm and hemifacial spasm. Then types A and B were approved for the treatment of cervical dystonias. More recently, type A has been approved for aesthetic purposes, palmoplantar hyperhidrosis and treatment of migraine and chronic tension headache.[2]

The application of botulinum toxin in the perioral region is a rapid and minimally invasive procedure. In addition, recent studies have shown substantial improvement in the signs of aging, including increased lip volume.[3,4] There are reports of botulinum toxin use for other purposes, such as gingival smile correction or perioral synkinesia, however there is scarce literature on the evaluation of the increase in the lip's volume with the application of the toxin in the perioral rythids.[5,6]

OBJECTIVE

To evaluate changes in shape and volume of the lips after the application of botulinum toxin in the perioral ridges, as well as the patients' satisfaction with the shape of the lips.

METHODS

A prospective, interventional, uncontrolled and non-randomized study was carried out. An already established technique was evaluated by this study. The patients were selected at the Dermatology Ambulatory of the Hospital Universitário Evangélico de Curitiba (Curitiba city, PR, Brazil), from July 2014 to August 2015. Adults who already wanted to undergo the application of botulinum toxin for aesthetic purposes were selected. There was no gender or phototype restriction, and only patients older than 18 were included.

Patients who had already undergone another type of treatment for increasing the volume of the lips were excluded. Other exclusion criteria were: history of intolerance to the drug, pregnancy, difficulty to communicate clearly, active use of anticoagulants, presence of scars, deformities or pathological anatomical alterations in the lips and autoimmune diseases.

After signing the Informed Term of Consent, the patients were evaluated with the assistance of a questionnaire containing questions related to the satisfaction with their lips. Also, measurements and standardized photographs of the lips were taken.

Botulinum toxin was then applied for aesthetic purposes, at individually defined sites in the patients, totaling 4 points in the upper lip.

The Dysport® 500U toxin (Ipsen®, Paris, France) was used diluted in 0.9% saline in the ratio 1:1.7 and kept under refrigeration (2°C to 8°C). Zero point five (0.5) UI was applied in each of the four points of the upper lip's perioral rhytids, along the vermilion border.

The selected patients returned for reassessment after 3 weeks, when measurements were repeated and standardized photographs were taken for comparative purposes.

Evaluation criteria

The evaluation of the outcomes was performed through the analysis of categorical and continuous variables. Changes in the lip's shape and size were gauged through measurements taken with a pachymeter, while the patient's satisfaction with the treatment was assessed using semi-quantitative questionnaires, and the impression of the blinded specialist physicians through the evaluation of standardized photographs.

Statistical evaluation

The data were compared between the different experimental timepoints of the evaluation and clinical re-assessment. The chi-squared test was used for analyzing the adherence and trend, while the Fisher's exact test was used to compare categorical variables. The data was expressed in absolute values and proportions, and the associations, in odds ratios. The paired Student's t-test and Wilcoxon's test were used for comparing continuous variables. The normality of distributions was assessed using the Shapiro-Wilk test. Semiquantitative questions (Likert scale) linked to the satisfaction with the lip's anatomy were evaluated for consistency using the Cronbach's alpha test. The authors prepared a score based on the four questions related to the satisfaction with the shape of the lips.

The initial sample size was determined based on a paired Student's-t test with a 80% strength and 0.05 alpha error for detection of a mean difference similar to the standard deviation of the quantitative measurements.

Values of two-tailed $p < 0.05$ were deemed significant.

The study was duly approved by the Research Ethics Committee of the Institution and registered under the number 34745714.9.0000.0100. The authors funded expenses incurred with the study, with absence of conflicts of interest.

RESULTS

A total of 19 female patients were evaluated (mean age = 47 years, SD =12.1). The mean value for the total dose of toxin units applied was 43U (SD = 3,4), with the amount injected in the lips being always the same – 0.5U per point – in the four points.

The lip's measurements were taken according to the segments seen in Figure 1.

It was possible to note a statistically significant ($p = 0.002$) increase in *Segment 3*, in the post-procedure evaluation. Similarly, the vermilion/philtrum ratio (*Segment 4 / Segment 2*) was also greater after the procedure ($p = 0.001$). Most of the patients (n = 10) were dissatisfied with or indifferent to their

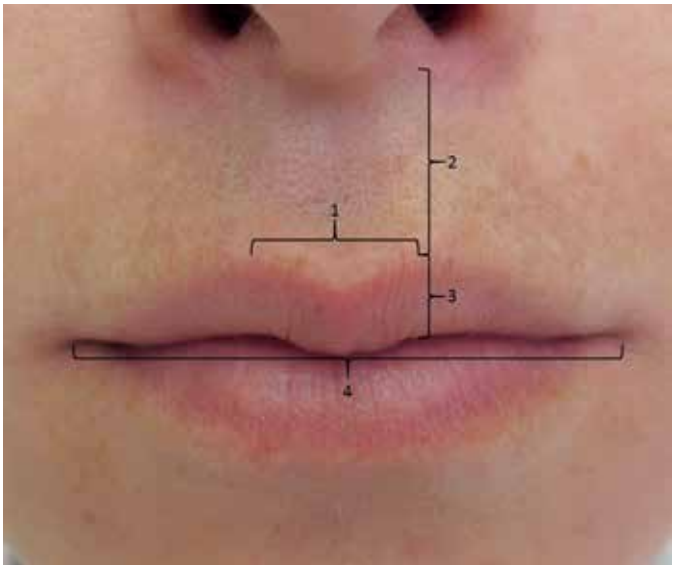


Figure 1: Measurements evaluated in the present study

lip's volume previously to the procedure, with 17 saying they were satisfied or very satisfied after the application of toxin (p = 0.003) (Figure 2).

The same was true for the evaluation of the lip's shape, where 16 patients said they were reasonably or very satisfied after the procedure (p = 0.048), as shown in the graphs below (Graphs 1 to 4).

Most patients deemed their lips as moderately or significantly more attractive after the treatment with toxin (p = 0.039), and 15 women perceived the change in their lips as a major contributor to the overall improvement of their faces. The perception of volumization was present in in all except for 1 patient.

Regarding side effects, no patient had difficulty to speak, 2 had some difficulty to eat in the first two weeks, and 4 had difficulty to smile. The patients were followed up, and after 30 days none of them sustained their complaints.

In this manner, it was possible to calculate the overall satisfaction score regarding the lips' appearance, taking into consideration their *volume*, *shape*, *attraction* and *contribution for the overall improvement of face appearance*, being this positive (p = 0.005).

Of the 19 initially included patients, 17 (89.5%) would undergo application of toxin again.

DISCUSSION

The use of botulinum toxin type A is a well-known procedure for the improvement of rhytids in the upper third of the face. Regarding the lower third of the face, despite the high frequency with which the procedure is performed, there are very few studies on the toxin's effects on the labial region. The technique has become increasingly popular, partly due to the doctors' confidence in the excellent efficacy and safety profile demonstrated by the botulinum toxin since 1987 in topical indications. In addition, physicians realized that muscle hyperactivity and volume depletion were important concomitant aesthetic determinants for the middle and lower face.

It is important to bear in mind that muscle anatomy and tissular relationships are very different from those found in the upper face, meaning that the doses used are smaller, and the application points must be selected more carefully in order to avoid undesirable effects.

As for the perioral region, the authors noticed that the lips are key points for the aesthetic appearance of the face. With the aging process, the lateral portions of the lips tend to become less visible and the distance between the columella and the upper lip's vermilion increases, resulting in the appearance of thin lips. This process becomes even more visible in smokers, nonetheless hereditary factors may often be relevant.

As discussed by Carruthers & Carruthers,[7] small doses of botulinum toxin can lead to localized microparesis of the orbicularis muscle, dramatically reducing the visibility of perioral lines.

However, in order to maintain the mouth's functional competence, it is important to take a conservative approach regarding the dosage and superficial injections. The authors in

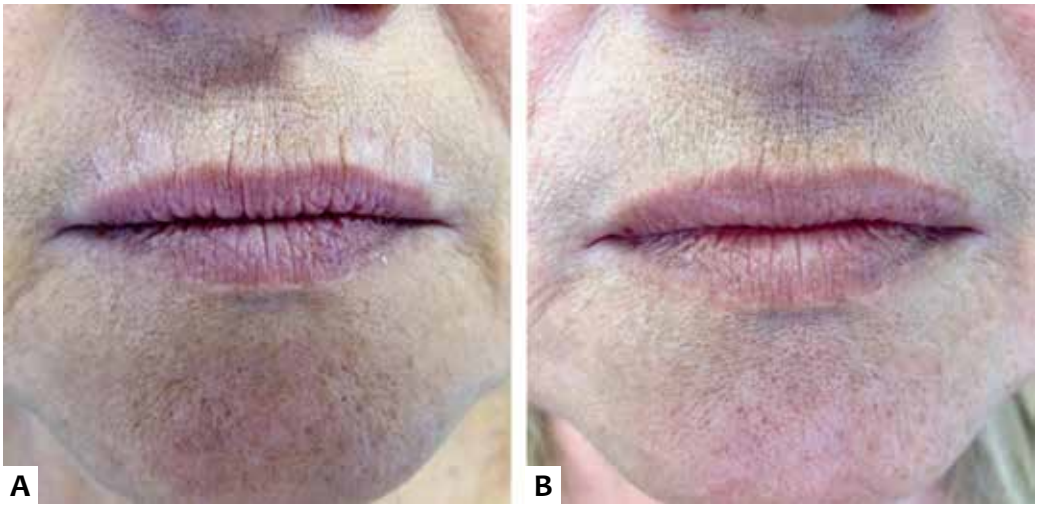
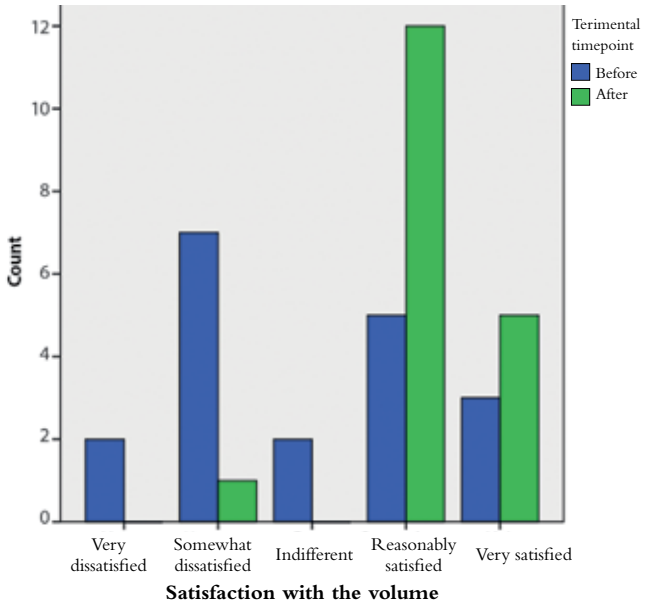
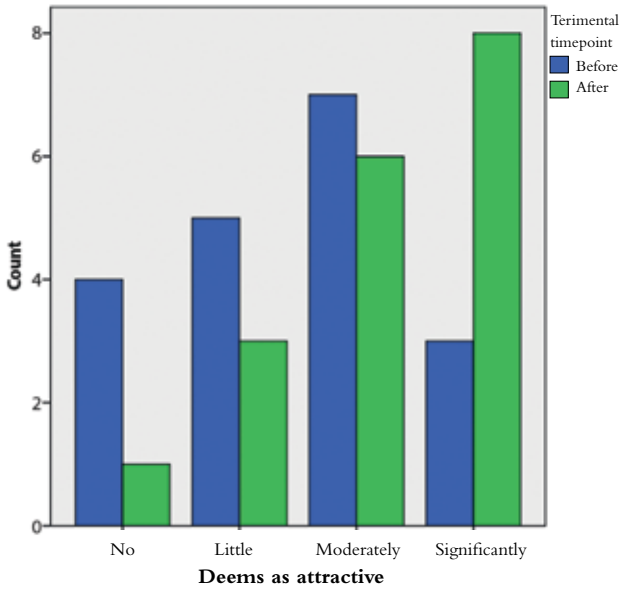


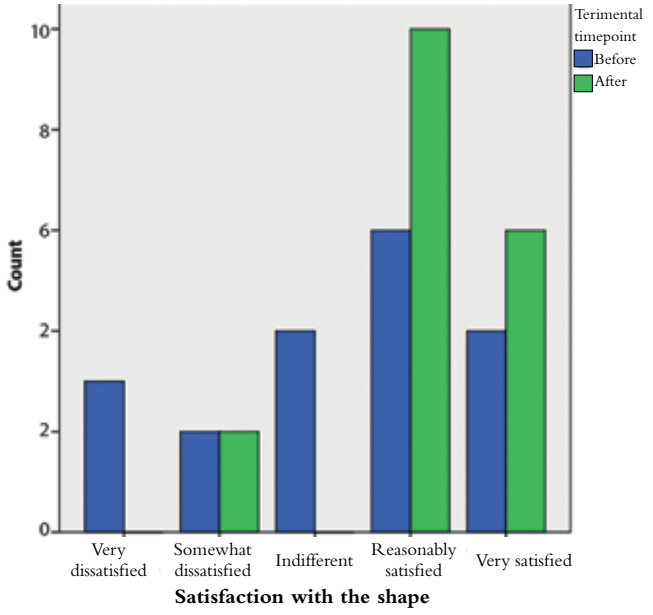
Figure 2: A - Pre-application. **B -** Post-application. It is possible to observe an elevation of the upper lip and lengthening of the vermilion



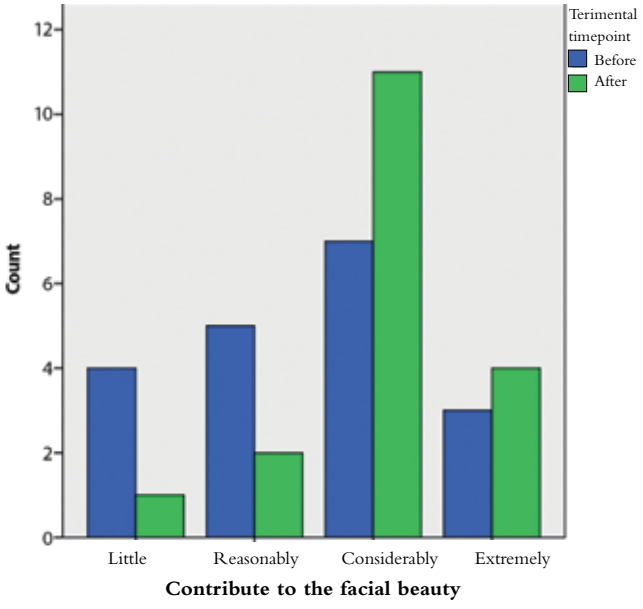
Graph 1: Patients' satisfaction regarding the volume of the lip before and after the application of botulinum toxin.



Graph 3: Patients' self-assessment of the degree of attractiveness attributed to the lips before and after the application of botulinum toxin



Graph 2: Patients' satisfaction regarding lip shape before and after the application of botulinum toxin



Graph 4: Patients' self-assessment of the contribution of the lips to the overall facial beauty before and after the application of botulinum toxin

question (the Carruthers) obtained satisfactory results with doses of 2 to 4U botulinum toxin per lip (without using more than 2U per lip quadrant). Due to the fact that the authors of the present article used a toxin with a higher diffusion index (Dysport), a decision was made for an even more conservative stance regarding the doses, which also yielded very satisfactory results.

The literature further emphasizes that the corners of the lips should be avoided due to the fact that injection in these sites cause undesirable weakness of the lip lift muscles, entailing difficulty to eat, whistle, and even leading to a propensity to drool. The midline is also preserved, avoiding the flattening of the cupid's bow – which has driven the authors of the present study's decision for applying the toxin in four points only.

Foster and Wulc [8] also described a technique for the use of botulinum toxin for perioral lines that is very similar to the one used in the present study for choosing the site of application. The patient is asked to pucker her or his lip – as in the kissing motion – so that the areas of muscular contraction adjacent to the lines become visible, facilitating the visualization and execution of the technique.

CONCLUSIONS

There was a change in the vertical measurements of the upper vermilion and the philtrum, with an increase in the first and a reduction in the second. In the present study, the patients had an elevation of the upper lip, which led to a shortening of the philtrum and lengthening of the vermilion. The authors believe that by applying the toxin in the vermilion's border, it is possible to obtain relaxation of the orbicularis muscle, allowing a greater tonus in the upper lip lift muscles.

The patients' satisfaction with their lips' appearance was positive – mainly regarding volume – and considered attractive, as assessed by the combined answers to the four questions (*shape*, *volume*, *attraction* and *contribution to overall appearance*).

The side effects were rare and mild, arising mainly as difficulty to speak and/or smile. Notwithstanding, 89% of the patients would undergo re-application of the toxin.

In this manner, botulinum toxin was proven as an important ally in the treatment of the lips region, and should be deemed as a promising method for improving the general appearance of the face in combination with other well-established treatments for this purpose.

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Surgical treatment and long-term follow-up of subcutaneous mycoses caused by dematiaceous fungi: chromoblastomycosis, phaeohyphomycosis and eumicetoma

Tratamento cirúrgico e seguimento a longo prazo das micoses subcutâneas causadas por fungos demáceos: cromoblastomicose, feoifomicose e eumicetoma

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ABSTRACT

Introduction*:* Subcutaneous mycoses caused by dematiaceous fungi are classified according to their characteristics in the tissue: chromoblastomycosis (with the presence of fumagoid corpuscles), phaeohyphomycosis (with dematiaceous septate hyphae) and eumicetoma (with grains composed of septate hyphae). Several treatments are proposed, among them, surgical excision. Surgical treatment is more indicated in cases where there is localized infection and where excision is possible, yielding good therapeutic outcomes and low recurrence rates.

Objective: To describe the experience of a dermatological service in the surgical treatment of subcutaneous mycosis cases caused by dematiaceous fungi, discussing the surgical approach and its results.

Methods: A retrospective study was carried out with the descriptive analysis of cases treated from April 2014 to December 2016, at a dermatological clinic in the Brazilian Southeast city of São Paulo. All cases diagnosed with subcutaneous mycoses caused by dematiaceous fungi were included and surgically treated with total exeresis of the lesion.

Results: A total of 7 cases were analyzed – 2 eumicetomas, 1 chromoblastomycosis and 4 phaeohyphomycoses. Only one on the cases was not treated at an ambulatory surgical center. All cases progressed without sequelae or recurrences during the clinical follow-up.

Conclusions: When surgical treatment is possible, the exeresis of the lesion is a good therapeutic option in cases of subcutaneous mycoses caused by dematiaceous fungi.

Keywords: chromoblastomycosis; phaeohyphomycosis; bacterial infections and mycoses; mycosis; mycetoma; ambulatory surgical procedures; bloodless medical and surgical procedures; histology; therapeutics

RESUMO

Introdução: *As micoses subcutâneas provocadas por fungos demáceos (MSCFD) são classificadas conforme sua apresentação no tecido: cromoblastomicose com presença de corpúsculos fumagoides, feoifomicose com hifas septadas demáceas e eumicetoma com grãos compostos por hifas septadas demáceas. Diversos tratamentos são propostos, entre eles a exérese cirúrgica. O tratamento cirúrgico é mais indicado nos casos em que há infecção localizada e passível de exérese, com bons resultados terapêuticos e baixa taxa de recidiva.*

Objetivo: *Apresentar a experiência de um serviço dermatológico no tratamento cirúrgico dos casos de MSCFD, discutindo as abordagens cirúrgicas e seus resultados.*

Métodos: *Estudo retrospectivo com análise descritiva dos casos atendidos no período de abril de 2014 a dezembro de 2016 em clínica dermatológica da cidade de São Paulo. Foram incluídos todos os casos com diagnóstico de MSCFD que foram submetidos à terapêutica cirúrgica com exérese total da lesão.*

Resultados: *Foram totalizados sete casos: dois de eumicetoma, um de cromoblastomicose e quatro de feoifomicose. De todos os casos apenas um não foi abordado em regime de centro cirúrgico ambulatorial. Todos evoluíram sem sequelas e sem recidivas no seguimento clínico.*

Conclusões: *A remoção da lesão cutânea é um boa opção terapêutica nos casos de MSCFD em que o procedimento cirúrgico for viável.*

Palavras-chave: *cromoblastomicose; feoifomicose; infecções bacterianas e micoses; micoses; micetoma; procedimentos cirúrgicos ambulatoriais; procedimentos médicos e cirúrgicos de sangue; histologia; terapêutica*

Original Articles

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INTRODUCTION

Subcutaneous mycoses are fungal infections located in the deep layers of the skin. They can be caused by both hyaline fungi, with no pigment in their structure, and by dematiaceous fungi that present melanin in their cellular wall.[1,2] Dematiaceous fungi are found throughout the planet, with a predilection for tropical areas, inhabiting the soil and vegetables (geophilic fungi).[3-5]

Subcutaneous mycoses caused by dematiaceous fungi (SMCDF) are classified according to their appearance in the tissue: chromoblastomycosis with presence of fumagoid corpuscles, phaeohyphomycosis with dematiaceous septate hyphae and eumycetoma with grains composed of dematiaceous septate hyphae.[1,6] These structures can be visualized in the direct mycological examination of the material harvested from the lesion or in the tissue biopsy histological analysis. Fungus culture is required to determine the agent's species.[2,3,6,7]

Several treatments are proposed in these cases, from the use of antifungals to thermotherapy and surgical excision. The choice between these therapies is made based on the analysis of several factors, such as manifestation of the lesion, clinical conditions and the patient's comorbidities, in addition to the availability of treatment when medical advice is sought.[2,4,8-10]

The present study is aimed at describing the experience of a dermatological clinic in the city of São Paulo (SP) - Brazil, in the surgical treatment of SMCDF cases, discussing surgical approaches and results.

METHODS

A retrospective study was conducted with the descriptive analysis of cases treated from April 2014 to December 2016, at a tertiary dermatologic clinic in the city of São Paulo, Brazil. All cases diagnosed with SMCDF that underwent surgical treatment with total lesion excision were included.

DESCRIPTION OF CASES

Case 1 consisted of a eumycetoma initially treated with antifungals for 24 months, without success. After having been treated surgically by the plastic surgery team, it progressed with healing (Figure 1). Case 2 consisted of a nodular lesion that was promptly removed after eumycetoma diagnosis (Figure 2). Case 3 involved a chromomycosis located in the patient's knee, that was not treated in a single surgical time due to the possibility of dehiscence: three sessions were performed, with an excellent final outcome (Figure 3).

Cases 4, 5 and 6 had lesions similar to each other, easily removed with surgical technique. Cases 4 and 5 showed cystic lesions on the feet – a classic symptom of phaeohyphomycosis (Figures 4 and 5). In case 4, there was an attempt of using drug therapy prior to the procedure, without any response. Case 6 presented a solid tumor near the knee (Figure 6) that was approached with total lesion excision (fusiform excisional biopsy). This patient had other cystic phaeohyphomycosis lesions in the limbs that were not surgically accessible, having been treated with antifungal after biopsy, which explains the prolonged medication time after the approach.

Case 7 had multiple phaeohyphomycosis lesions on the dorsum of the hand, for the patient used plants' thorns to puncture lesions, inoculating new dematiaceous hyphae with this habit. Several excisional sessions were carried out with a sterile needle up until healing was achieved (Figure 7).

RESULTS

There were seven cases in total: 2 eumycetomas, 1 chromoblastomycosis and 4 phaeohyphomycosis. Only one of these cases was not treated in ambulatorial surgical center setting. None presented recurrence after the surgical treatment. The characteristics of the seven cases are detailed in Table 1. The diagnoses were defined based on the association of the clinical appearances, isolation of the etiological agents and the morphology observed in the histology of the tissues.

All cases progressed without sequelae and absence of recurrences in the clinical follow-up.

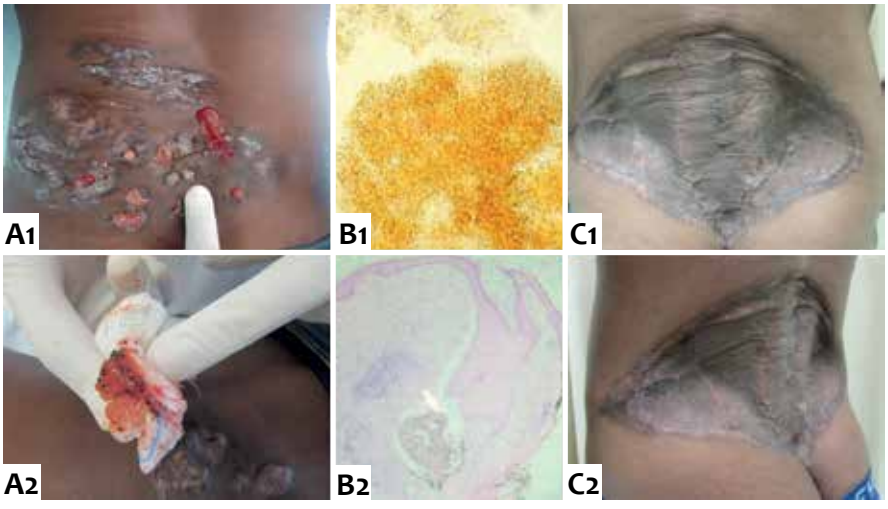

Figure 1: Eumycetoma, in the lower back region. Clinical appearance with increased volume, fistulas and discharge of purulent secretion, and grains to the expression (**A1** and **A2**). Identification of the grain by direct mycological examination (**B1**) and histology (**B2**). Clinical appearance after surgical excision (**C1 and C2**)

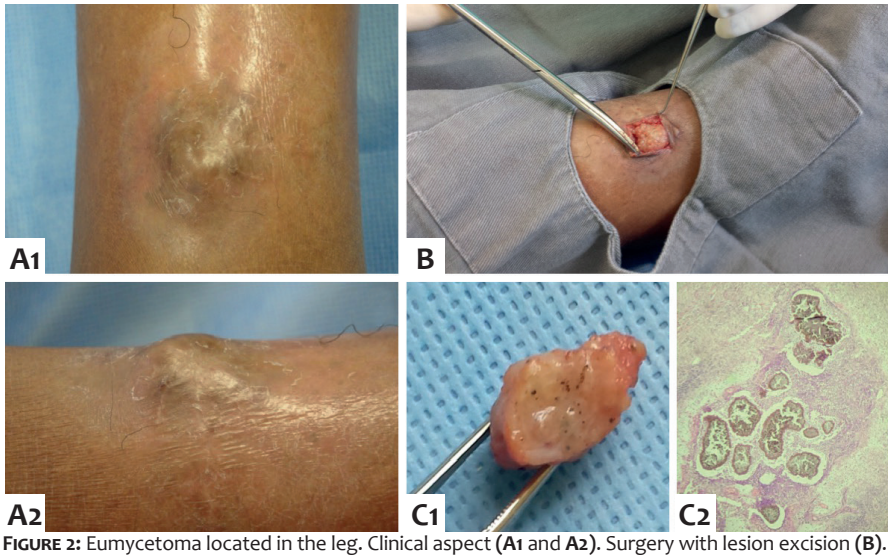

Figure 2: Eumycetoma located in the leg. Clinical aspect (**A1** and **A2**). Surgery with lesion excision (**B**). Histology's macroscopic (**C1**) and microscopic (**C2**) aspects of the lesion; identifying the grains (**C2**)

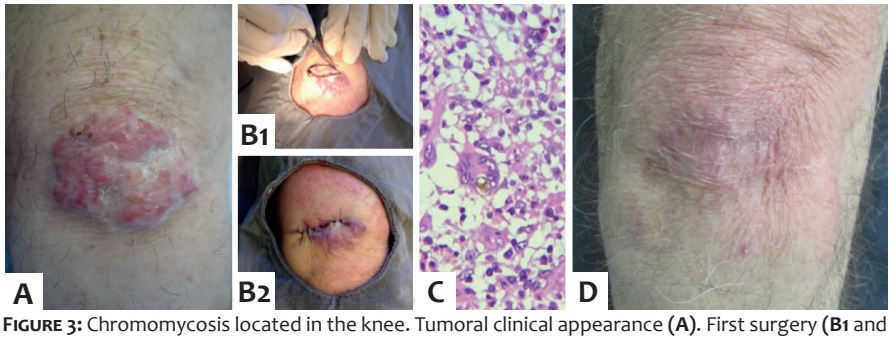

Figure 3: Chromomycosis located in the knee. Tumoral clinical appearance (**A**). First surgery (**B1** and **B2**). Histology identifying fungoid corpuscles (**C**). Post-treatment appearance at the end of the total removal (**D**).

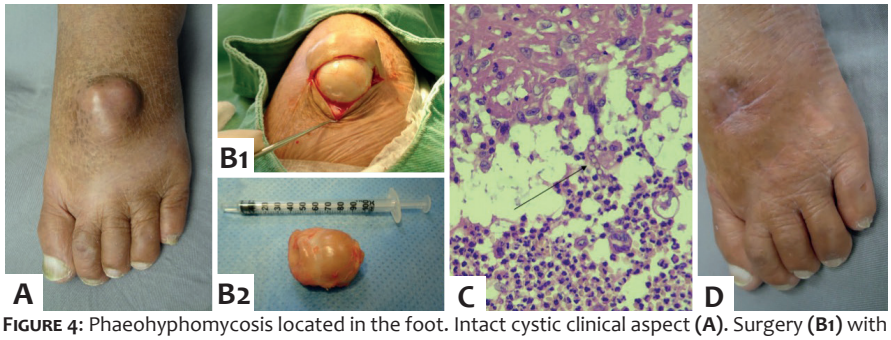

Figure 4: Phaeohyphomycosis located in the foot. Intact cystic clinical aspect (**A**). Surgery (**B1**) with macroscopic aspect of the removed lesion (**B2**). Histology with arrow identifying dematiaceous hyphae in the tissue (**C**). Clinical aspect after surgical excision (**D**).

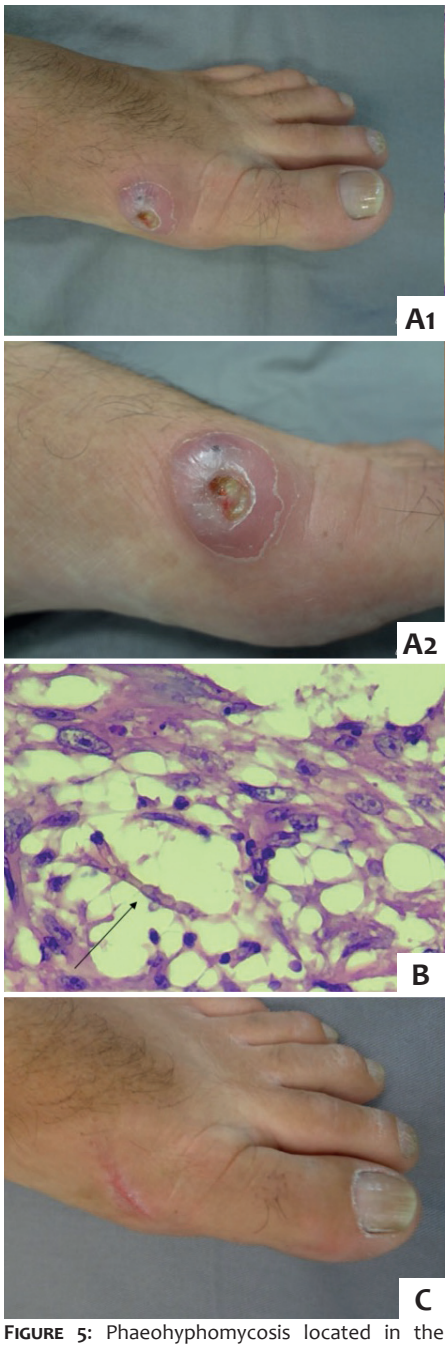

Figure 5: Phaeohyphomycosis located in the foot. Ruptured cystic clinical aspect (**A1** and **A2**). Histology with arrow identifying dematiaceous hyphae in the tissue (**B**). Clinical aspect after surgical excision (**C**)

DISCUSSION

Currently, SMCDF treatment can be divided into medicament and / or surgical based. Surgical treatment is more indicated in cases where there is localized infection and exeresis is feasible.[1,10] Although widely used, medicament based treatment should be introduced with caution, since it is protracted, and patients with SMCDF frequently are elderly and have conditions that alone require their own daily doses of medication.[3,8]

In the cases presented in this paper, surgical removal was proven a safe option. The authors did not observe any perioperative complications, such as infection, dehiscence or collections formation. In addition, despite the advanced age or immunosuppression associated with most cases, it was not possible to observe any clinical complication resulting from the operative event. Except for Case 1 (Figure 1), all patients were operated in an ambulatorial basis under local anesthesia, which simplified

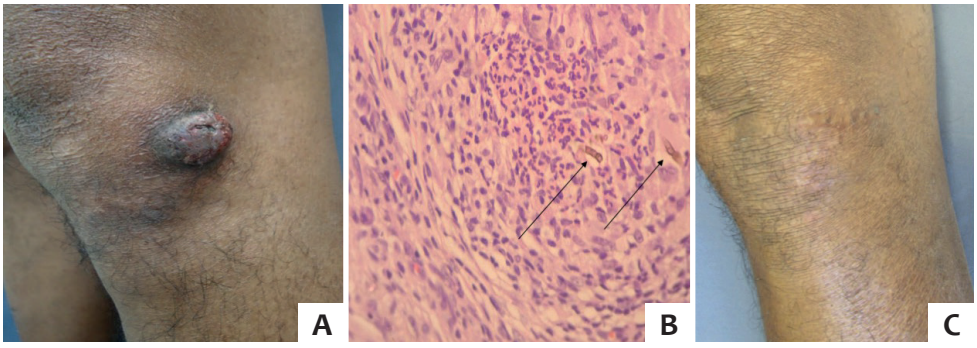

Figure 5: Phaeohyphomycosis located in the knee. Intact clinical aspect **(A).** Histology with arrows identifying septate dematiaceous hyphae in the tissue **(B).** Clinical aspect after surgical excision **(C).**

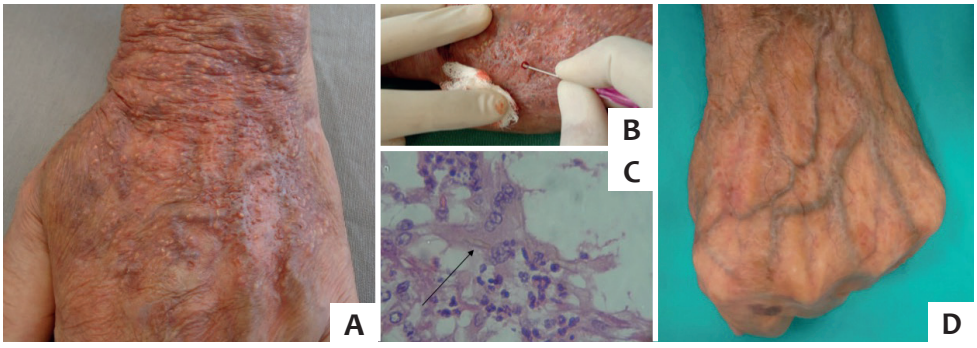

Figure 7: Phaeohyphomycosis located in the hand. Clinical aspect of milia **(A).** Exeresis of small lesions performed one by one with a needle **(B).** Histology with arrow identifying septate dematiaceous hyphae in the tissue **(C).** Clinical appearance after all surgical excision sessions **(D).**

Table 1: **Characteristics of the case series: patients' clinical aspects, identification of agents by complementary exams and therapeutic approaches**

		CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7
Patient data	Gender	Male	Male	Male	Male	Male	Male	Male
	Age	16	62	76	79	44	45	79
	Comorbidity	n.a.	SAH	COPD	SAH / CHF	Kidney transplantation	Kidney transplantation	Lymphoma
Characteristics of the lesion	Previous trauma	Yes	No	No	No	No	No	Yes
	Clinical aspect	Classic Triad	Nodule	Tumor	Cyst	Cyst	Tumor	Milia
	Time of development	12 months	24 months	12 months	24 months	8 months	1 week	2 months
	Location	lower back	leg	knee	foot	foot	knee	hand
Diagnosis	Direct examination	grains	negative	negative	hyphae	hyphae	hyphae	hyphae
	Culture	*M. pseudomycetomatis*	Negative	*Fonsecacea pedrosoi*	*Exophiala sp*	*Phialophora sp*	*Exophiala sp*	*Phialemonium sp*
	Histology	Eumycetoma	Eumicetoma	Chromomycosis	Phaeohyphomycosis	Phaeohyphomycosis	Phaeohyphomycosis	Phaeohyphomycosis
Surgical treatment	N° of procedures	2	1	3	1	1	1	1
	Disease free	14 months	25 months	17 months	41 months	70 months	40 months	62 months
Antifungal	Which	ITRA + TERB	n.a.	n.a.	ITRA + SMX-TMP	n.a.	TERB + ITRA	ITRA + TERB
	When	pre	n.a.	n.a.	pre	n.a.	oost	TERB pre / ITRA
Post	How long	24 months	n.a.	n.a.	1 month	n.a.	11 months	TERB 9 months / ITRA 3 months
Recurrence		no	no	no	no	no	no	no

**SAH: Systemic arterial hypertension, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, ITRA: Itraconazole, TERB: Terbinafine, SMX-TMP: Sulfamethoxazole-trimethoprim*

the treatment and considerably reduced the morbidity and risk of procedure.

Surgical treatment of SMCDF, regardless of whether or not it was associated with systemic antifungal therapy, did not predispose to the dissemination or implantation of the infectious agent. In the period of clinical follow-up ranging from 14 to 70 months (mean = 38.4 months), no new lesions were observed at the site of surgical treatment.

Due to the multiplicity of clinical presentations, the surgical techniques employed varied according to the specificities of each case. Cases characterized by subcutaneous nodules or cysts (Cases 2, 4 and 5) were well delimited, which facilitated dissection and the complete removal of the lesion. Tumor-like cases (Cases 3 and 6) were removed using fusiform excision and

direct closure. Due to the size and anatomical location of the lesion in Case 3, a decision was made for a three-stage excision. This approach did not trigger the cutaneous implantation of the agent or any other postoperative complication.

CONCLUSION

In the authors' experience, surgical treatment was proven effective, simple and safe in cases where the infection is anatomically delimited. The antifungal agents' toxicity associated with the usually affected patient's clinical / immunological profile, makes surgery an optimal therapeutic option, which should be regarded as the first-choice treatment whenever surgical removal is feasible. ●

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Cryosurgery in the treatment of hypertrophic granulation tissue in cutaneous wounds

Criocirurgia no tratamento do tecido de granulação hipetrófico nas feridas cutâneas

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ABSTRACT

Introduction*:* Cryosurgery is a safe and effective treatment modality that uses liquid nitrogen for tissue destruction.

Objective: To demonstrate the effectiveness of cryosurgery in the treatment of hypertrophic granulation tissue in cutaneous wounds.

Methods: Cutaneous wounds with hypertrophic granulation tissue were treated with the nitrogen spray applied from a distance of 5cm from the area to be treated, at a 90º angle. The freezing time was two 5-second cycles and the number of sessions ranged from 1 to 3. The assessments of results were based on weekly clinical and photographic comparisons, as well on the measurement of the wound's and hypertrophic granulation tissue's areas using a planimeter, up until the healing process was completed. The results were statistically analyzed.

Results: Twenty patients with cutaneous wounds located on the head, trunk and limbs were treated. The average weekly percentage reduction compared to the baseline area was 32.5%. The results were statistically significant.

Conclusions: Cryosurgery is a practical, cost effective and non-invasive method and can be indicated for the treatment of hypertrophic granulation tissue in cutaneous wounds.

Keywords: granulation tissue; cryosurgery; therapeutics

RESUMO

Introdução: *A criocirurgia é uma forma segura e eficaz de tratamento que utiliza o nitrogênio líquido para destruição tecidual.*

Objetivo: *Demonstrar a eficiência da criocirurgia no tratamento do tecido de granulação hipertrófico nas feridas cutâneas.*

Métodos: *As feridas com tecido de granulação hipertrófico foram tratadas com o nitrogênio em spray aplicado a uma distância de 5cm da área em ângulo de 90º. O tempo de congelamento foi de 02 ciclos de 05 segundos e o número de sessões variou de 01 ou 03. A avaliação dos resultados foi feita através de comparação semanal, clínica e fotográfica, alem de mensuração da área das feridas e do tecido de granulação hipertrófico, através de um planímetro, até que se completasse o processo de cicatrização. Os resultados foram analisados estatisticamente.*

Resultados: *Foram tratados 20 pacientes com feridas cutâneas localizadas na cabeça, tronco e membros. A média do percentual de redução semanal em relação à área inicial foi de 32,5%. Os resultados tiveram significância estatística.*

Conclusões: *A criocirurgia é um método prático, de baixo custo e pouco invasivo, podendo ser indicada para o tratamento do tecido de granulação hipertrófico nas feridas cutâneas.*

Palavras-chave: *tecido de granulação; criocirurgia; terapêutica*

Original Articles

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INTRODUCTION

The presence of granulation tissue and reepithelialization are necessary for the healing of a cutaneous wound. The granulation tissue replaces cells that have lost their function. It occurs in physiological situations or due to multiple pathological conditions in the body. However, in some cases, the production of hypertrophic granulation tissue (HGT), which develops beyond the surface of the wound, resulting in an elevated mass, or peduncle, hampers healing in several ways, for instance preventing the migration of epithelial cells on the surface of the wound, increasing the risk of infection or causing pain, discomfort and difficulty in healing.[1] Cryosurgery is a treatment modality that uses liquid nitrogen, which became commercially available in 1940. Since then it has been commonly used in the freezing of cutaneous neoplasms due to its safety and effectiveness.[2] The objective of the present article is to demonstrate the efficiency of cryosurgery in the treatment of HGT in cutaneous wounds.

METHODS

A retrospective study was carried out with the data contained in the medical records of 20 patients originated at the Dermatology Ambulatory of the Fundação Pró-Hansen in the Brazilian southern city of Curitiba (PR), Brazil, bearing cutaneous wounds with HGT, due to ulceration of the lower limbs and surgical wounds left to heal by second intention, from 2012 to 2014. The patients who accepted to take part in the study signed a Term of Free and Informed Consent, also allowing use of photographs related to their conditions. Exclusion criteria were: presence of severe coagulopathies, local infection, decompensated diabetes, cryofibrinogenemia, cryoglobulinemia, thrombophlebitis, deep venous thrombosis and wounds with malignant neoplasia.

In the study, the Cry-ac[3]® (Brymil Corporation, USA for Alcon Pharmaceuticals Cham, Switzerland) was used with the spray technique employing the largest diameter tip (A) (Figure 1).

Nitrogen was applied at a distance of approximately 5cm from the HGT area, at a 90º angle. The freezing time corresponded to approximately 2 cycles of 5 seconds, slightly varying according to the area to be frozen, with the number of sessions varying from 1 to 3. Large lesions were divided into quadrants for the application of liquid nitrogen – always limited to HGT – thus avoiding interfering with the migration of keratinocytes to the center of the wound. In the presence of fibrous borders, surgical debridement was performed.

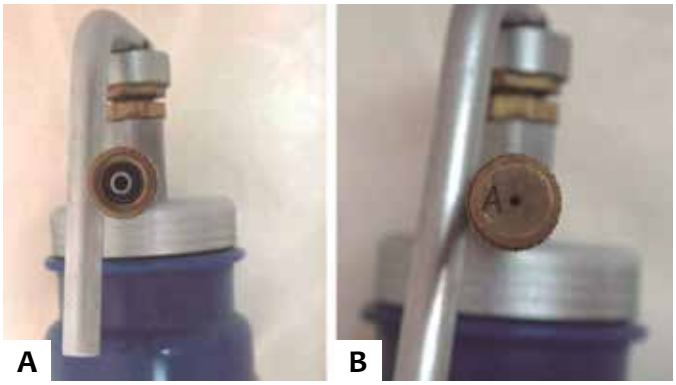

Figure 1: A – Cry-ac-3 Brymil® device, **B –** Tip with greater diameter

The procedures were always performed by the same dermatologist physician.

In the postoperative period, the patients received dressings with neomycin and bacitracin ointment, which were replaced twice a day after the wound had been cleansed with saline solution. For wounds located in the lower limbs, the patient was instructed to prepare the crepe bandage with aimed at containing exudate and occasional small bleedings.

Clinical observation, photographic documentation and measurement of the areas of the wounds and the HGT were performed weekly for the assessment of results. The measurement of the areas were carried out using a decal that was later analyzed by a polar planimeter (Fa.OTT, type 16, Kempten, Germany). The device is comprised of two hinged metallic rods that are joined by a disk equipped with a counter. The free end of one of the rods is held fixed, while the free end of the second rod is moved over the perimeter of the flat surface to be measured – in this case the decal – allowing the calculation of the area of each lesion.

In the statistical analysis, the results of quantitative variables were described by mean values, medians, minimum and maximum values, and standard deviations. Qualitative variables were described by frequencies and percentages. The comparison of two groups regarding quantitative variables was performed using the non-parametric Mann-Whitney test. The association between quantitative variables was evaluated by estimating the Spearman correlation coefficient. Values of $p < 0.05$ indicated statistical significance. The data were analyzed using the software IBM SPSS v.20.0.

RESULTS

This study describes outcomes in 20 individuals bearers of cutaneous wounds with HGT (7 men and 13 women), with a mean age of 60.1 years (min = 37 years, max = 86). (Table 1)

The mean area of the wounds was 28.6 cm², with the largest being 157.1 cm² (lower limbs), and the smallest 1.2 cm² (head). The mean area of the HGT was 8 cm², with the largest being 37.7 cm² (lower limbs) and the smallest 1.2 cm² (head). The fastest healing occurred in 7 days, in a lumbar lesion, probably due to the fact that the triggering factor was removed (contact eczema caused by the adhesive plaster). The longest healing time occurred in lesions in the lower limbs. The number of sessions ranged from 1 to 3. The average area reduction per week was 4.4 cm², with a minimum of 0.63 cm² and a maximum of 13.1 cm². The weekly mean reduction percentage as compared to the baseline area was 32.5%, and ranged from 8.3% to 100% (Tables 1 and 2). The results suggest that there was statistical significance for these associations, in turn lending significance to the paired comparisons between the wounds' areas and the number of cryosurgery sessions ($p < 0.001$), the wounds' areas and the healing time ($p < 0.001$), the wounds' durations and the

Table 1: Patient data

Patient No.	Gender	Age (in years)	Anatomical site	Etiology	Wound area (in cm^2)	Duration (in weeks)	HGT area (in cm^2)	Number of cryosurgery sessions	Therapeutic outcome (HGT)	Wound healing time (weeks)
01	M	74	Head	Basal cell carcinoma excision	9,43	04	9,43	01	CURED	03
02	M	46	Head	Sebaceous nevus excision	42,4	08	15,7	02	CURED	04
03	F	49	Lower limb	Leg ulcer	21,99	08	3,14	01	CURED	03
04	F	59	Head	Basal cell carcinoma excision	12,56	03	10,18	01	CURED	03
05	F	72	Head	Basal cell carcinoma excision	11,30	04	5,65	01	CURED	03
06	M	59	Head	Basal cell carcinoma excision	6,28	04	6,28	01	CURED	02
07	F	70	Lower limb	Squamous cell carcinoma excision	14,85	04	1,57	02	CURED	04
08	F	63	Head	Basal cell carcinoma excision	1,2	04	1,2	01	CURED	02
09	M	37	Upper limb	Viral warts excision	4,71	03	4,71	01	CURED	02
10	F	47	Lower limb	Plantar perforation	19,6	16	3,14	02	CURED	12
11	F	61	Lower limb	Pyoderma gangrenosum	30,52	20	4,89	02	CURED	12
12	F	40	Trunk	Seborrheic keratosis excision	1,9	04	1,9	01	CURED	02
13	F	48	Trunk	Melanocytic nevus excision	2,54	03	2,54	01	CURED	02
14	M	66	Lower limb	Squamous cell carcinoma excision	157,0	08	7,95	02	CURED	12
15	F	43	Trunk	Seborrheic keratosis excision	3,14	03	3,14	01	CURED	01
16	F	86	Lower limb	Leg ulcer	28,27	24	19,63	03	CURED	08
17	M	75	Lower limb	Leg ulcer	6,28	04	6,28	01	CURED	02
18	M	56	Lower limb	Leg ulcer	75,4	24	37,7	03	CURED	08
19	F	81	Lower limb	Plantar perforation	9,42	28	9,42	02	CURED	12
20	F	69	Lower limb	Leg ulcer	113,1	48	6,28	02	CURED	12

HGT: Hypertrophic granulation tissue

Table 2: General descriptive statistics of the sample

	N.	Mean	Median	Min	Max	Standard Deviation
Idade (years)	20	60.1	60.0	37.0	86.0	14.1
Wound area (cm2)	20	28.6	11.9	1.2	157.0	41.0
Duration (weeks)	20	11.2	4.0	3.0	48.0	12.0
HGT area (cm2)	20	8.0	6.0	1.2	37.7	8.4
Number of cryotherapy sessions	20	1.6	1.0	1.0	3.0	0.7
Wound healing time (weeks)	20	5.5	3.0	1.0	12.0	4.3
Weekly area decrease (cm2)	20	4.4	3.1	0.63	13.1	3.6
Weekly area decrease percentage as compared to baseline	20	32.5	33.3	8.3	100.0	23.2

HGT: Hypertrophic granulation tissue

healing time (p <0.001), and the HGT areas with the number of cryosurgery sessions (0.046). However, the values of the correlation coefficients (0.45) suggest that these associations are not strong, despite being statistically significant. The correlation between the HGT area and the wounds' healing times was not statistically significant (P = 0.067) (Table 3). The results suggest the presence of statistical significance in the associations of the wound duration with the anatomic site (p = 0.037), the number of cryosurgery sessions with the anatomic site (p = 0.048), the wounds' healing times with the anatomic sites (P = 0.048), and the weekly area reduction percentage regarding the initial area with the anatomical site (p = 0.036). There was absence of statistical significance for the association between the wounds' areas and the anatomical site (p = 0.149), the HGT areas with the anatomical site (p = 0.660), and also the association between the weekly wound area reductions with the anatomical site (P = 0.961) (Table 4).

DISCUSSION

In 1913, the American neurosurgeon Dr. Irving S. Cooper was the first used cryosurgery with liquid nitrogen in brain tumors. In 1967, Dr. Setrag A. Zacarian developed a handheld device termed Kryospray, which popularized the use of this device.3

It is characterized by being cost effective and offering a fast recovery for the patient, who can return to his professional activities in a shorter time, as compared to other therapeutic methods. Cryosurgery produces selective destruction of compromised tissue, while the stroma promotes the subsequent repair of the wound. The collagen's and cartilage fibers' resistance to the damage caused by freezing favors the healing of the lesion.[4]

Liquid nitrogen based cryosurgery has been widely used given it is safe, offers good effectiveness, is easy to handle, yields good therapeutic and cosmetic results, and does not need anesthesia. The rapid loss of heat promotes the freezing of the skin's nerve endings, causing a pre-anesthetic effect. This freezing creates a momentary, uncomfortable burning sensation, which is however self-limited. Cryosurgery has been used for the treatment of a wide spectrum of diseases, encompassing benign, premalignant and malignant cutaneous lesions. Liquid nitrogen also stimulates the immune response and is currently deemed as the best cryogen.[5]

Freezing promotes crystallization of intracellular and extracellular water, culminating in cell death. Vascular stasis also occurs, contributing to the tissue's necrosis. It is important to note that this tissue destruction is selective. (Figure 2)

The pathophysiology of HGT formation is still unclear, however probable etiologies can be grouped into: inflammatory nature (type 1), causes linked to the wound's occlusive environment (type 2), and causes linked to some type of cellular imbalance (type 3). Regardless of the cause, it is important to rule out the possibility of malignancy. Type 1 is treated with the removal of the inflammatory or irritating factor. In cases of infection, it is important that the treatment includes systemic antibiotic therapy. Type 2 responds well to dressing changes – usually a permeable film that favors gas exchange at the interface of wound and dressing. In type 3 there may be internal or external causes of cellular imbalance. If external, they should be treated according to signs and symptoms using the same strategies used for types 1 and 2. If internal, the treatment is still unknown.[1]

Other treatment options described in the literature include mechanical, curettage or shaving debridement; chemical

Table 3: Evaluation of the association between quantitative variables

	N.	Spearman's correlation coefficient	p-value
Wound area (cm2) X No. of cryosurgery sessions	20	0.75	<0.001
Wound area (cm2) X Wound healing time (weeks)	20	0.82	<0.001
Wound duration (weeks) X No. of cryosurgery sessions	20	0.81	<0.001
Wound duration (weeks) X Wound healing time (weeks)	20	0.84	<0.001
HGT area (cm2) X No. of cryosurgery sessions	20	0.45	0.046
HGT area (cm2) X Wound healing time (weeks)	20	0.42	0.067

HGT area (cm2) X Wound healing time (weeks)

Table 4: Comparison of anatomical sites regarding quantitative variables

Variable	Anatomical site	N.	Mean	Median	Min	Max	Standard Deviation	p- value*
Wound area (cm^2)	Head	6	13.9	10.4	1.3	42.4	14.6	
	Limbs	11	43.7	22.0	4.71	157.0	50.0	0,149
Duration (weeks)	Head	6	4.5	4.0	3.0	8.0	1.8	
	Limbs	11	17.0	16.0	3.0	48.0	13.7	0,037
HGT area (cm2)	Head	6	8.1	7.9	1.3	15.7	4.9	
	Limbs	11	9.5	6.3	1.6	37.7	10.5	0,660
Number of cryotherapy sessions	Head	6	1.2	1.0	1.0	2.0	0.4	
	Limbs	11	1.9	2.0	1.0	3.0	0.7	0,048
Wound healing time (weeks)	Head	6	2.8	3.0	2.0	4.0	0.8	
	Limbs	11	7.9	8.0	2.0	12.0	4.4	0,048
Weekly area decrease (cm^2)	Head	6	4.2	3.5	0.6	10.6	3.4	
	Limbs	11	5.2	3.5	0.79	13	4.0	0,961
Weekly area decrease percentage as compared to baseline	Head	6	37.5	33.3	25.0	50.0	10.2	
	Limbs	11	20.5	12.5	8.33	50	16.7	0,036

* *Non-parametric Mann-Whitney test, p <0.05.*

* *HGT: Hypertrophic granulation tissue.*

* *Due to the small number of cases with a thorax wound (3 cases), this anatomical site was not analyzed in the comparison.*

cauterization, laser therapy, topical silver nitrate, phenol, copper sulphate and aluminum chloride.[6-9]

Mechanical removal of hypergranulation may cause a return to the inflammatory phase, resulting in a new wound, while the application of caustic agents may cause pain.[6] In turn, silver nitrate, if used frequently in large areas, can cause methemoglobinemia and hyponatraemia.[10,11]

The use of imiquimod has also been reported in the treatment of HGT in plantar perforation, with complete healing occurring after a 18-week period.[12]

The fact that there are several therapeutic options based on different methods demonstrates that HGT is a therapeutic problem, with lack of scientific reports on the advances in the area.[6]

In the present study, it was possible to observe that HGT interferes in the wound healing process, making reepithelialization difficult, due to the relief produced in the center of the wound, which interferes with the migration of keratinocytes. When left untreated, HGT can hinder healing for several weeks, producing a large volume of yellowish exudate. After treatment with cryosurgery the authors of the present article observed improvement of healing in the first week due to the flattening of the wound bed, which facilitates reepithelialization. (Figure 3)

Patients with extensive wounds with HGT in the lower limbs describe intense local pain. After the onset of reepithelialization and at the point which the skin has covered the wound, there is a reduction of the exudate and pain sensation (Figure 4A-4B-4C). In the present study, these signs were observed in

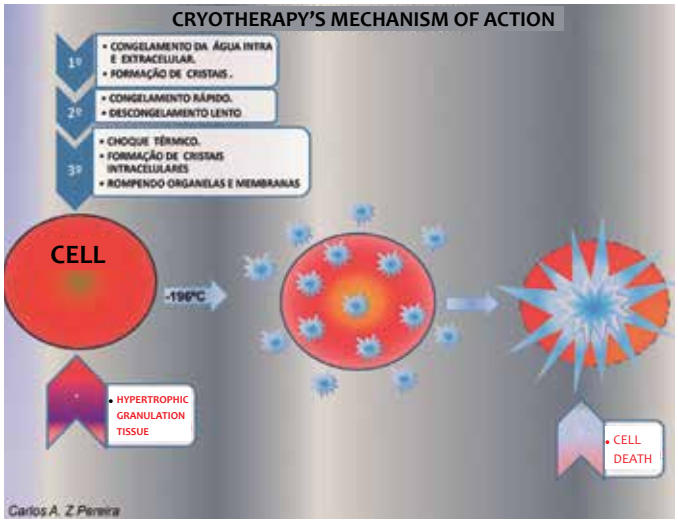

Figure 2: Schematic representation of the HGT freezing process using liquid nitrogen

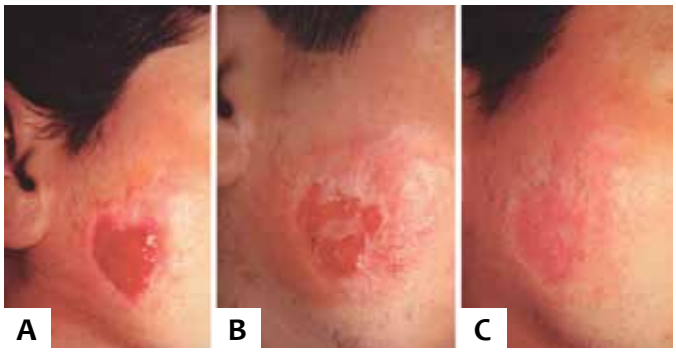

Figure 3: A - Surgical wound with HGT, **B -** Partial reepithelialization after 1 cryosurgery session **C -** Complete reepithelialization of the wound after 4 weeks and 2 cryosurgery sessions

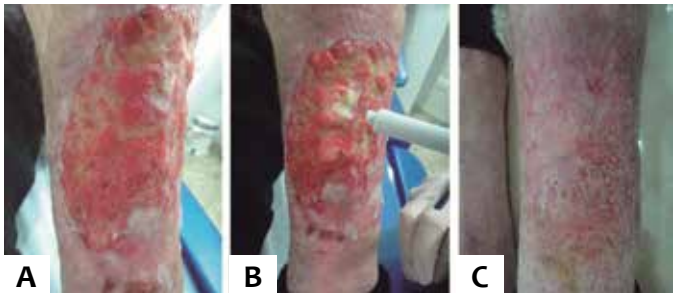

Figure 4: A - Surgical wound with HGT, **B -** Application of liquid nitrogen. **C -** After 2 sessions of cryosurgery, with complete reepithelialization of the wound in 12 weeks.

3 patients who had presence of HGT in the surgical wound, when dressing was performed in the postoperative period with antibiotic and clostebol cream, which has healing action.

In surgical wounds resulting from the excision of malignant neoplasias left to heal by second intention and developing with HGT, it is necessary to evaluate the histological examination's safety margins, in order to ensure the complete excision of the tumor.

In cases of leg ulcers that course with infection, it is important to request the culture and antibiogram before starting the antibiotic therapy.

Granulation tissue is important in the healing process of full thickness wounds, however when it becomes hypertrophic it should be diagnosed and treated as early as possible. Surgical wounds of partial thickness resulting from excision using the shaving technique can heal with the formation of HGT, as seen in patients who underwent excision of sebaceous and melanocytic nevi (Table 1).

No complications are observed in the cryosurgery technique, provided that the patients comply with the instructions, cleansing the wound and changing dressings using the recommended cream.

The treatment of ulcers with HGT in the lower limbs is difficult and prolonged, especially if the etiology is pyoderma gangrenosum or plantar perforation due to leprosy neuropathy. In these cases it is possible to make use of cryosurgery with antibiotic therapy, and treat the underlying disease. In the present study, the wounds that presented the longest cicatrization time were located in the lower limbs (Tables 1 and 4).

CONCLUSIONS

It is important to detect the formation of hypertrophic granulation tissue in the early stages in order to avoid long treatments that generate expenses and discomfort for the patient. Cryosurgery is a practical, cost effective, noninvasive method with a low incidence of complications and excellent therapeutic outcome, and can be indicated for the treatment of HGT in cutaneous wounds.

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Adverse reactions caused by the use of sunscreens

Reações adversas ocasionadas por uso de protetores solares

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ABSTRACT

Introduction: Overexposure of the skin to the sunlight can cause photoaging and promote the emergence of malignant neoplasms. Sunscreens are used to prevent these alterations and may occasionally cause adverse reactions in children and adults.

Objective: To analyze the frequency and types of adverse reactions caused by sunscreens in adults and children.

Methods: Data analysis of *in vivo*, non-invasive clinical studies performed at a clinical research institute.

Results: Data from 2,263 adults and 523 children were evaluated, with 13.92% and 4.44%, respectively, presenting some type of reaction.

Conclusions: Sunscreens are effective in preventing photoaging and skin cancer. Cosmetic formulations containing sunscreens may cause adverse reactions with low prevalence.

Keywords: sunscreening agents; control and sanitary supervision of cosmetics; sun protection factor; cosmetics

RESUMO

Introdução: *O excesso de exposição da pele ao sol pode ocasionar o fotoenvelhecimento e favorecer o surgimento de neoplasias malignas na pele. Assim, os protetores solares tornaram-se amplamente utilizados para a prevenção de danos solares, a curto e longo prazo. Podem ocasionalmente provocar reações adversas em crianças e adultos.*

Objetivo: *Analisar a frequencia e os tipos de reações adversas ocasionadas por protetores solares em adultos e crianças.*

Métodos: *Análise de banco de dados sobre estudos clínicos não invasivos in vivo, em face e corpo, realizados em instituto de pesquisa clínica, em São Paulo, Brasil.*

Resultados: *Foram avaliados de janeiro de 2014 a dezembro de 2015, dados de 2263 adultos e 523 crianças. 13,92% dos adultos e 4,44% das crianças apresentaram algum tipo de reação adversa leve.*

Conclusões: *Observou-se que os protetores solares são eficazes na prevenção do fotoenvelhecimento e câncer de pele. As formulações cosméticas com filtros solares podem ocasionar reações adversas com baixa prevalência.*

Palavras-chave: *protetores solares; controle e fiscalização de cosméticos; fator de proteção solar; cosméticos*

Original Articles

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INTRODUCTION

The skin is the human body's organ that comes in contact with the internal and external environments, thus exerting protective functions against microorganisms, harmful substances and radiations, in addition to helping to keep body temperature constant, preventing excessive loss of water, and producing vitamin D.[1] The skin's degree of exposure to the sun and its constant tanning can influence photoaging. Individuals exposed to sunny climates, living in regions where the ultraviolet (UV) radiation index is normally high, and who lack photoprotection habits may experience a higher degree of photoaging.[2] Another long-term consequence of excessive UV exposure is linked to cutaneous malignant neoplasms, which range from precancerous lesions – such as actinic keratosis – to invasive cancers – such as melanoma.[3]

Ultraviolet radiation is classified into A (UVA), B (UVB) and C (UVC), with UVC radiation being filtered by the Earth's ozone layer. Ultraviolet radiation type A (320nm-400nm) has a greater ability to penetrate the skin and is involved in most photoallergic reactions, some phototoxic reactions, carcinogenesis, and cutaneous photoaging.4 Ultraviolet radiation was classified as a Class I carcinogen by the International Agency for Research on Cancer.[5] The adverse effects range from cell necrosis to genomic instability.[6,7] Although UVB has been classified as a "causer of sunburn" and UVA as a "causer aging" by the lay public, a photobiological research focused on genotoxicity and immunomodulation found that skin cancer can be caused by both UVA and UVB radiation.[8,7]

Epidemiological data show a significant increase in the incidence of cutaneous neoplasms, especially non-melanoma epidermal tumors, in several countries. In 2016, the Brazilian National Cancer Institute (Inca) estimated 80,850 new cases of nonmelanoma skin cancer in men and 94,910 in women. These figures correspond to an estimated risk of 81.66 new cases per 100,000 men and 91.98 per 100,000 women.

Sunscreens have become widely used for the prevention of sun damage in the short and long terms, and are classified and regulated as medicaments in the USA, Canada and Australia, and as cosmetics in Europe.[9,10] In Brazil, according to the National Sanitary Surveillance Agency (ANVISA), a sunscreen is any cosmetic preparation intended to come into contact with the skin and lips for the exclusive or main purpose of protection against UVB and UVA rays by absorbing, dispersing or reflecting the radiation.[11] Sunscreens are currently influenced by the fast paced emergence of innovations, meaning that their formulations may present multiple UV blocks, in addition to excipients and other ingredients.[12] The use of sunscreens has been considered one of the most effective measures in the prevention of cutaneous neoplasias. Public health authorities recommend regular use in activities that imply exposure to the sunlight, such as working and practicing sports outdoors. However, the use of sunscreen alone should never be combined with increased exposure to the sunlight.[13] Some studies have suggested the existence of correlation between the use of sunscreen and melanoma, suggesting that the use of sunscreen increases the users' time of exposure to the sunlight, due to the fact that they would deem themselves exempt from the potential damage caused by the sun. It is possible to conclude, therefore, that the greater exposure to UV rays would lead to malignant alterations.[14,15] For this reason, photo-education campaigns have been stimulated and carried out, mainly in tropical countries. A recent European study evidenced that 87.1% of 1,816 dermatological patients reported the use of sunscreen.[16]

For adequate efficacy, a sunscreen formulation must contain chemical elements with absorption spectrum in the UVA and UVB radiation bands, in addition to being photostable. Moreover, for the ideal protective effect, the filter must be able to form a homogeneous film, distributing its ingredients evenly across the skin's surface.[17] Children need special photoprotection, as they are more susceptible to environmental threats than adults. Exposure to the sun during childhood and adolescence seems to set the conditions for the development of both melanoma and non-melanoma epidermal tumors in adulthood.[13] A study on the use of sunscreens in children included 157 patients aged three to 17 years. Ten children (6.4%) presented positive responses to contact phototesting when a standardized sequence of nine UV filters –or their own sunscreens – were applied: 4.5% reacted to UV filters and 5.7% reacted to their own sunscreens. The UV filters that caused reactions more frequently were benzophenone-3 and octyl methoxycinnamate.[18]

Photo-education campaigns have been important due to the fact that currently there is a lack of knowledge about photoprotection, justifying the necessity of an educational effort linked to the subject. Photo-education shows that sunscreens are not the only way to protect human skin from excessive exposure to the sun and that there are other forms of protection, such as the use of tents, sunglasses, photoprotective clothing and observation of the hours of risky exposure (10:00 am to 4:00 pm). Protection will be very effective when the various measures to reduce exposure to sunlight are used in combination.

OBJECTIVE

The objective of the present study was to analyze adverse reactions caused by sunscreens in adults and children, based on the results of *in vivo,* non-invasive clinical studies, performed at the Instituto de Pesquisa Dermato-Cosmética, located in the city of Campinas, São Paulo (SP), Brazil.

METHODS

An open, prospective clinical study was carried out from January 2014 to December 2015.

The recruitment of participants was conducted by Allergisa – Pesquisa DermatoCosmética Ltda., located in Campinas, São Paulo (SP), Brazil, where the analysis of the database relating to the results also took place. All clinical trials analyzed were conducted in accordance with the Declaration of Helsinki, the Brazilian National Health Council (CNS) Resolution No. 466/12 ANVISA, and the Document of the Americas and ICH E6 of Good Clinical Practice, complying with the directives es-

tablished by the Research Ethics Committee of the Institution. A total of 2,263 adults over the age of 18 and 523 children over 6 years of age were evaluated. The different clinical trials were based on the dermatological tests model described in ANVISA's safety evaluation guide for cosmetic products (Brazil, 2003).19

The volunteers were informed of the purpose, methodology and duration, advantages and clinical restrictions related to the study. Participants confirmed their interest in taking part by signing a Term of Consent. The technical documentation and database were made available to the researchers conducting the present study and will be kept on file for 5 years.

The participants of the analyzed surveys are healthy individuals, without complaints or reports of exacerbated cutaneous sensitivity and absence of history of reactions to the studied product's category. The products were used for a minimum of 21 days. The sunscreens application areas were the body and face. The volunteers were instructed on use of the products, with those observing the guidelines continuously throughout the proposed period having been selected for analysis. In cases of adverse events, dermatologist physician physicians evaluated the participants.

RESULTS

Based on the tabulation of the results analyzed, it was found that 13.92% of the adults and 4.44% of the children presented adverse reactions to the sunscreens (Figure 1).

During the course and at the end of each noninvasive clinical trial of the sunscreens, participants were given the opportunity to report possible adverse reactions. All possibilities of adverse reactions or clinical signs (depicted in Chart 1) were evaluated, diagnosed and treated by a dermatologist physician.

Adverse reactions diagnosed in adults by the dermatologist physician during the study period were: erythema, desquamation and erythematous papules and, in children, erythema, edema and vesicles. Adverse reactions were reported by the participants, however the final clinical diagnosis and treatment were conducted and completed by a dermatologist of the institution where the study was carried out.

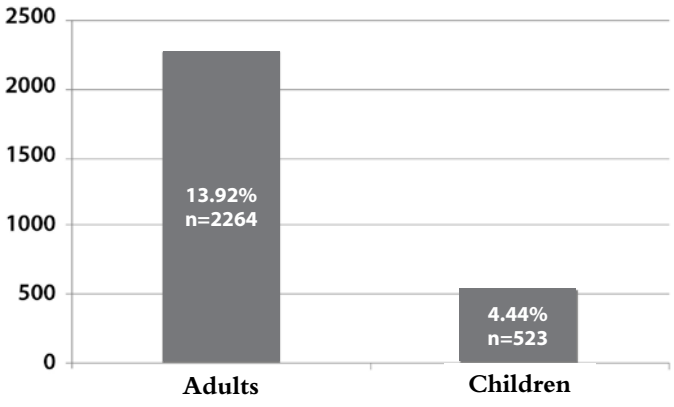

Chart 1: Analysis of adverse reactions of sunscreens in adults and children

Chart 1: Analysis of adverse reactions of sunscreens in adults and children

	ANALYZED GROUPS	
Period	**Adults**	**Children**
24 meses*	Erythema, desquamation and erythematous papules	Erythema, edema, and vesicular lesions

**January 2014 to December 2015*

DISCUSSION

The sunscreens market is constantly growing due to the fact that people are increasingly aware of the harmful effects of UV radiation, and also because of scientific progress and the emergence of new active principles, excipients and UV blockers.[12]

The compatibility among the components of a sunscreen, its effectiveness and safety are of paramount importance for safe use. The adverse reactions to these formulations are not frequent; nonetheless, the sensitization to a sunscreen's components may occur. It is worth noting that the use of sunscreens does not enable prolonged exposure to the sunlight, meaning that it is necessary to avoid exposure between 10:00am and 04:00pm in addition to make use of physical methods of protection against the sun, such as gloves and hats, among others.[9]

Regarding children, especially those under six years of age, photoprotection should be sought by associating the use of sunscreens with protective clothing, avoiding exposure at peak times of solar radiation.[20-22] This is due to the fact that some factors, such as the correct amount used and homogenization of the sunscreen over the entire body surface that will be exposed, are implied in the effectiveness of the photoprotection. Despite the fact that tests are performed prior to releasing the products in the marketplace, adverse reactions to cosmetics due to individual susceptibility to formulation components should also be considered,.[23,24]

Adverse reactions to sunscreens are described as sensations of local heat, erythema and pruritus, which may or may not disappear after a few hours. These phenomena were well documented, especially regarding sunscreens used in the 1990s.[25,26]

Several UV filters that are marketed as organic products are known to trigger allergic and photoallergic reactions, accounting for 55% to 80% of these cases.[27-29] The lipophilic nature of organic UV blockers as well as their small molecules allow greater penetration into the skin, a basic requirement for the onset of an allergic response.[30] Adverse reactions usually occur in the face, in special around the eyes.[26] Pustisek et al. [9] reported that adverse reactions to sunscreens are relatively rare and include irritation, and contact urticaria and dermatitis by primary, allergic, phototoxic and photoallergic irritations.

In an Australian study, 703 individuals applied a water-resistant sunscreen containing SPF 15 on a daily basis. The results

indicated that 114 (18.9%) of them developed adverse reactions to the sunscreen, with these reactions being diagnosed as inflammatory or acneiform eruptions, as well as contact urticarias.[31]

In the present study, the clinical signs of adverse reactions in children assessed and exposed to sunscreens were erythema, edema and vesicular lesions. In adults, clinically evident adverse reactions were erythema, desquamation and papules (Chart 1). The Brazilian National Sanitary Surveillance Agency (ANVISA) stated in 2013 that 7% of the 136 notifications of adverse events received by its cosmetics oversight sector referred to sunscreens.[32]

Despite adverse effects, sunscreens are important for protecting the skin from UVA and UVB radiation, and are effective in preventing damage caused by the sun, however they should be combined to other protective measures. Photo-education campaigns should be encouraged, as they are effective in preventing serious damage to the skin caused by excessive exposure to the sunlight. There is a clear need for mobilization of health authorities and governments, which should turn their attention to the treatment, as well as to the prevention and education of the general population regarding diseases of the skin.[20,33]

CONCLUSION

Sunscreens are effective in preventing photoaging and skin cancer, and their use has increased over the last decade, as people are increasingly aware of the harmful effects of excessive UV radiation. Diverse solar radiation blockers contained in the cosmetic formulation of sunscreens can cause adverse reactions, with low prevalence. ●

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Original Articles

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Nutraceutical compound increases collagen, elastin and hyaluronic acid synthesis

Composto nutracêutico aumenta a síntese de colágeno, elastina e ácido hialurônico

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ABSTRACT

Introduction*:* The use of nutraceutical products in order to attenuate signs of skin aging has been proposed in the literature. The stimulus to the synthesis of substances that support the dermis is one of the mechanisms linked to this effect.

Objective*:* To evaluate the effectiveness of a nutraceutical compound containing lutein, lycopene, vitamin C and manganese for the synthesis of collagen, elastin and hyaluronic acid.

Methods*:* An in vitro study was carried out based on the culture of human fibroblasts treated with the investigated product in different non-cytotoxic concentrations. The quantification of the elastin and collagen was performed with the assistance of spectrophotometric measurements. Hyaluronic acid was measure using a immunoenzymatic method.

Results*:* Cell cultures treated with the different concentrations of the product showed a significantly higher amount of synthesized collagen, elastin and hyaluronic acid as compared to the untreated culture ($p < 0.05$).

Conclusions*:* The use of the nutraceutical compound containing lycopene, vitamin C, lutein and manganese has shown in vitro efficacy for stimulating the synthesis of collagen, elastin and hyaluronic acid, components that are crucial for providing the dermis' supporting structure, being responsible for the skin's firmness and elasticity.

Keywords: Dermatology; Dietary Supplements; Skin Aging

RESUMO

Introdução: O uso de produtos nutracêuticos com a finalidade de atenuar os sinais do envelhecimento da pele tem sido proposto na literatura. O estímulo à síntese de elementos de sustentação da derme é um dos mecanismos relacionados a esse efeito.

Objetivo: Avaliar a eficácia de um nutracêutico contendo luteína, licopeno, vitamina C e mangânes na síntese de colágeno, elastina e ácido hialurônico.

Métodos: Estudo realizado in vitro, através de cultura de fibroblastos humanos tratadas com o produto investigado em diferentes concentrações não citotóxicas. A quantificação de elastina e colágeno foi determinada através de medidas espectrofotométricas enquanto que a de ácido hialurônico foi determinada por método imunoenzimático.

Resultados: As culturas celulares tratadas com as diferentes concentrações do produto apresentaram quantidade sintetizada de colágeno, elastina e ácido hialurônico significativamente maior quando comparadas com a cultura não tratada ($p<0,05$).

Conclusões: O uso de nutracêutico contendo licopeno, vitamina C, luteína e manganês demonstrou eficácia *in vitro* no estímulo à síntese de colágeno, elastina e ácido hialurônico, elementos essenciais na estrutura de sustentação da derme e responsáveis pelas características de firmeza e elasticidade da pele.

Palavras-chave: dermatologia; suplementos dietéticos; envelhecimento da pele

INTRODUCTION

The interest of dermatology for oral nutrients supplementation aimed at controlling the cutaneous aging process has been increasing substantially.

Modern life, especially in large urban centers, imposes a condition that favors inadequate ingestion of nutrients, with an impact on the skin's and adnexa's health.[1] Excessive work, stressful routines, inadequate sleeping periods, and diets based on industrialized foods with high levels of carbohydrates and fats, as well as reduced content of vitamins and trace elements, are conditions that lead to the development of a picture described as "hidden hunger", meaning a borderline deficiency of certain nutrients, nevertheless without the clinical evidence of malnutrition.[2]

In the process of skin aging, in addition to the intrinsic cellular functional decline that is common to all organs, there are extrinsic factors, such as ultraviolet radiation, which can intensify the aging process via a complex biological mechanism that affects the various skin layers, is special the dermis' connective tissue.[3] Alterations in the components of the extracellular matrix responsible for the supporting structure of the dermis [4] – elastin, collagen and hyaluronic acid – induce the loss of viscoelasticity in the cutaneous tissue, with reduction of firmness and elasticity, clinically culminating with the emergence and accentuation of wrinkles, furrows and flaccidity.[5]

In the pathogenesis of photoaging, reactive oxygen species have a central role, consuming and damaging enzymatic and non-enzymatic antioxidant systems of the skin, destabilizing molecules and triggering chain reactions, causing damage to membranes and structural proteins.[3] One of the primary events in reactive oxygen species (ROS) induced photodamage is the activation of transcription factors – such as the nuclear factor kappa B (NFkB) and the activator protein-1 (AP-1). These factors are involved in the regulation of the expression of several genes responsible for inflammation, tissue remodeling, oncogenesis, apoptosis and many degenerative processes associated with aging.[6,7] Baseline levels of matrix metalloproteinases (Matrix Metalloproteinases - MMPs) are higher in aged skins as compared to younger skins, with the activation of AP-1 leading to an increase in the levels of MMPs, with greater collagen and elastin degradation.[5]

Recent evidence has shown that diets with a high content of vegetables, fruits and grains may reduce the risk of numerous diseases, with this benefit being linked to the presence of antioxidant substances.8

Antioxidants act on different levels protecting organisms against free radicals and are the first defense mechanism aimed at preventing their formation, particularly by inhibiting chain reactions with iron and copper.

In addition, antioxidants are capable to intercept free radicals generated by the cellular metabolism or exogenous sources, preventing their action on lipids, amino acids, polyunsaturated fatty acids' double bond, and DNA bases, avoiding cellular structural damage.[9]

Carotenoids and vitamin C stand out among nutrients with antioxidant action intended for the prevention and treatment of cutaneous aging. They are not synthesized by the body and should be acquired through diet or oral supplementation.[10]

Vitamin C is a powerful free radicals neutralizer. Its use, either topically or orally, has been proposed in programs aimed at mitigating the aging process.[5]

Previous studies have demonstrated the benefit of using carotenoids in the prevention and treatment of damages caused by sunlight and photoaging.[10] Oral supplementation with lycopene and lutein has been evaluated within a program of aging prevention and treatment, with encouraging results.[11]

In this way, the objective of the present study was to evaluate the efficacy of a nutraceutical product containing lycopene, lutein, vitamin C and manganese in the synthesis of the skin's structural supporting elements, using human fibroblast culture models.

METHODS

Ethical aspects

The experimental conditions adopted – the use of human cells under optimum cultivation conditions – are in line with the current methodologies applied, accepted and validated by the international scientific community. The human cell cultures used in the present study were commercially acquired from qualified and certified international companies.

Methodological procedures

Culture of human fibroblasts

Human fibroblasts (Clonetics, Cambrex / Lonza, USA) were commercially obtained, grown and expanded in culture medium containing 90% RPMI-1640 and 10% fetal bovine serum (GIBCO Life Technologies, Baltimore, USA), plus antibiotic solution 0.02 µg/mL gentamicin (Sigma Chemical St. Louis, USA) and 0.25 µg/mL amphotericin B (GIBCO Life Technologies, Baltimore, USA), having been seeded in 75cm^2 vials (Nunc, USA) and kept in a humidified incubator (Thermo Fisher) with 5% CO2 atmosphere at 37 °C. The culture medium was changed every 48 hours up until the cells had 70-80% confluence, being subsequently trypsinized and counted in Neubauer's chamber for determination of cell density. After having been counted, the fibroblasts were established by the sowing of 1.5x105 cells/well or 1x104 cells/well in plates containing 6 or 96 wells (Nunc, USA), respectively.

For the determination of the non-cytotoxic concentrations of the nutraceutical compound, a preliminary cytotoxicity trial was performed using the XTT method (data not shown). Twenty-four hours after the initial seeding, the cell cultures were treated with three non-cytotoxic concentrations of the nutraceutical compound (0.065 mg/mL, 0.0325 mg/mL and 0.0163 mg/mL) for 72 hours. Subsequently, the culture's supernatant was collected for evaluation of the proposed parameters.

Evaluation of the collagen, elastin and hyaluronic acid

The extracellular matrix elements were measured in the fibroblast culture's supernatant using commercially available kits. The levels of collagen and elastin were determined by colorimetric trial (Biocolor, Belfast, Ireland), while hyaluronic acid levels were quantified by immunoenzymatic trial (ELISA sandwich) (R&D Systems, USA). The data obtained from the quantification of collagen, elastin and hyaluronic acid were expressed in pg/mL, mg/mL and ng/mL, respectively, and computed based on the standard curve's reference values.

Statistical analysis

For the characterization of the statistical data, a parametric method for analysis of variance (P) (ANOVA) was applied followed by a multiple comparison test, termed Dunnett. In all groups studied, those whose P values were less than 0.05 were considered statistically significant.

Studied product

The test product contains lycopene, vitamin C, manganese and lutein.

RESULTS

Evaluation of elastin synthesis

The nutraceutical product led to an increase in the synthesis of elastin in culture of human fibroblasts, incubated for 72 hours with the product, when applied at concentrations of 0.065, 0.0325 and 0.0163 (mg / mL), at 27%, 22% and 21%, respectively, when compared to the Basal Control group (Graph 1). The result was statistically significant ($p < 0.05$) at the concentration of 0.065 mg/mL.

Evaluation of collagen synthesis

The nutraceutical product was capable to significantly increase ($p < 0.05$) collagen levels at concentrations of 0.0650, 0.0325 and 0.0163 (mg/mL), yielding an increase of 9.49, 9.75 and 10%, 12%, respectively, *vis a vis* the Basal Control, when applied in culture of human fibroblasts for a period of 72 hours (Graph 2).

Evaluation of hyaluronic acid synthesis

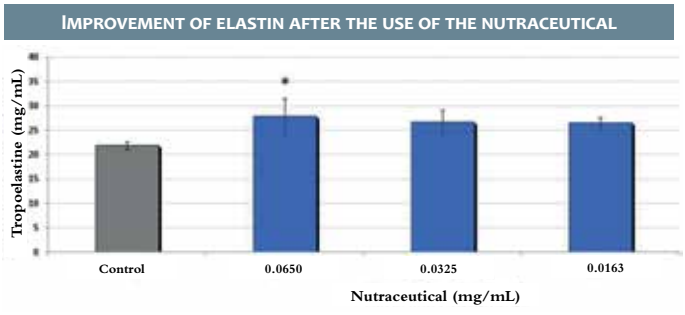
The nutraceutical product increased the concentration of hyaluronic acid in culture of human fibroblasts, incubated for 72 hours with the product, when applied at concentrations of 0.065, 0.0325 and 0.0163 (mg/mL), at 53%, 29% and 11%, respectively, when compared with the Basal Control group. The result was statistically significant ($p < 0.05$) for the 0.065 and 0.0325 mg/mL concentrations. (Graph 3)

DISCUSSION

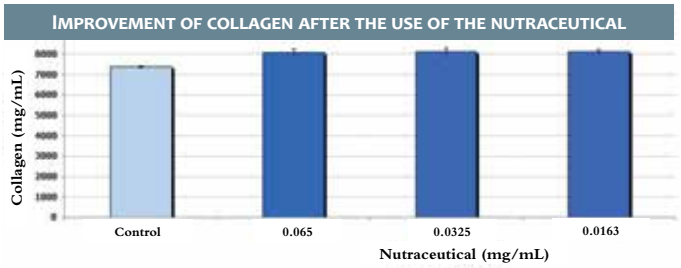
The increase in life expectancy has raised concerns about the development of preventive and restorative measures for the aging process.17 Measures already recognized as effective for the prevention and treatment of cutaneous aging include the adequate use of sunscreens18 and cosmetic products with therapeutic action (cosmeceuticals)[10,19] acting primarily through antioxidation and hydration.

More recently, evidence of the nutritional impact on the skin has been presented.[4]

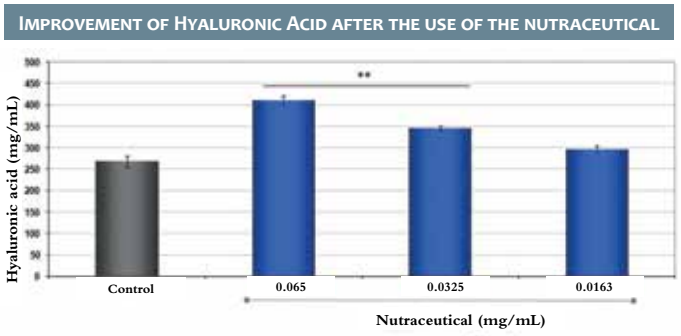
A previous study19 evaluated the clinical efficacy of an oral supplement based on marine protein, concentrated acerola, concentrated grape seed extract, and tomato extract. After 360 days of use, the volunteers treated with the product had clinical evidence of improvement in the signs related to skin aging. These signs included the improvement of wrinkles, solar melanoses, hydration, lushness and improvement of the general ap-



GRAPH 1: Results regarding the quantification of elastin in the control fibroblast culture (untreated) and in that treated with the nutraceutical product in different concentrations



GRAPH 2: Results regarding the quantification of collagen in the control fibroblast culture (untreated) and in that treated with the nutraceutical product in different concentrations



GRAPH 3: Results regarding the quantification of hyaluronic acid in the control fibroblast culture (untreated) and in that treated with the nutraceutical product in different concentrations

pearance of the skin, associated to the ultrasonic improvement in the density of both photoprotected and photoexposed skin.

Among the agents studied, vitamin C and carotenoids – in particular lycopene and lutein – have been linked, especially in associations, to benefits for improving the quality of the dermis' supporting structure.[9,10] In 2006, Heinrich et al.[11] evaluated the use of oral supplementation with carotenoids containing lycopene and lutein, demonstrating improvement in clinical parameters such as density, skin thickness, roughness and scaling. The mechanism by which this action takes place is not yet completely established, however it is believed to involve these elements' strong antioxidant properties, reducing the oxidative stress and its destructive effects on cellular structures, such as fibroblasts.5 Nevertheless, the effects of the association of vitamin C, lycopene, lutein and manganese assessed in the present study seems not to be restricted to the inhibition of the degradation of ROS-induced collagen and elastin. The results showed that there was a significant increase in the synthesis of collagen, elastin and hyaluronic acid, three essential components of the extracellular matrix that are responsible for the dermis' supporting structure.

The present study's findings may derive from the associated effects of lutein and lycopene, which are important agents with anti-inflammatory and antioxidant action;[12] of manganese, a necessary element for optimal activity of the enzymes involved in the synthesis of glycosaminoglycans,[13] and vitamin C, a cofactor in the hydroxylation of proline and lysine, essential amino acids in the process of collagen synthesis and capable to inhibit the accumulation of degraded elastin.[14]

Lutein is able to modify the extracellular matrix's remodeling that occurs after exposure to ultraviolet radiation, through a beneficial effect on the regulation of metalloproteinases, in addition to inhibitory effects on cell loss, cell membrane damage and elastin expression.[5]

In addition, lutein increased the synthesis of hyaluronic acid in *in vitro* studies by increasing the expression of hyaluronan synthetase,[3] which can justify the improvement in parameters such as skin roughness, since hyaluronic acid plays an important role in the maintenance of cutaneous hydration, anti-oxidation, as well as acting as a signaling molecule in response to skin damage.[15,16]

It is inferred from the stimulus to the synthesis of collagen and elastic fibers, and hyaluronic acid that the nutritional association presented is capable of positively interfering in the skin aging process, particularly in maintaining the dermis' viscoelasticity properties, thus allowing a greater firmness and elasticity of the skin.

CONCLUSION

The use of an association containing vitamin C, lutein, lycopene and manganese has demonstrated the ability to stimulate the synthesis of collagen, elastin and hyaluronic acid in a fibroblast culture model, contributing to the improvement of the dermis' supporting structure. As a result, it can slow down the skin aging process. ●

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Original Articles

The median-frontal flap for nasal reconstruction

Retalho mediofrontal para reconstrução nasal

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ABSTRACT

Introduction: The use of a median-frontal flap for nasal reconstruction was first described in 600 B.C., and it is still widely used for the reconstruction of nasal tumoral lesions.
Objective: To report the experience of a medical school's plastic surgery service in the use of this flap type.
Methods: A retrospective descriptive study was carried out with a series of 35 cases surgically treated from January 2005 to June 2015.
Results: The patients' mean age was 68.6 (± 10.8) years, with a predominance of the male gender (68.6%). The median-frontal flap was used for reconstruction after resection of tumors, with basal cell carcinoma being the most frequent.
Conclusions: The median-frontal flap is the ideal reconstructive choice for many patients, with good aesthetic and functional outcomes.
Keywords: surgical flaps; reconstruction; nose; nose neoplasms

RESUMO

Introdução: *O retalho mediofrontal foi descrito 600 anos antes de Cristo para a reconstrução nasal, mas é ainda muito utilizado na reconstrução das lesões nasais tumorais.*
Objetivo: *Relatar a experiência de um serviço universitário de cirurgia plástica no uso desse retalho.*
Métodos: *Foi realizado o estudo restrospectivo descritivo de uma série de 35 casos operados em período de dez anos e seis meses.*
Resultados: *A idade média dos pacientes foi de 68,6 anos com predomínio do gênero masculino. O retalho mediofrontal foi utilizado para reconstrução após ressecção de tumores, sendo o carcinoma basocelular o mais frequente.*
Conclusões: *O retalho mediofrontal representa a escolha ideal reconstrutiva para muitos pacientes com bom resultado estético e funcional.*
Palavras-chave: *retalhos cirúrgicos; reconstrução; nariz; neoplasias nasais*

INTRODUCTION

The history of nasal reconstruction has its roots in ancient times. Adultery was punished with the amputation of the nose in ancient India, with reports of reconstructive surgeries performed in the nasal region.[1]

The nose's skin is one of the most common sites for skin cancer and one of the most complex anatomical regions for reconstruction.[2] The first advances in the search for techniques capable of improving the outcomes of nasal flaps were accomplished between the years of 1874 and 1879 by Carpue et al., who proposed to fold the edges of frontal flaps in order to reduce the bloody area, thus decreasing infection, fibrosis and retraction, as well as leading to better aesthetic results.[3,4] Today the paramedian frontal flap is a standard procedure in nasal reconstructive surgery, allowing the reconstruction of extensive nasal defects.

Skin tumors are the main indication for nasal reconstruction surgery nowadays.[5] Basal cell carcinoma is the most common tumor in this region, followed by squamous cell carcinoma.[1] The Brazilian southern city of Florianópolis has a high index of incidence of cutaneous tumors due to the fact that most of the population is of Caucasian origin and has the habit of exposure to the sun.

The present article is aimed at demonstrating the median-frontal flap's versatility for extensive nasal reconstruction. The Plastic Surgery Department, University Hospital, Universidade Federal de Santa Catarina (HU-UFSC, Santa Catarina State, Brazil) aims at using this technique as a standard, which promotes training in the method and leads to positive results with fewer interventions.

METHODS

A retrospective descriptive study was carried out with a case series, based on a review of medical records and an images database of patients bearers of tumors in the nose, who underwent surgery at the Plastic Surgery and Burns Department at the HU-UFSC, in the period spanning from January 2005 to June 2015.

The following variables were analyzed: *age*, *gender*, *histological type*, *affected nasal subunits*, *postoperative complications*, *type of anesthesia*, *tumor recurrence* and *number of surgical interventions*. The following nasal anatomical subunits quoted in the literature were considered:6 1) nasal root, 2) nasal dorsum, 3) lateral wall, 4) tip, 5) ala, 6) columella.

Statistical analysis was performed with the help of the SPSS (Statistical Package for Social Sciences) version 19.0 software. The continuous variables were represented by mean values and standard deviations, while categories, by absolute values and percentages. The Student's t-test was used to compare mean values. The significance level (alpha) was set at 5%.

The study strictly complied with the ethical principles set by the 2013 revision of the Declaration of Helsinki. The patients signed a term of consent allowing the use of their medical records and the publication of images.

TECHNIQUE DESCRIPTION

The median-frontal flap is the gold standard for any nasal reconstruction due to the large amount of tissue it provides, with good color and texture resemblance regarding the nose's skin. Surgery can be performed under sedation or preferably with general anesthesia. The primary defect should be evaluated before the execution of the median-frontal flap. Following the evaluation and marking, the patient is placed in dorsal decubitus and local injection of anesthetic and hemostatic solution is carried out. Next, the lesion's resection is performed with safety margins.

The following technique was used for the execution of the median-frontal flap:

1. Maintenance of the axial direction whenever possible.

2. Use of a pedicle ipsilateral to the defect with a variable width of 1.3 to 1.5cm, located 2cm from the lateral of the midline.

3. The initial flap elevation is carried out distally. The upper third is detached only with skin and subcutaneous tissue. The dissection is deepened in the middle third of the frontal region, incorporating the muscle in the flap.

4. Subsequently, the dissection is performed subperiosteally 1cm above the eyebrow, continuing up until the orbits rhyme, along the configuration of the supratrochlear artery, as shown in figure 1A.

5. The medial rotation of the pedicle is carried out.

6. The insertion of the flap in the recipient area is performed by means of an absorbable suture along its entire border, aimed at reducing the risk of postoperative bleeding.

7. In case of bone and / or cartilage loss, the first option of donor areas are the septal and conchal cartilages.[8] Primary suture is performed in the lower third of the frontal region, while in the upper two-thirds healing takes place by second intention.

9. Between 4 and 6 weeks later the section of the pedicle is performed with local anesthesia.

RESULTS

The HU-UFSC's Plastic Surgery and Burns Department performed 35 surgeries of nasal reconstruction with median-frontal flap following resection of tumors during the evaluated period. Regarding the study sample, the mean age was 68.6 (± 10.8), ranging from 36 to 80 years. The male gender was the most prevalent, with 24 (68.6%) individuals. Regarding the histological type, basal cell carcinoma had predominance, with 19 (54.3%) cases, followed by squamous cell carcinoma, with 16 (45.7%) cases. The predominant nasal anatomic subunit was the "5-6". Table 1 shows the characteristics of the patients included in the study.

Regarding perioperative complications, the authors found a prevalence of 2 cases (5.7%) of nasal tip necrosis, 3 (8.6%) of hematomas and 1 (2.9%) of infection. Hematoma occurred in the first six hours, with all three cases undergoing re-intervention. One case had infection, treated with oral antibiotic therapy for 7 days. General anesthesia was the most used method, having been employed in 33 cases (94.2%). During the follow-up period, 3 (8.6%) patients had tumor recurrence. The mean number of interventions was 2.49 (SD = 0.81, min = 2, max = 5). Table 2 shows the patients' perioperative characteristics.

Figure 1A shows the patient in the preoperative period, Figure 1B shows the tumor resection marking on the nasal dorsum, and Figure 1C illustrates the transoperative period after the tumor's resection with the marking of the median-frontal flap. Figure 1D shows the immediate postoperative and Figure 1E, the postoperative 60 days later.

DISCUSSION

The median-frontal flap is the gold standard for any nasal reconstruction given the amount of tissue it provides and the similarity of color and texture to those of the nose's skin.[7] Indications for nasal reconstruction arise from multifactorial cases. In the present study, this flap type was used after nasal tumor resection in 35 cases operated at the HU-UFSC's Plastic Surgery and Burns Department.

Table 1: Characteristics of patients with diagnosis of skin tumor who underwent resection and reconstruction with median-frontal flap (n = 35)

Age (years) µ	68.6 (±10.8)	36-80
Male gender ¥	24	68.6%
Tumor's histological type ¥		
Basal cell carcinoma	19	54.3%
Basal cell carcinoma	16	45.7%
Affected nasal anatomic subunits ¥		
1-2	3	8.6%
3-4	9	25.7%
5-6	13	37.1%
7	5	14.3%

µ Mean ± standard deviation, minimum-maximum; ¥ Absolute value - percentage

Table 2: Perioperative characteristics of the patients (n = 35)

Operative complications ¥		
Nasal tip necrosis	2	5.7%
Hematoma	3	8.6%
Infection	1	2.9%
Absence of complications	29	82.9%
Anesthetic type ¥		
General venous + inhalation	33	94.2%
Local + sedation	2	5.71%
Tumor recurrence ¥	3	8.6%
Number of interventions µ	2,49 (0,81)	(2-5)

µ Mean ± (standard deviation, minimum-maximum; ¥ Absolute value - percentage

Tumors – mainly basal cell carcinoma and epidermoid carcinoma – are the main surgical indication for nasal reconstruction.[5] Basal cell carcinoma (BCC) was the most frequent histological subtype found (54.3%) after resection of the lesion, followed by the squamous cell carcinoma (45.7%), corroborating the literature's data.[8] The nasal pyramid is the most common site for malignant tumors of the head and neck, which have particular predilection for areas exposed to the sun.[9]

In the present study, there was a higher incidence (37.1%) of lesions in the nasal ala and columella (subunits 5-6). On the other hand, (41.50%) the literature reports a higher incidence in the nasal dorsum.

The mean age of the operated patients was 68.6 (± 10.8), ranging from 36 to 80 years. According to the literature, the elderly experience more cutaneous neoplasias as compared to the younger population.[1]

In the reported cases, the male gender was the most prevalent, with 24 (68.6%) occurrences. According to data from the Brazilian National Cancer Institute (Inca), there is an estimated risk of 100.75 new cases per 100,000 men and 82.24 per 100,000 women, regarding the onset of nonmelanoma cutaneous neoplasms.[10]

The choice of reconstructive method is based on the size, location and depth of the defect to be corrected. In the present study the median-frontal flap was used as the best therapeutic option for the cases demanding reconstruction. The outcomes were deemed satisfactory for both the patient and the medical team. Refinements are required in most cases, with the mean value of interventions calculated at 2.49 (SD = 0.81, min = 2, max = 5) in the present study. A cohort study published by Santos Stahl et al.11 in 2013 shows that performing a two-stage reconstruction – rather than a three-stage procedure – for the refinement of the flap does not increase the rate of complications like partial ischemia or flap necrosis.

Surgery can be performed under sedation or, preferably, with general anesthesia, which was used in 94.2% of the studied cases. The gold standard in the treatment of cutaneous neoplasms is the removal of the lesion followed by a freezing biopsy aimed at defining the surgical margins. Unfortunately in the authors' medical service this treatment is not usually offered due to possible difficulties for performing the examination. The Head and Neck Surgery team performed most of the resections. Late reconstruction was performed in 5 cases.

Potential complications of the median-frontal flap include bleeding, pain, inadequate healing, infection, dehiscence, distortion of free margins, and flap necrosis.[12] Of the cases evaluated, 17.2% had postoperative complications, with hematoma being the most common. Cases that progressed with hematoma required surgical re-intervention.

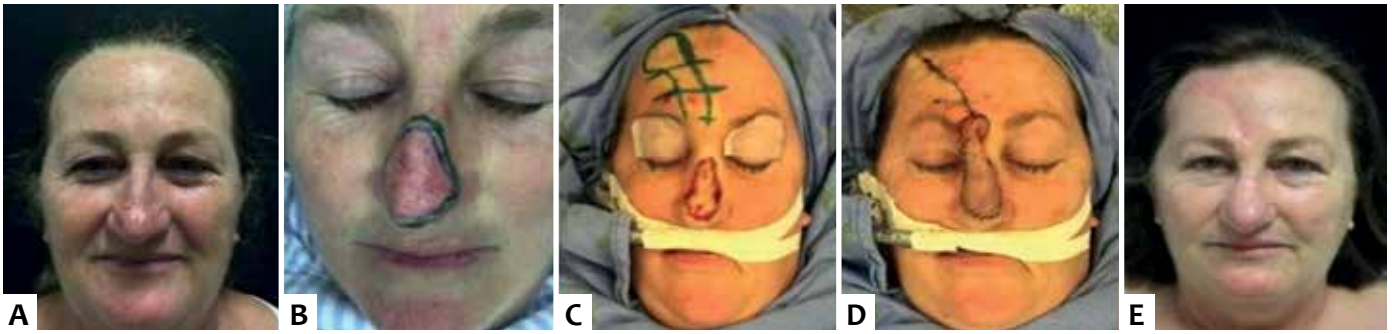

Figure 1: A - Preoperative. **B** - Marking. **C** - Tumor's post-resection. **D** - Immediate postoperative. **E** - Sixty days after surgery

CONCLUSION

The frontal flap is the ideal reconstructive choice in many patients and can be performed safely and reliably in a hospital setting.

This technique allows the restoration of the nose's function, preserving good ventilatory permeability and good aesthetic outcome. Therefore, the technique was instituted as the standard method for nasal reconstruction after resection of neoplasias in the authors' medical service.

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Original Articles

The effect of intraoral 2,940nm non-ablative Erbium:YAG laser on the rejuvenation of the upper lip: a pilot study

Efeito do laser não ablativo Erbium YAG 2940nm intraoral no rejuvenescimento do lábio superior: estudo-piloto

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ABSTRACT

Introduction: Increased distance between the base of the nose and lip's vermilion is difficult to treat, and often there are restrictions for the use of botulinum toxin and cutaneous fillers.
Objective: To describe a new technique for the treatment of the upper lip ptosis.
Methods: A prospective pilot study was conducted with 15 female patients bearing increased distance between the base of the nose and the labial cutaneous-mucosal transition line. Five weekly sessions of intraoral non-ablative 2,940nm Er:YAG laser were performed. For the evaluation of outcomes, standardized records were performed with a 3D photographic camera, and comparative measurements of the philtrum's height and the nasolabial angle were taken before and after the treatment.
Results: There was a shortening ranging from 2 to 4 mm in the philtrum's measurements, and a decrease in the nasolabial angle, in addition to increased firmness of the skin in the upper lip.
Conclusion: Intraoral non-ablative 2,940nm Er:YAG laser can be a therapeutic option for the treatment of upper lip ptosis.
Keywords: Aging; Lasers; Lip

RESUMO

Introdução: *O aumento da distância entre a base do nariz e o vermelhão do lábio é de difícil tratamento, e muitas vezes apresenta limites para o uso de toxina botulínica e preenchedores.*
Objetivo: *Descrever nova técnica para o tratamento da ptose do lábio superior.*
Métodos: *Realizado estudo-piloto prospectivo com 15 pacientes do sexo feminino que apresentavam aumento da distância entre a base do nariz e a linha de transição cutâneo-mucosa labial. Foram realizadas cinco sessões semanais de laser não ablativo Er:YAG 2940nm intraoral. Para a avaliação dos resultados, foram feitos registro padronizado com câmera fotográfica de 3D e medidas comparativas da altura do filtro e do ângulo subnasal, antes e após o tratamento.*
Resultado: *Observou-se encurtamento que variou de dois a 4mm nas medidas do filtro, e diminuição do ângulo subnasal, além de maior firmeza da pele do lábio superior.*
Conclusão: *O laser não ablativo Er:YAG 2940nm intraoral pode ser opção terapêutica para a ptose do lábio superior.*
Palavras-chave: *Rejuvenescimento; Lasers; Lábio*

INTRODUCTION

The increase in the distance between the base of the nose and the cutaneous-mucosal line of the lips, resulting from sagging skin, which loses turgor and elasticity, is an important characteristic in the natural process of chronological aging and photoaging processes of the lower third of the face. In young people, the upper lip presents a slight convexity in the region of the cupid's bow and the philtrum, however there is flattening and elongation in this region over time. Also, the vermilion of the lips is characteristically turgid in young people; nevertheless

its thickness decreases with the aging process, and perioral wrinkles emerge at the same time (Figure 1).

Although botulinum toxin and hyaluronic acid are of great help in facial rejuvenation, the increase in the height of the upper lip's cutaneous portion limits its use in minimally invasive procedures.[1] In this manner, in order to treat this condition, it is necessary to resort to surgical techniques, which not all patients are willing to undergo. [2-4]

Non-ablative Er:YAG laser is a relatively new technology. This 2,940nm laser exerts a thermal effect that remodels the collagen and also stimulates the induction of neocollagenesis when applied to the oral mucosa set at the *smooth* mode. Among the few existing publications on this technology, some address the reduction of the nasogenian fold and perioral wrinkles. [5-8]

METHODS

A prospective pilot study was conducted with 15 volunteer women aged 45 to 72 years, and II to IV Fitzpatrick phototypes, originary from Santiago, Chile. The patients were submitted to five weekly sessions of intraoral non-ablative 2,940nm Er:YAG laser (Dynamis® SP, Fotona, Ljubljana, Slovenia) set at the *smooth* mode, with the following parameters: 9J/cm^2, 1.8Hz, Spot 7mm. The shots were geometrically delivered in four rows and were performed only in the inner region of the labial mucosa. The exclusion criterion was trauma and active bacterial or viral infections in the treatment area. The study complied with the Helsinki Declaration.

The evaluations were performed based on standardized photographs taken with the Vectra H1® camera (Canfield, NJ, USA), which generates 3D images and measurements of the length of the philtrum and nasolabial angle, before and after the five weekly laser sessions, aimed at providing a quantitative measurement of the results (Figure 2).

RESULTS

Based on the quantitative evaluation of the philtrum's distance, it was possible to conclude that 60% of patients experienced a 4mm decrease in the philtrum's length, while 30% of them had a 3mm decrease, and 20% had a 2mm decrease (Figure 3).

Analyzing the standardized photographs with the Vectra H1 camera, it was possible to observe an improvement in the projection of the upper lip: 40% of the cases had a 5º decrease in the nasolabial angle, while 60% of cases experienced a 3º decrease.

As a consequence, there was a slight increase of the prominence of the cupid's bow and a slight eversion of the vermilion in all cases (Figure 4).

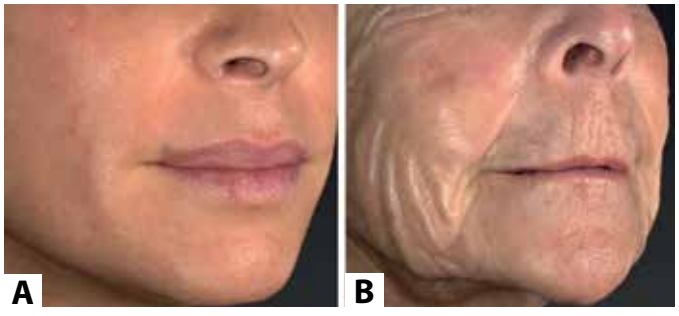

Figure 1: Perioral Aging - **A:** Young lips; **B:** Aged lips

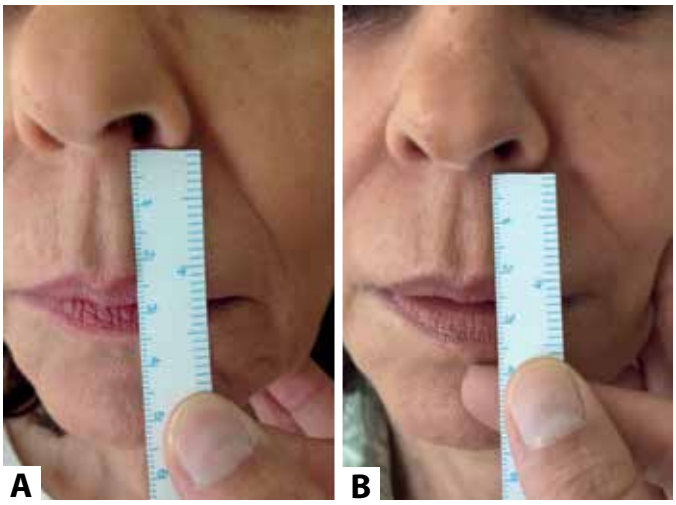

Figure 2: Measurement of the philtrum's length
A: Before; **B:** After five non-ablative intraoral Er:YAG laser sessions

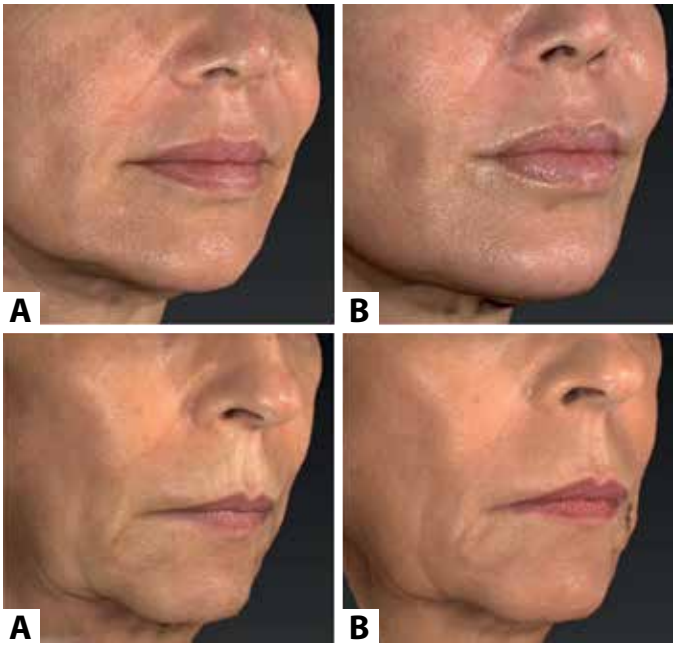

Figure 3: A - Before; **B** - After five laser sessions

DISCUSSION

In the global approach to rejuvenation with minimally invasive procedures, increasing the distance between the base of the nose and the lip's cutaneous-mucosal transition is a proposition that has few therapeutic alternatives.

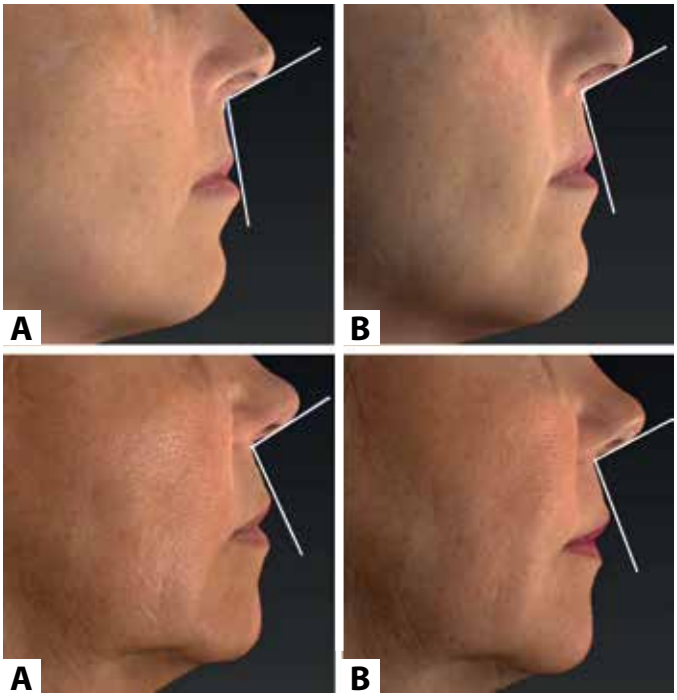

Figure 4: Modification of the subnasal angle - **A:** Before, **B:** After five laser sessions

The injection of botulinum toxin in the orbicularis muscle of the lips can be used with the purpose of inducing eversion of the vermillion, however its use is limited by the limited number of units that can be applied in this region due to the risk of the impact it might have on the harmony of the facial mimicry of the lower third and on the chewing process.

As a matter of fact, although widely used in the perioral region, hyaluronic acid based cutaneous fillings produce a highly unsightly effect that go against the rules of facial proportionality 3 in case the vermilion's volume is increased to compensate for the vertical elongation of the cutaneous portion of the upper lip.

The literature cites surgical techniques that can be used to correct ptosis in the upper lip, 2-4 however many patients prefer less invasive procedures that offer no possibility of scars.

After five non-ablative 2,940nm Er:YAG laser intraoral treatment sessions carried out in this pilot study, it was possible to demonstrate the presence of a decrease in the philtrum's length and vermilion eversion.

In 2013, Gaspar & Gasti successfully used this same method for the treatment of nasolabial folds and perioral rhytids. Just as in the present study, it yielded good results and no patient discomfort or complications were reported.

In this manner, the described alternative procedure leads to moderate results, however there is absence of ablation, recovery period and complications.

CONCLUSION

Intraoral non-ablative Er:YAG laser improves sagging and shortens the upper lip after several sessions, meaning that this technique is an interesting tool in the treatment of perioral rejuvenation. ●

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Review article

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Current concepts in the use of poly-L-lactic acid for facial rejuvenation: literature review and practical aspects

Conceitos atuais no uso do ácido poli-l-láctico para rejuvenescimento facial: revisão e aspectos práticos

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ABSTRACT

The concept of facial rejuvenation currently includes a three-dimensional perspective, which recognizes as signs of aging not only the loss of the skin's texture and the emergence of expression wrinkles, but also the volumetric losses secondary to bone remodeling and redistribution of facial fat. This article was aimed at reviewing the literature on poly-L-lactic acid for facial rejuvenation – including its indications, injection techniques, expected results and possible adverse effects – and offer practical guidelines, based on the authors' 12-year experience with the product.

Keywords: skin aging; injections; collagen

RESUMO

O conceito de rejuvenescimento facial abrange atualmente visão tridimensional, que reconhece como sinais de envelhecimento não só a perda da textura cutânea e as rugas de expressão, mas também as perdas volumétricas secundárias à remodelação óssea e a redistribuição da gordura facial. O objetivo do presente artigo é apresentar uma revisão da literatura sobre o ácido poli-l-láctico para rejuvenescimento facial, incluindo suas indicações, técnicas de injeção, resultados esperados e possíveis efeitos adversos.

Palavras-chave: *envelhecimento da pele; injeções; colágeno*

INTRODUCTION

Up until the 1990s, the concept of facial rejuvenation was limited to a two-dimensional perspective, focused on reducing wrinkles and furrows. With the improvement of the facial anatomical knowledge, this concept was expanded and nowadays encompasses a three-dimensional perspective, which recognizes as signs of aging not only the loss of cutaneous texture and expression wrinkles, but also the volumetric losses secondary to bone remodeling and redistribution of facial fat.[1] Thus, approaches that recognize the balance between the various facial structures, observing the individual patient's gender, ethnicity and personal goals, allow for more natural and harmonious treatment outcomes. Several products and therapeutic strategies for facial rejuvenation are available today. Since its introduction a little over 15 years ago, poly-L-lactic acid has been used increasingly, which calls for the need to deepen the knowledge about its indications, injection techniques, expected results and possible adverse effects. The present article is aimed at presenting a literature review on poly-1-lactic acid for facial rejuvenation, while demonstrating the 12-year experience with the product in order to offer to the reader some guidelines on its use in the dermatological practice.

PHYSIOLOGY OF FACIAL AGING

Skin Aging

The knowledge of the correlation between the various skin layers, especially the dermis and hypodermis, and the changes they undergo during aging, is crucial for the understanding of the skin's flaccidity, and the poly-L-lactic acid's mechanism of action and its indications for rejuvenation.[2,3] In chronological aging, the thickness of the dermis decreases as a result of biochemical and structural changes in collagen and elastic fibers as well as in the fundamental substance.[4,5] There is a reduction in collagen synthesis and an increase in its degradation due to an increase in the levels of collagenase. The cutaneous content of collagen is reduced by about 1% per year throughout adult life, starting at around 40 years of age in women and a little later, around 50 years of age in men. The remaining collagen fibers are disorganized, more compact and fragmented. Elastic fibers decrease in number and diameter. The amount of mucopolysaccharides of the fundamental substance is reduced, in special hyaluronic acid. These changes negatively affect the skin's turgor and collagen.[6] The hypodermis thins due to aging, weight loss, or the practice of high-performance sports, where there is reduction in the body mass index. On palpation, these patients report feeling their skin is thin and lacking consistency, lacking "filling matter". The changes that occur in these tissues can have great influence in the surrounding areas, leading to a cascade of secondary events. Although the main complaints that lead the patient to seek treatment are wrinkles and furrows, it is important to consider that these changes are a result of the slow and progressive alteration that occurs in all facial structures.[7,8]

Alterations of other structures

Craniofacial bone remodeling is an important contributor to facial aging.[9] Shaw and Kahn found changes in the orbit's contour (superomedial and inferolateral remodeling), glabella resorption, and piriform fossa widening, among other alterations.[10] Regarding the muscles, it is unclear whether histologic aging occurs with age or whether they undergo physiological changes in response to the aging process of the underlying structures. Le Louarn et al. proposed that the deep fat pads beneath the facial mimetic muscles would be responsible for their curvilinear shapes and would contribute to the anterior projection characteristic of a young face.[11] They also suggested that the volumetric loss beneath these muscles that occurs during aging, would lead to the shortening and flattening of these structures, thus contributing to the changes that characterize facial aging.[11] The young face has a larger amount of fat distributed uniformly, allowing a smooth transition from one area to another and lending a more rounded, three-dimensional topography, delineated by a series of arcs and convexities.[1] Thus, there is no clear distinction between areas such as the temples, eyelids and malar region, but only an uninterrupted reflection of light originating from a convex surface.[3] In a series of innovative studies, Rohrich and Pessa demonstrated that facial fat is distributed into independent compartments with specific anatomical relationships among them, and that many of the retention ligaments that support facial subcutaneous tissue originate within the septal walls located between these compartments.[12] Since deep fat is compartmentalized, the loss of volume in deep compartments would lead to predictable changes in facial topography.

LITERATURE REVIEW ON POLY-L-LACTIC ACID

Below is a review of the literature, based on a survey performed on the PubMed database. The authors of the present article searched all publications involving poly-1-lactic acid, selecting for reading and discussion those considered more relevant for the purpose of preparing a synthesis of the current knowledge about the product and its use in facial rejuvenation.

History

Poly-1-lactic acid was approved in Europe as a cutaneous filler in 1999 under the trade name New-Fill® (Biotech Industry SA).[8] In 2004, it was approved by the USA Food and Drug Administration for the treatment of HIV-associated lipoatrophy, under the trade name Sculptra® (Dermik Laboratories, Sanofi Aventis, USA). In 2009, the indication was expanded to aesthetic treatments in immunocompetent patients.[13] By 2006, more than 150,000 patients had been treated with poly-L-lactic acid in more than 30 countries.[14] The product has been available in Brazil for roughly 12 years. In 2006, Danny Vleggaar reported his experience in treating more than 2,000 patients.[15] Since then, many studies have been published attesting the safety, efficacy and durability of the outcomes obtained with poly-1-lactic acid.[16]

Physical and chemical properties

Poly-1-lactic acid – the crystalline form of polylactic acid – is an injectable synthetic polymer of the alpha-hydroxy acids family, of amphiphilic, biocompatible and biodegradable nature, with the properties of self-organization and formation of colloidal micelles in aqueous medium. The polymer has been used for many years in absorbable suture yarns and nanoparticles for drug release control.[17-19] The product is made available in the form of a lyophilized powder in a sterile vial containing non-pyrogenic mannitol (which improves the lyophilization of the particles), croscarmellose (an emulsifying agent that maintains particle distribution after reconstitution), and microparticles of poly-1-lactic acid measuring 40 to 63 micrometers in diameter.[14] The particles' size is large enough to prevent phagocytosis by macrophages or passage through the capillary walls, but also small enough to allow their injection using 26G needles.[19]

Mechanism of action

Poly-1-lactic acid is a biostimulator of collagen. Its clinical effects are due to the stimulation of a desired controlled inflammatory response, which leads to the slow degradation of the material and culminates with the deposition of collagen in the tissue.[17] Once injected into the skin, local subclinical inflammatory response occurs, with the recruitment of monocytes, macrophages and fibroblasts. One capsule is formed around each microsphere individually. As poly-1-lactic acid is metabolized,

the increased fibroblast collagen deposition remains, with resulting increase in dermal thickness.[16,20] Fibroplasia therefore determines aesthetic results, however there is no evidence of residual fibrosis.[16,17,21] Type I collagen production begins about 10 days after the application and continues for a period ranging from 8 to 24 months, while the product is degraded and the subclinical inflammatory response fades.[22,23]

Poly-1-lactic acid is degraded by hydrolysis, followed by the lactic acid's oxidation process, which yields pyruvic acid. The release of CO_2 occurs in the presence of acetyl-coenzyme A and, consequently, decomposition into citrate, which is incorporated into the Krebs cycle and results in the formation of CO_2 and water, which can be eliminated through urine, feces and breathing. No significant amount of degradation residues is found in vital organs, and the product is completely eliminated in roughly 18 months.[17,24]

Animal studies have demonstrated that the implantation of solid particles of poly-1-lactic acid produces a cascade of events that results in the formation of new tissue.[21,25] After the injection of reconstituted poly-1-lactic acid in the volar portion of the forearm, Lemperle et al. observed cellular response involving macrophages, lymphocytes and giant cells, similar to that observed in mice.[26]

Goldberg et al. investigated the human tissue response to injectable poly-L-lactic acid through the evaluation of collagen formation and inflammatory reaction in 14 volunteers. Three sessions of poly-1-lactic acid injection were performed in the retroauricular region, with an interval of four weeks. Skin biopsies were obtained at the baseline and at 3, 6 and 12 months after the first injection allowing the qualitative and quantitative analysis of collagen type I and III levels. In addition, measurements aimed at evaluating inflammatory responses were also taken at the experimental timepoints. The mean level of type I collagen increased significantly at 6 months as compared to the baseline. Histological assessment of the inflammation suggested that none of the volunteers had moderate or severe inflammation in the 3, 6 and 12-month analyzes.[27]

Clinical implications of the mechanism of action

The mechanism of action of poly-1-lactic acid has important practical implications, including the application technique, optimization of outcomes and minimization of the product's adverse effects.[23] The technical differences between its use as a biostimulator and as facial cutaneous fillers are small, nevertheless crucial for the safety and success in results.[14,16,20,21] After the application of poly-1-lactic acid, the injected volume promotes a readily observable change that remains for 2 to 3 days up until the diluent is completely absorbed, which allows the prior evaluation of future results.[23] The poly-L-lactic acid's biostimulatory mechanism allows the correction of facial furrows and wrinkles through the production of collagen, with a gradual increase in tissue volume.[14,16,17] As outcomes may not be clearly visible for weeks after the application, it is important to await for the biological response that occurs between the applications. Also, additional treatments should be performed at intervals of at least 4 weeks, so that overcorrection is avoided.[22] The response time and correction degree depend primarily on each patient's characteristics, varying according to the age, gender, skin quality, phototype and eating habits. Each treatment with poly-1-lactic acid will lead to the formation of collagen, whose magnitude will also depend on the concentration and volume used, which should be individualized. Subsequent injections promote continuous stimulation of the tissue response, with deposition of new extracellular matrix and collagen, resulting in volume restoration and facial contour improvement. A study using cutaneous ultrasonography demonstrated a 4-6mm increase in the dermal thickness of the nasolabial and mandibular regions after bilateral injections of poly-1-lactic acid in HIV patients who had lipoatrophy caused by antiretroviral treatment.28 In addition, it was shown that the results remained for 2 years or longer.[17,20] An ultrasound study measured the thickness of the dermis in 33 patients with HIV-associated lipoatrophy, and treatment with 4 sessions of poly-L-lactic acid led to an increase of 151% in thickness at 12 months, and of 196% at 24 months, confirming that the effect of neocollagenesis continues many months after the injection of the product.[29]

Clinical efficacy summary

After having its efficacy and safety proven in patients with HIV infection [28,30-32] even in the long-term,[33,34] poly-L-lactic acid was subjected to randomized studies in immunocompetent patients. Poly-1-lactic acid was more effective than human collagen for the treatment of nasolabial sulcus in a randomized, multicenter, blinded evaluation,35 also leading to a higher overall satisfaction rate among patients.36 The overall improvement was of 100% three weeks after the third treatment session, remaining above 85% 25 months after the first injection of poly-1-lactic acid. These results led to product approval in the US and in several other countries. Likewise, the product was evaluated in a South Korean randomized study, having been considered not inferior to hyaluronic acid in the treatment of nasolabial folds of moderate to severe intensity.[37] The most encompassing study was conducted in Europe involving 2,131 patients and 7,185 treatment sessions with poly-1-lactic acid, with 95% of patients satisfied with their aesthetic results.15 In addition to randomized studies, several single arm studies have been reported in the literature and commented on review articles and consensus panels about the facial and extrafacial use of poly-1-lactic acid.[2,38-40]

POLYL-LACTIC ACID INDICATIONS

Poly-1-lactic acid is indicated for the improvement of sagging skin caused by aging, volumetric correction of depressed areas such as furrows, wrinkles, cutaneous depressions, atrophic scars and alterations resulting from lipoatrophy or bone remodeling of the treated area. In practice, this implies improving the quality and stiffening of the skin (for example, in acne scars), improving sagging and facial contour, leading to overall facial rejuvenation. Due to the fact that poly-L-lactic acid is used to treat changes caused by volumetric loss secondary to bone resorption, lipoatrophy and skin aging, it is currently recommended that the

product be applied in different planes, such as the supraperiosteal, subcutaneous and subdermal planes. It is worth noting that the application is not performed directly on wrinkles, lines and furrows (two-dimensional application), but rather on flaccid and atrophic facial areas (three-dimensional application), aimed at treating the underlying loss of volume.

In the experience of the authors of the present article, this approach is capable of yielding the harmonic and natural outcomes desired by many patients. Poly-1-lactic acid should be avoided in dynamic and sphincteric areas of the face, such as the lips and the periorbital region, since repetitive movement may lead to accumulation of the product and subsequent emergence of nodules, sometimes with delayed resolution.[41]

In addition to indications for facial treatment, poly-1-lactic acid can be used in other body sites, such as the medial face of the arms, neck, chest region, abdomen and buttocks.[39,42-46] Although the published experience with its extrafacial use is limited, preliminary data and clinical experience suggest that this product is a versatile option to treat sagging skin, loss of volume and contour in many body areas.[39,47] In addition, there are descriptions in the literature of applications in cases of post-operative tissue loss [48] and nipple reconstruction after surgery for breast cancer.[49] It is worth noting that in some body regions, such as the neck and pectoral region, the reduction of skin thickness due to loss of elastin and collagen is more relevant than the loss of volume seen on the face and hands. Thus, the aesthetic enhancement of these regions is more focused on the improvement of the skin's quality than on the loss of volume.

Poly-1-lactic acid is contraindicated in cases of infection or local inflammatory process, active autoimmune diseases, collagen diseases (Chart 1) and pregnancy, presence of definitive cutaneous fillers, or when there is history of keloids or hypertrophic scars. In addition, the product should not be used in people who are hypersensitive to any of its components.

PATIENT EVALUATION

General aspects

Based on the fact that two different faces do not age identically, there is no single algorithm to follow.[8] A younger patient often needs less product and fewer treatment sessions than an elderly patient.

Another relevant point is that treatments for rejuvenation in general should be performed cautiously, for some adverse effects can produce impacts both for the patient and physician. Cautiousness begins by obtaining a detailed anamnesis of medications in use – especially anticoagulants – as well as on the history of recurrent herpes simplex, inflammatory processes (for example, upper airways, sinus, dental or any structure located close to the area to be treated) and autoimmune diseases, including collagen related conditions (Chart 1). It is crucial to question whether the patient has already undergone some type of filling procedure and whether there has been any reaction to the filling substance previously used.

Evaluation of the face

Facial analysis is a process of observation and palpation that allows the determination of the nature and extent of facial structural changes. The treatment depends on the extent of the changes observed in each structural layer and the similarity of these changes between the layers. For example, a young patient with lipoatrophy due to the use of antiretrovirals only needs volumization of atrophic adipose fat pads. Most patients, however, tend to lose volume in all structural layers, implying that the face should be treated entirely, in a way that the treatment leads to more satisfactory results and outcomes are closer to the natural one. Therefore it is worthwhile to initially assess the integrity of each tissue: skin, fat, muscle and bone. Next, it is important to estimate the role of each tissue in the changes in shape, proportions and topography observed (the contribution of each structural layer to the facial appearance can easily be observed in patients with congenital facial asymmetry). The analysis of light and shadow regions evidences areas of prominence and depression (convexities and concavities) that contribute to the alterations – sometimes subtle – in the facial shape and topography. Palpation of shadow areas may reveal areas of atrophy. The evaluation of the orbits' shapes, the bone support beneath the frontal region and the nose, and the proportions of the different areas of the face, yields information that goes beyond the "lines and folds", assisting in obtaining a global picture of the structural changes in the face and of the interdependence between them.

The face should be observed in a three-dimensional way, so that it can be assessed whether the correction of one area can have an impact on another.

Pre-treatment guidelines

Photographs of individuals in different decades of life arranged in chronological progression are often used to illustrate the depth of malar and mandibular atrophy, nasolabial folds, and marionette lines. However, it is possible to observe that changes in younger patients are not linked to the loss of facial volume, but to changes in the skin's texture. In this manner, before planning a rejuvenation treatment, it is necessary to assess the patient's face, make her or him aware of how the signs of aging can be modified by the available treatment options, and address additional concerns. The physician and patient must come to a common agreement on a realistic and comprehensive facial rejuvenation plan aiming at preserving facial balance. For example, patients with very marked aging or lipoatrophy should be made aware that their treatment might require a substantial amount of the product so that a desirable outcome is achieved.

CHART 1: Main collagen related diseases that contraindicate the use of poly-1-lactic acid

- Rheumatoid arthritis and its variants
- Lupus
- Scleroderma
- Sjögren's Syndrome
- Polymyositis / dermatomyositis

Advising the patient on the product's mechanism of action facilitates the understanding of the need for a time interval for the results to become visible (some improvement can already be seen in most patients after the second treatment session) and on the need to undergo at least 3 applications with monthly intervals. Regarding the result's duration, it is important to clarify that it may vary depending on the products used, the procedures performed, the patient's general health and lifestyle.[47] Figure 1 illustrates the clinical results obtained after the treatment of a patient with 3 sessions of Sculptra, 1 bottle per session.

Figure 1: Aesthetic results following the application of poly-L-lactic acid. Frontal **(A)** and oblique **(B)** views of the patient

POLY-L-LACTIC ACID APPLICATION

The appropriate technique for the preparation and application of poly-1-lactic acid is critical for the optimization of results. This includes the correct reconstitution and hydration of the product, application in the specific areas under local anesthesia, and massaging of the entire injected area after the procedure, ensuring the appropriate dispersion of the product.2,14,17,39,50-52 Chart 2 summarizes the key points in the process.

Reconstitution and hydration

The vial's contents should be reconstituted with 8 ml of sterile water for injections. The vial should not be shaken immediately after reconstitution so as to avoid the deposition of the still unhydrated particles in the vial's wall. After reconstitution, the product should be allowed to stand for 24 to 72 hours prior to application. Storage of the product should preferably be done at room temperature up to 30 °C or under refrigeration, at 2 °C to 8 °C, for up to 72 hours. The longer the resting time, the greater the hydration and, therefore, the easier it is to perform applications without obstruction of the needle. Immediately prior to use, the product should be gently shaken for better homogenization. Chart 3 shows a "step by step" description of this process.

Application sites

The selection of dynamically stable sites of application, with sufficient dermal thickness to allow appropriate depth of injection may assist in obtaining more favorable results. Chart 4 shows a summary of the anatomical location of the applications, while Figure 2 shows the locations where the product should not be applied. In the upper third of the face, poly-1-lactic acid should not be applied into the frontal and periorbital regions, for the musculature is hyperdynamic in these sites.[39] In the temporal fossa, there should be attention with the superficial temporal artery, which is at the level of the temporal fascia. The application in this area should preferably be carried out supraperiosteally – since it is a more secure plane – in 0.3 ml boli.16 The middle third of the face is a common area of projection and volume loss. The projection of the face is mainly due to the bone support of the maxilla and the zygomatic arch. In aging, the resorption of these bone structures can be corrected with the application of poly-1-lactic acid in the supraperiosteal plane. It can be performed with 1 to 4 boli, as necessary, observing the distance of 1cm between them.[16] The reabsorption of the pyriform fossa during aging results in the accentuation of the nasolabial sulcus, an increase in the distance between the columella and the upper lip, and the fall of the nasal tip. The restoration of this support is implemented with the application of poly-L-lactic acid in boli (0.3 to 0.5 ml / bolus) in the supraperiosteal plane, which is the safest for the pyriform fossa, given that the angular artery becomes more superficial in this region. The superficial fat compartments of the middle third of the face are the nasolabial fat pad and 3 distinct compartments of malar fat: medial malar fat pad, central malar fat pad, and temporolateral fat pad. Submalar fat atrophy is treated with applications in the subcutaneous plane using a cannula, with the fan retroinjection technique (0.2ml / cm^2 or 0.2ml per retroinjection). The temporolateral fat pad connects the temporal fat to the cervical fat, laying superficially to the parotid gland.[12] The loss of volume in this area creates concavities in the temporal and preauricular regions, increasing the demarcation of the zygomatic arch. The restoration of the lateral contour of the face is achieved by the application of the poly-1-lactic acid along the temporolateral fat pad. In the preauricular region, which extends from the angle of the mandible to the zygomatic arch, the application is preferably

Chart 2: Key points on the facial use of poly-L-lactic acid

Step	Recommendations
Dilution	8 ml sterile water for injection Cleanse the vial's stopper with antiseptic Use a 10 ml sterile syringe and a 21G needle, aspirate 8 mL of sterile water for injection and add slowly to the vial
Hydration	Allow the vial to stand at room temperature for at least 24 hours (ideally 48 hours) and up to 72 hours
Storage after reconstitution	72h hours at room temperature and up to 30 °C
Preparation immediately before application	Add 2 ml of lidocaine (with or without epinephrine) to the vial immediately before the application The final volume is 10 ml, with 8 mL of poly-L-lactic acid hydrated with distilled water and 2 ml of anesthetic. Homogenize the solution by rolling the vial between the palms. Do not shake vigorously to avoid foaming within the vial. Poly-L-lactic acid is ready for use.
Application	Always aspire before injecting to minimize the risk of intravascular injection, especially in the middle third of the face and temporal region. Application planes: subdermal, subcutaneous and supraperiosteal: • Subdermal and supraperiosteal application: needles 24G ¾, 25G or 26G ½ • Subcutaneous application: cannulas 21G and 23G Always massage after application of poly-L-lactic acid
Amount	It depends on the area of the skin surface to be treated: • Supraperiosteal application: 0.1mL - 0.3mL / cm 2, in bolus • Subcutaneous application: 0.2mL / cm2, fan retroinjection • Subdermal application: 0.02mL – 0.05mL per beam, linear retroinjection No more than one vial per hemiface per each session
Number of sessions and intervals	• Three sessions per patient, on average • Young patients may require fewer sessions • Patients with more advanced degree of aging may require more sessions • Intervals of 4 to 6 weeks between sessions • Avoid overcorrection
Caution	• The injection should be in subcutaneous and supraperiosteal planes • Avoid superficial injection into the dermis in order to prevent the formation of papules and nodules • Aspirate before injecting to minimize the risk of intravascular application
Avoiding obstruction of the needle / cannula	• After reconstitution, leave to hydrate for 24 to 72 hours before application • Shake the vial gently to avoid foaming • Homogenize the syringe's contents during application, by carefully shaking
Fixing obstructions of the needle / cannula	• Do not force the plunger • Remove the needle from the skin, move the syringe's plunger in both directions and check whether its lumen has been cleared • In case the needle's lumen has not been cleared, replace it • Check the presence of foam in the syringe and discard it (the foam) before resuming the application • Use syringes with thread
Post-treatment care	• Massage immediately after each application and at the end of the procedure • Massage each treated area for 1 to 2 minutes • Advise the patient about the importance of massaging at home, which should be performed 2 to 3 times a day, for 7 straight days

Chart 3: "Step-by-step" of the reconstitution and hydration of poly-L-lactic acid

- Cleanse the vial's stopper with antiseptic solution;
- Using a 18G or 21G needle and a 10 ml sterile disposable syringe, aspirate 8 mL of sterile water for injection and SLOWLY inject into the product's vial;
- Allow the vial to stand at least 24 hours, WITHOUT SHAKING IT, to ensure complete hydration. The product can be stored at room temperature and up to 30°C, or under refrigeration, of 2°C to 8°C, for 72 hours;
- Inject the reconstituted product within 72 hours after reconstitution, for exclusive use in the same patient;
- Gently the product before use, for homogenization.

Figure 2: Facial site where poly-L-lactic acid should not be applied

performed with a cannula in the superficial subcutaneous plane, anteriorly to the parotid gland and to the masseter muscle, using the fan retroinjection technique.[16] Application in appropriate anatomical regions of the lower third of the face restores the contour of the chin and mandible, which undergo remodeling during aging. The irregularities of the lower face's contour can be treated by supraperiosteal bolus applications (0.1 to 0.3 ml / cm2) along the chin's border aimed at promoting the increase of its anterior projection; in the region lateral to the mentum *(prejowl* sulcus) and along the jaw's body and angle, aimed at restoring the mandible support and redefine the facial contour. For the treatment of flaccidity in the lateral region of the face, resulting from dermal atrophy due to degeneration of collagen and elastic fibers, it is recommended to apply poly-L-lactic acid using the linear retroinjection technique with a needle in the subdermal plane, with a layout of several parallel beams (0.02 to 0.05 ml / beam). As a result, a traction vector is created by neocollagenesis, contributing to the lifting effect on the lateral region of the face. Applications should not be performed in the perioral region, as this area has hyperdynamic muscles.[39]

Preparation and anesthesia

Photographic documentation is very important due to the fact that the injection of poly-L-lactic acid is a serial procedure, with gradual emergence of results over the months.[53] The patient should be photographed in 5 positions (frontal, right and left diagonals, and right and left profiles). The areas to be treated should be marked with the patient seated. It is recommended that topical anesthetic be applied 30-60 minutes before the procedure, with some authors adding the anesthetic to the solution immediately before the application.[53] The authors of the present study recommend 2ml of 2% lidocaine, totaling a volume of 10ml. Some authors recommend the infraorbital and mental nerves blocks. Still others apply ice before and after the injection of poly-L-lactic acid to decrease pain, stimulate vasoconstriction, and reduce the formation of echymoses.[52] Skin antisepsis should be performed with 2% alcoholic chlorhexidine in order to avoid infectious complications in the post-procedure.

Chart 4: Sites and technical aspects of the facial application.

Local	Reparos anatômicos e detalhes técnicos
Site	Anatomical repairs and technical details
Medial malar region	Supraperiosteal injection on the zygomatic bone, maxilla and canine / pyriform fossa. Injection in the deep subcutaneous plane, where the fat pads are decreased in size.
Lateral region of the face	Inject the superficial subcutaneous fat, anteriorly to the parotid gland and the masseter muscle
Jaw and mentum	Supraperiosteal injection on the mentum and pre-maxillary sulcus.
Temporal fossa / lateral eyebrow	Supraperiosteal injection at the origin of the temporalis muscle. Supraperiosteal injection in the eyebrow's tail. Periorbital supraperiosteal injections applied through the orbicularis muscle should be avoided, as this approach can lead to the formation of papule, possibly resulting from the product's accumulation during muscle contraction.

Application technique

Figure 3 shows the sites for supraperiosteal, subdermal and subcutaneous application of poly-1-lactic acid. The product should be injected using 1ml or 3ml syringes and needles and/or cannulas according to the application plan. 24G, 25G or 26G needles and/or 21G, 22G or 23G cannulas can be used. Aiming at minimizing the risk of needle obstruction, the solution should desirably be at room temperature at the time of application.

Poly-1-lactic acid should be injected into the supraperiosteal plane in areas with bone support (0.1 to 0.3 ml / cm^2), or in the subcutaneous tissue where there is no bone structure (0.2 ml / cm^2). Intradermal injections should be avoided due to the increased risk of papules and nodules. In the supraperiosteal plane, the deposit application technique is the most appropriate. The product is injected in the form of small boli using 24G 3/4 needles. The needle should be continuously inserted into the skin at a 90° angle up until the moment it touches the periosteum. Next, the reflux (aspirate) maneuver should be performed to avoid intravascular application, subsequently injecting a volume ranging from 0.1 to 0.3 ml / bolus. In the subcutaneous plane, it is recommended the use of 22G cannulas, with the previous preparation of a puncture with a larger gauge needle, using the fan retroinjection technique, which consists of a retrograde injection performed from a single entry point, covering more extensive areas – such as the preauricular and malar regions – slowly depositing 0.2ml/cm^2 or 0.2ml/retroinjection. The injection should be halted when three-quarters of the cannula become visible, aiming at avoiding the superficialization of the product, which could lead to the emergence of papules and nodules. The application should be carried out in a continuous pace during the backwards movement of the needle in order to avoid the deposit of boli, which, according to the depth, can lead to the formation of papules or nodules. The syringe should be kept parallel to the surface of the skin during the application, which keeps the needle pervious during the procedure. The substance should be shaken intermittently in the syringe during the procedure.

Post-procedure

Massaging the treated area is crucial in the application of poly-L-lactic acid, for it ensures uniform distribution of the substance and leads to better outcomes. It is recommended to use 2% degerming chlorhexidine, for its antiseptic effect and facilitation of the massage. The patient should be instructed to wash her or his hands and face, and massage the application area 2 to 3 times per day for five minutes, for 7 straight days, use emollient creams to minimize friction.

Frequency and number of applications

For a given patient, the surface area to be treated is the only factor determining the amount of poly-L-lactic acid to be applied during a session, with the volumetric correction obtained at the end of treatment being determined by the number of sessions.[39] The amount of product used depends on the each patient's need, according to the degree of aging. Younger patients or more volumetric faces usually need fewer sessions and a lower total amount of the product. In practice, for planning the number of vials needed for the full treatment (3 sessions), the ratio 1 vial / decade of life is used for 30 years old or older patients. Thus, a 30-year-old patient needs three bottles, a 40-year-old, four bottles, and so on. In general, most patients should receive the contents of 1 to 2 vials (half a bottle on each side) per session. It is important to ensure uniform distribution of the product in each treated region; the injection should not concentrate in any

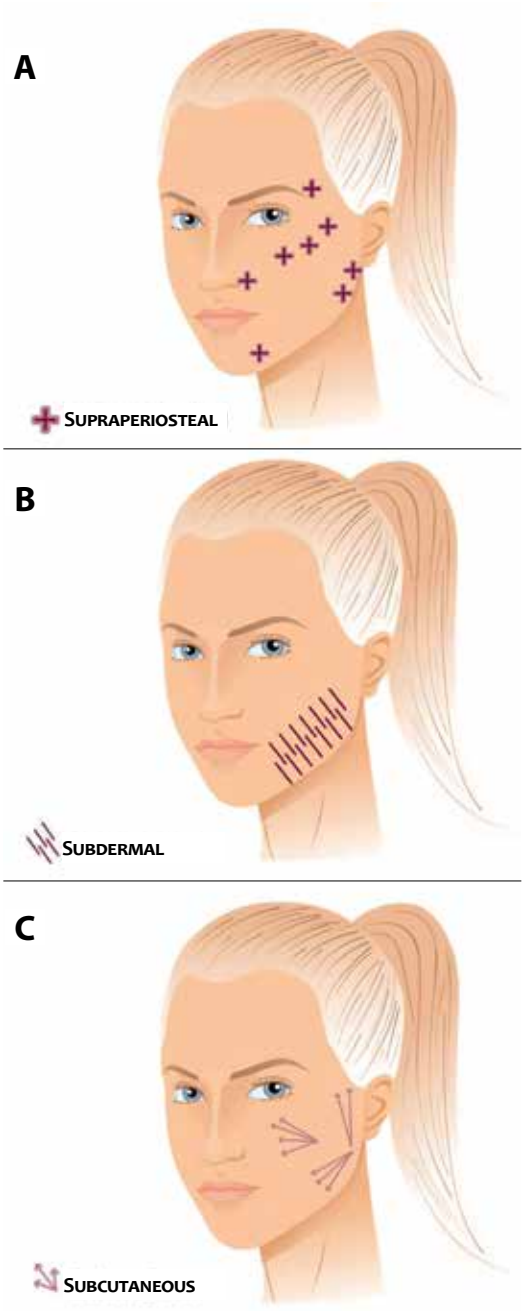

FIGURE 3: Supraperiosteal **(A),** subdermal **(B)** and subcutaneous **(C)** sites of application of poly-L-lactic acid

particular focus or vary according to specific aesthetic defects. Treatment may continue up until the patient is satisfied with the results, which usually occurs after 3 to 5 sessions. The rule "treat, wait and evaluate" should be used to guide the subsequent injections.38 The usual recommendation is to schedule a re-evaluation for a possible new treatment for between 4 and 6 weeks after the first application.[52] Maintenance treatment is usually performed 1 year after the initial treatment. At these sessions, lesser amounts of poly-L-lactic acid, and fewer applications (often 1 or 2) are generally necessary.[54]

ADVERSE EFFECTS

Cutaneous injection procedures often cause some discomfort, erythema, edema or hematoma, which are usually transient and resolve spontaneously. On the other hand, potentially more serious effects are uncommon. These are complications caused by the use of different products injected into the face, causing papules, non-inflammatory nodules and granulomas, infections and vascular phenomena, such as skin necrosis and even blindness. Although it has been used for decades in a generally safe manner, poly-L-lactic acid can cause the adverse effects described below.

Papules, nodules and granulomas

Papules, nodules and granulomas are terms that have been used interchangeably in practice, however in fact they describe different clinical situations. Papules and nodules are non-inflammatory, and have good prognosis and easy resolution, while inflammatory nodules and granulomas can be chronic and difficult to resolve. Due to the acid-poly-L-lactic acid's crystalloid microparticles, the most common adverse effect are papules and nodules caused by the accumulation of material, usually caused by inadequate reconstitution.55 Subcutaneous papules are invisible but palpable (<5mm), while non-inflammatory nodules are protruding. Both may develop several weeks after the injection of poly-L-lactic acid, being asymptomatic. Their frequency may be minimized if the recommended application technique is attentively observed (Chart 2). Just after the product was approved in Europe in 1999, application of poly-L-lactic acid was recommended following reconstitution to a volume ≤ 3ml, 2 hours before the injection.[56] Sessions were performed with very short time intervals (7 to 10 days). In addition, the applications were very superficial and also carried out in hyperdynamic areas. As a result, the incidence of papules and nodules was very high, ranging from 10% to 44% in the literature reports.[15,31,33,35,57] More recently, the frequency of these adverse effects decreased to around 1%, due to changes in the product's reconstitution in greater volume of sterile water for injection, among other technical recommendations (Chart 2).[2,41,57] Many papules or nodules are not visible, do not cause functional or aesthetic impact and can resolve spontaneously. In cases of visible or persistent lesions, vigorous massage, intralesional injection of corticosteroids or surgical excision may be options.[38,58]

Late granulomas are clinically characterized by inflammatory nodules that appear months or years after the injection, persisting and increasing over time.[55,58] Although they have been initially attributed to hypersensitivity phenomena to the material, it is currently known that they may harbor chronic infections. This complication is rare (<0.1%) and seems to be systemic in nature, comprising an exaggerated response of the host to the material injected, infections caused by slow growth bacteria, and the formation of biofilms. Biofilms are sessile bacterial colonies where microorganisms are strongly adhered to a substrate comprised of exopolysaccharides extracellular matrix. This adherence hampers the penetration of antibiotics, explaining the long development of these lesions and the difficult treatment. The biofilm may exist in latent form for long periods and be triggered by trauma, handling and injections. Laboratory confirmation is considerably difficult and biopsies are generally necessary for correct histological identification and collection of material for the culture of bacteria, mycobacteria and fungi.[59] In the absence of results, research with molecular techniques can be carried out. Treatment of late inflammatory nodules is designed to attempt to stop the increased secretion of interstitial substances and invasion of inflammatory cells in the lesion. This includes the use of corticosteroids, antibiotics (systemic and / or intralesional) and antimetabolites, such as 5-fluorouracil, which has activity against gram-negative bateria.39 Hyaluronidase can assist in disintegrating the biofilm's matrix.

Infections

The risk of acute or late infections can be minimized using strict asepsis and antisepsis at the time of application (Chart 2). Acute infections are clinically characterized by inflammatory nodules in the first days after the procedure and are diagnosed via ultrasound, bacteriological examination and culture. Treatment should be conducted with systemic antibiotics and drainage of the material, in case there is fluctuation.

Vascular phenomena

Cutaneous necrosis may be caused by intravascular injection, vasospasm or extrinsic compression caused by the injection of any product. Symptoms of the ischemia are pain, bleaching and reticulated erythema, accompanied by skin necrosis and ulceration on subsequent days.

Blindness has been described in cases of autologous fat, hyaluronic acid and collagen injections, being caused by the impairment of the central retinal and ophthalmic arteries. The material may be accidentally injected into a distal branch of the ophthalmic artery – such as the supratrochlear artery – retrogradely flowing via extraorbital peripheral branches, being propelled towards the main trunk of the ophthalmic artery, thus possibly causing blindness. The low viscosity of the poly-L-lactic acid solution allows aspiration to make sure that the needle is not within a vessel. Also, it prevents vascular compression in the region, which is an advantage regarding other more viscous materials.

ASSOCIATION OF PROCEDURES

The use of poly-L-lactic acid in combination with other facial rejuvenation procedures has found some supportive evidence in the literature, largely in studies conducted by the same authors.[60] Fabi and Goldman reported their experience with 90 patients treated with intense pulsed light immediately before undergoing the application of the product diluted in 7ml bacteriostatic solution and 1ml lidocaine, between the years of 2003 and 2011. They observed that the combination is safe and effective, with absence of significant increase in complications as compared to the injection of poly-L-lactic acid alone. This combination can be used to treat photodamage and sagging skin at the same time. In another study performed by the same authors, they discussed aspects that should be questioned in the combination of techniques that affect the dermis: 1) Is there an increase in the complication rate?, 2) Is there denaturation or distortion of the implanted material if the second technique is superimposed?, 3) Does the new stimulus interrupt or modify the active dermal response? These issues are not yet fully understood. In these authors' experience, the application of pulsed light followed by the application of micro focused ultrasound and poly-L-lactic acid seems safe when performed in this sequence. Finally, the group of authors proposed the use of micro focused ultrasound immediately before the application of poly-L-lactic acid, on the same day, aiming at treating multiple planes. These authors concluded that this combination provides a synergistic and effective approach for the treatment of multiple planes of the face, neck and chest. The combination of hyaluronic acid and poly-L-lactic acid is also possible in the same session if applied in different areas.

CONCLUSIONS

Despite the enormous range of injectable products for facial volumization, including hyaluronic acid in its different presentations, calcium hydroxyapatite and polymethylmethacrylate, poly-L-lactic acid is unique in its mechanism of action, which promotes local and gradual tissular reaction, resulting in neocollagenesis. The use of this collagen biostimulator employing current techniques, which consider changes in different facial structures due to the aging process, allows a more holistic approach to facial rejuvenation, leading to long lasting effects in the improvement of contours and facial sagging. It is worth noting that the final outcome of the treatment with poly-L-lactic acid depends on a careful facial assessment and appropriate treatment indication. It also depends on the use of the correct technique of preparation and application of the product and, last but not least, on the patients' individual characteristics. ●

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Diagnostic imaging

Lichen planopilaris: the importance of early diagnosis

Líquen plano pilar: a importância do diagnóstico precoce

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ABSTRACT

Lichen planopilaris is a rare disorder that belongs to the primary scarring alopecia type. The present study describes the case of a female patient bearing desquamative erythematous plaques and follicular plugs bilaterally in the frontoparietal region, associated with positive pull test. The biopsy's result was consistent with lichen planopilaris and the patient was treated with prednisone associated with clobetasol, with regrowth of the hair in the affected area. The treatment of this pathology is a challenge due to the lack of data on efficacy of therapies and constant recurrence. The picture is irreversible if not treated early. This paper describes a classic case of a case of lichen planopilaris with good therapeutic response, highlighting the importance of early diagnosis, due to the fact that most cicatricial alopecias do not produce scarring in their initial stage and should for this reason be managed as an emergency in trichology.

Keywords: alopecia; early diagnosis; lichen planus

RESUMO

O líquen plano pilar é desordem rara da ordem das alopecias cicatriciais primárias. Descreve-se um caso de paciente do sexo feminino, portadora de placas eritêmato-descamativas e plugues foliculares em região frontoparietal bilateralmente, associados a teste de tração positivo. Após biópsia compatível com líquen plano pilar, a paciente foi tratada com prednisona associada a clobetasol, apresentando repilação da área acometida. O tratamento dessa patologia é um desafio devido à escassez de dados sobre eficácia das terapêuticas e constante recidiva. Trata-se de quadro irreversível se não for tratado precocemente. É descrito um caso clássico de líquen plano pilar com boa resposta terapêutica, destacando-se a importância do diagnóstico precoce, já que em fase inicial a maioria das alopecias cicatriciais é não cicatricial, devendo, por esse motivo, ser manejada como emergência em tricologia.

Palavras-chave: *alopecia; diagnóstico precoce; líquen plano*

INTRODUCTION

Described by Pringle in 1985, lichen planopilaris (LPP) is a rare inflammatory disorder mediated by lymphocytes.[1-3] It is classified as a primary lymphocytic cicatricial alopecia [1,3,4] – the same classification received by discoid erythematosus lupus (DEL), central centrifugal cicatricial alopecia, pseudopelade of Brocq (PBB) among others.[1] The destruction of the hair follicle and replacement by fibrosis is a natural development in cicatricial alopecias.[1,2]

Lichen planopilaris has chronic course, unpredictable development and, probably, autoimmune pathogenesis, [2,3] with an unknown inflammatory process against an autoantigen.[1] Drugs,

infections, genetic factors and immunological abnormalities are described as possible triggering factors.[1]

The authors of the present paper describe a case with classic manifestations of LPP, highlighting the importance of early diagnosis.

CASE REPORT

A 43-year-old female patient reported erythema and desquamation on the scalp with onset three months before, and intense pruritus associated with hair loss. She described previous use of clobetasol without improvement, denying comorbidities or use of any other medications. Dermatological examination showed erythematous-desquamative plaques with follicular plugs in the frontoparietal region bilaterally, (Figure 1) and positive pull test. Perifollicular and interfollicular erythema associated with tubular perifollicular scales were observed using trichoscopy (Figure 2). There were no nail or mucosal alterations at examination. The hypotheses of LPP and seborrheic dermatitis were raised. The lesion's biopsy yielded an anatomopathological study compatible with LPP (Figure 3). General laboratory tests were requested, resulting in serologies with absence of alterations. The patient started to use 40 mg/day oral prednisone, associated with 0.05% topical clobetasol twice daily, in addition to hydration. The patient progressed with great clinical improvement 30 days after the beginning of the treatment (Figure 4). The weaning off of the corticoid was then started up until it could be suspended. The patient is being follow-up and experienced hair regrowth of the affected area, at present with four months of remission, after the total suspension of systemic and topical corticosteroids (Figure 5).

DISCUSSION

Lichen planopilaris (LPP) is considered a variant of lichen planus (LP) with follicular involvement1,2 and can be classified into 3 forms: classical, frontal fibrosing alopecia (FFA) and Graham-Little-Piccardi-Lasseur syndrome (GLPLS).[1-3] These forms are differentiated by their distribution on the scalp and the patient's age group, however they have overlapping characteristics, such as perifollicular inflammation, follicular hyperkeratosis, and cicatricial alopecia.[2]

In FFA, there is a characteristic involvement of the frontotemporal area of postmenopausal women with an association of eyebrow lesion in a percentage that ranges from 50 to 83% of the cases.[1,3] In GLPLS, it is possible to observe the triad of cicatricial alopecia in the scalp preceding non-cicatricial alopecia in the axillae and groins, accompanied by generalized lichenoid follicular papules.[1,3]

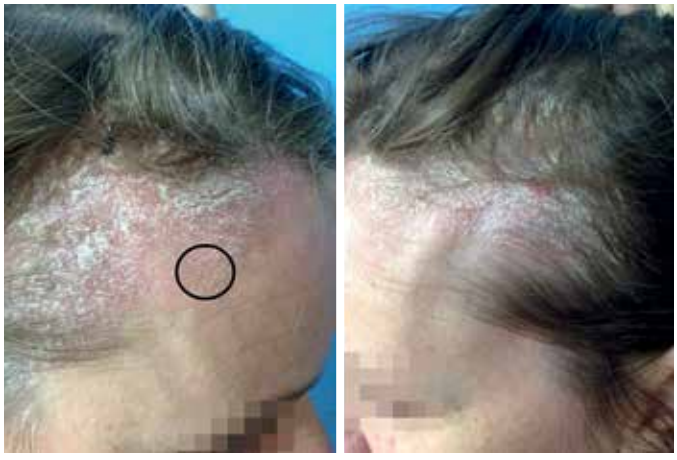

Figure 1: Erythematous-desquamative plaques with follicular plugs in the scalp's frontoparietal region bilaterally. The follicular plugs are more evident inside the black circle

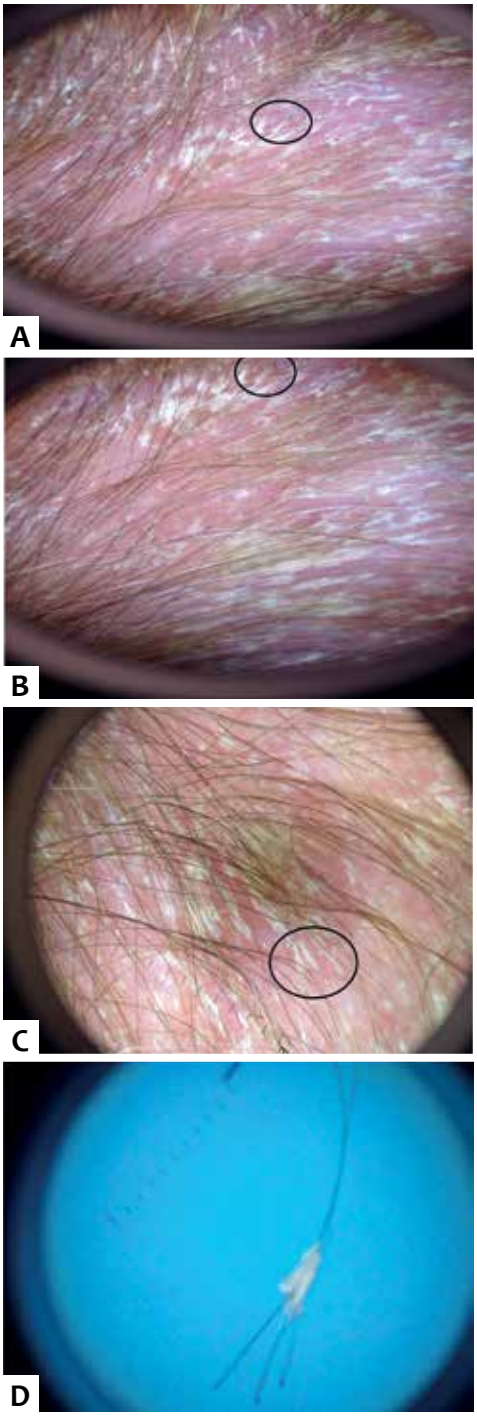

Figure 2: Trichoscopy allowed to observe perifollicular and interfollicular erythemas associated with tubular perifollicular scales. The scales are more evident in the areas in Figures **A, B** and **C**. In **D** it is possible to observe through the trichoscopy of the hair that fell when performing the pull test. It is also possible to observe the tubular perifollicular scaling.

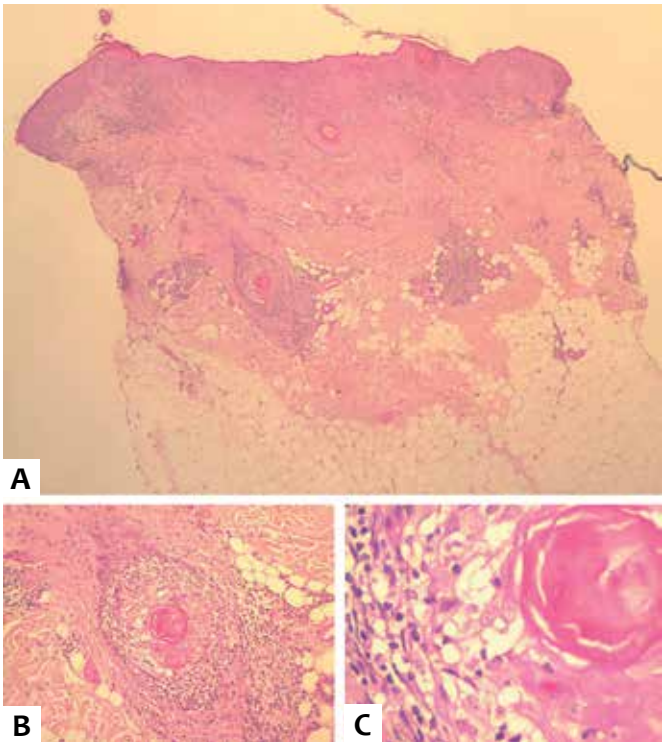

Figure 3: A - HE20x It is possible to observe a discrete epithelial hyperplasia, hyperkeratosis and lymph histiocytic infiltrate of perifollicular lichenoid pattern compatible with lichen planopilaris. **B** - HE100x. Also, it was possible to observe an inflammatory infiltrate centered on the hair follicle. **C** - HE400x detail of the inflammatory infiltrate centered on the hair follicle

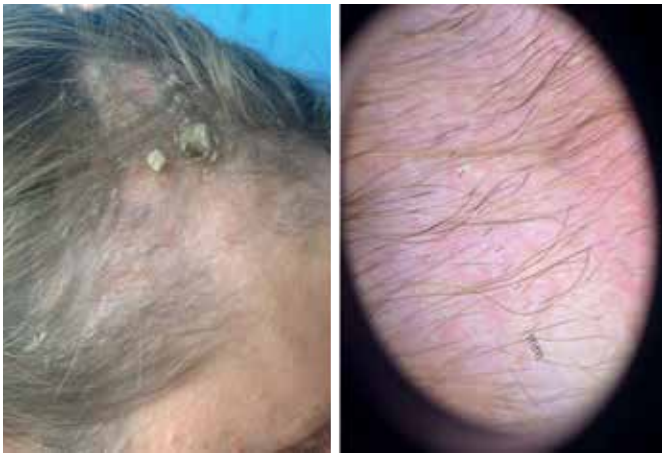

Figure 4: After one month of therapy it was possible to observe improvement, with the reduction of perifollicular and interfollicular erythema and scaling of the scalp

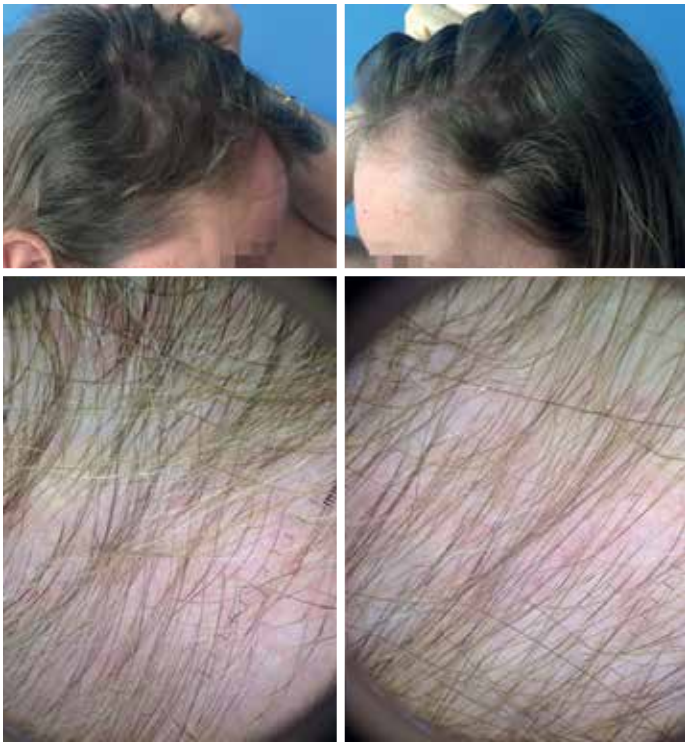

Figure 5: Clinical progression with hair re-growth in the area and improvement of erythema and desquamation four months after the corticosteroid had been suspended

The case reported is compatible with classical LPP, the most common variant affecting women,[1-3] which frequently has its onset between the fifth and the seventh decades of life.2,3 The involvement of the scalp is irregular and occurs in the form of plaques, mainly in the apex1-[3,5,6] and in the parietal region, as observed in the studied patient. Nevertheless, any region of the scalp can be affected.[2,3]

The first observed clinical signs are hyperkeratosis, follicular plugs and perifollicular erythema, [3,5,6] associated with a positive pull test.3 Trichoscopy of early stages evidence perifollicular and interfollicular erythema associated with tubular perifollicular scales. Many patients are misdiagnosed with seborrheic dermatitis at this stage,[5] entailing a delay in the treatment and worsening of the prognosis. Atrophic scars replace the lesions later on, with definitive loss of follicular orifices, which makes the first irreversible.[1-3,5,6]

Complaints of pruritus and burning sensation are common,[1,3,5,6] as well as the association with the skin, nail and mucosal LP lesions.[1]

It is estimated that at the time of diagnosis 17 to 28% of patients have evidence of LP 3 in other places of the body, meaning a complete physical examination is of paramount importance.[1,3,5]

Differential diagnosis is performed with seborrheic dermatitis, DEL and PBB.[1] Biopsy of the lesions is necessary to differentiate them at the initial stage.[3,6] Lichen planopilaris' histopathology shows inflammation with epithelial hyperplasia, hyperkeratosis and degeneration of the basal layer.[1-3] The peripheral lymphocytic infiltrate mainly affects the region that lays between the infundibulum and the isthmus, coursing with the destruction of the bulge.[2,3,5,6] If LPP is not expanding with perifollicular inflammation and hyperkeratosis, it is impossible to differentiate it from PBB,[1-3] which some authors do not consider a different entity, but the final stage of LPP.[1,3]

The treatment of LPP is a challenge because of the scarcity of data on the efficacy of therapies and inconsistent response to treatment, with constant recurrences.[1,3,5,7,8] However, it becomes irreversible if not treated early, entailing that early diagnosis and treatment are mandatory.1,3,8 Hair re-growth in areas of existing alopecia is unlikely, meaning that the treatment's objectives are to improve the patient's symptoms and halt the progression of the disease.[1-3,8]

High potency topical corticosteroid [7,8] (level of evidence B) and / or intralesional triamcinolone acetonide (level of evidence D) are reported to be first-line therapies, with 66 to 70% and 40 to 50% remission rates, respectively.[8] In the absence of response within four months, the methods should be alternated.[3,8] The second-line treatment is systemic therapy, which is ideal for fast developing cases or those that are unresponsive to topical medicaments.[3,8] First and second-line treatments are usually associated, as was the option in the reported case, which was characterized by the rapid progression and history of previous use of topical corticosteroids without improvement.

Among second-line options are oral corticosteroids, with 82% remission within one year.[8] The recommended dose corresponds to 1mg / kg / day or 30-40mg / day prednisone for up to four months.[1,3,8] As for antimalarials, Chiang et al. described improvement of 69% within six months, and of 83% within 12 months, based on the LPP's activity score, with the use of hydroxychloroquine.[5] Nonetheless, Donati et al. challenged the basically clinical nature of this improvement score and performed a photographic follow-up study with the use of hydroxychloroquine, however without obtaining good results.4 In refractory cases, oral cyclosporine is described as an option.[1,3,8]

Other therapeutic options are oral retinoids, tetracycline, thalidomide and mycophenolate mofetil, which have been reported in limited studies.[3,8] The PPAR (peroxisome proliferator activated receptor-g) antagonist – pioglitazone – did not show lasting results.[9]

In cases with progression to cicatricial alopecia, hair transplantation is an option, however there is risk of recurrence of the disease in the transplanted areas. In this manner, it is suggested that a 2-year interval (without disease activity) be observed before it is indicated. In addition, the patient should be advised that the integration of the grafts might be reduced.[2]

The authors of the present paper have described a rare case of LPP with good therapeutic response, highlighting the importance of early diagnosis, since most cicatricial alopecias are of the non-cicatricial type in their initial phase and should therefore be managed as a trichology emergency. *

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Hidradenitis suppurativa: V-Y plasty as a therapeutic option

Hidradenite supurativa: V-Y plastia como opção terapêutica

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ABSTRACT

Hidradenitis suppurativa is a chronic inflammatory, recurrent and debilitating skin disease. Its etiopathogenesis involves follicular occlusion and genetic, environmental and immunological factors. Diagnosis is predominantly clinical, and the therapeutic approach is a major challenge due to its impact on the patient's quality of life. The surgical option is the most indicated in severe cases, nevertheless there is no consensus on the ideal treatment, as outcomes are diverse, and the aesthetic aspect after the procedure is generally unfavorable. This article was aimed at reporting a surgical option with primary wound closure, whose aesthetic result was superior to those derived from traditional techniques.

Keywords: Hidradenitis Suppurativa; Hidradenitis; Dermatologic Surgical Procedures; Dermatology; Therapeutics

RESUMO

Hidradenite supurativa é doença inflamatória crônica, recorrente e debilitante. Sua etiopatogênese envolve oclusão folicular e fatores genéticos, ambientais e imunológicos. O diagnóstico é predominantemente clínico e a abordagem terapêutica é o principal desafio da doença, devido seu impacto na qualidade de vida. Em casos graves a opção cirúrgica é a mais indicada. Não há consenso sobre o tratamento ideal, pois os resultados são variados e o aspecto estético após o procedimento é geralmente desfavorável. O objetivo deste artigo é relatar uma opção cirúrgica com fechamento primário da ferida, cujo resultado estético foi superior ao das técnicas tradicionais.

Palavras-chave: *hidradenite supurativa; hidradenite; procedimentos cirúrgicos dermatológicos; dermatologia; terapêutica*

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INTRODUCTION

Hidradenitis suppurativa (HS), also called inverse acne or Verneuil's disease, is a chronic, recurrent and debilitating inflammatory disease that usually manifests after puberty with painful lesions in the apocrine glands areas, most commonly in the axillary, inguinal and anogenital regions.1 Currently, infundibular keratosis and follicular occlusion are known to be the most important factors in the pathogenesis of HS, and are linked to genetic predisposition, environmental factors and changes in the immune system.1-4 The cytokines involved in this process are still being studied, however increases in IL-17, IL-1b, IL-10, TNF-α and IL-23 have already been described, suggesting the disease's autoinflammatory character, which would justify the use of biological medications in its treatment.[4-6]

Its prevalence is estimated in the range of 1% to 4%, and some factors such as smoking habits, obesity and secondary bacterial colonization are strongly associated with HS[3,5] The diagnosis is based on clinical analysis and is characterized by painful nodules, abscesses, *sinus,* cicatricial bands, and comedones in the typical cutaneous topographies: axillary, inguinal, perianal, and infra-mammary regions, in addition to the buttocks. It is a chronic disease with frequent recurrences.[5]

Treatment is the crux of the discussion due to the significant impact of HS on the patient's quality of life. Recently, studies have proven the presence of correlation between HS and increased risk of cardiovascular events.[7] The indicated initial approach includes loosing weight, quitting smoking, managing the pain, treating infections and wearing appropriate clothing.[5,8,9] The Hurley's clinic classification is useful to indicate the severity of the disease and provide guidelines on the choice of therapeutic modality. This classification separates patients into three groups based on the presence and extent of scarring and sinus tracts: a) Stage I - single or multiple abscess, without sinus or scar; b) Stage II - one or more recurrent abscesses with sinus and scar formation, c) Stage III - multiple sinuses interconnected with abscesses in the entire affected area.[5,9] Patients with mild to moderate degree of the disease can choose the treatment with topical and systemic antibiotic therapy and, depending on to the response, evaluate the use of immunobiologicals such as infliximab and adalimumab. [2,5,8,9] In cases of severe and / or refractory disease and Hurley's stages II and III, the surgical option is the ideal approach. The use of CO_2 laser based excision can be considered for Stage III.[2]

The authors of the present paper present a case of a patient bearing HS, in which the surgical technique employed led to superior outcomes when compared to other methods described and commonly used.

CLINICAL CASE

A 16-year-old female patient sought care complaining of an axillary lesion that had emerged two years before. Clinical examination revealed bilateral extensive lesions in the axillary region, with abscesses, sinuous tracts and cicatricial lesions (Figure 1). Due to the clinical diagnosis of severe hidradenitis suppurativa (Hurley's Stage III), the authors decided for surgical treatment after oral antibiotic therapy. The v-y plasty technique was chosen, with the incision being demarcated in multiple "v" shapes (Figure 2), followed by the complete excision of the lesion (Figure 3), closure of the wound by approaching the flaps (Figure 4), and primary suture with drain placement (Figure 5).

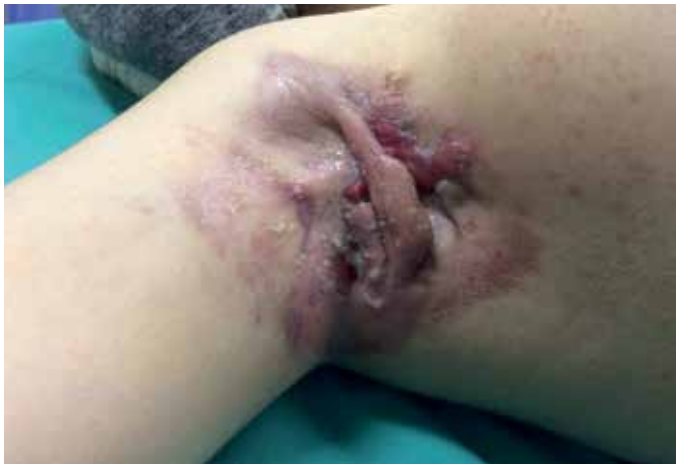

Figure 1: Clinical examination of the right axillary region revealed abscesses, sinuous tracts and cicatricial lesions

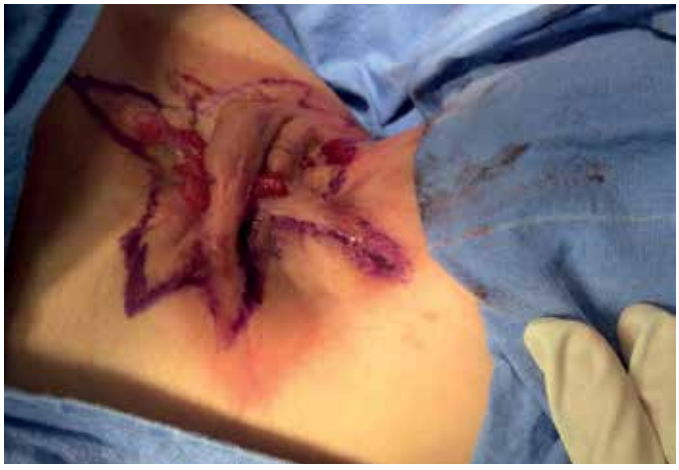

Figure 2: Demarcation of the surgical incision with multiple "v" shapes, circularly arranged in the axillary region

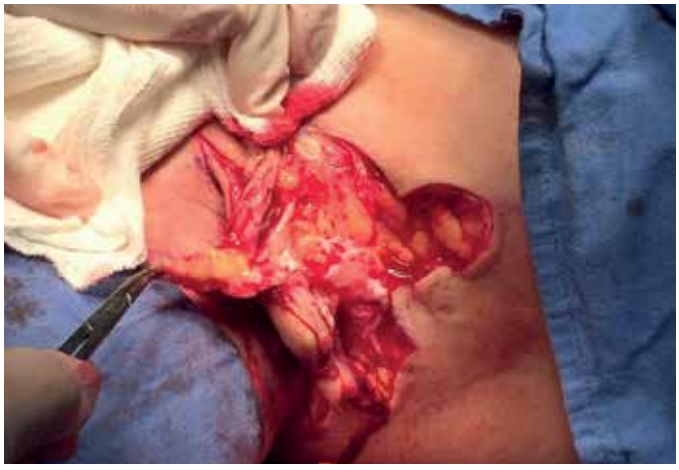

Figure 3: Complete excision of the lesion up until the subcutaneous tissue

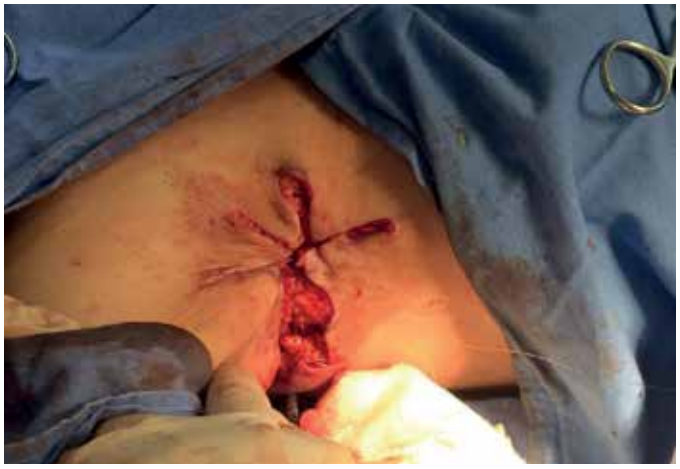

Figure 4: Approximation of the resulting flaps

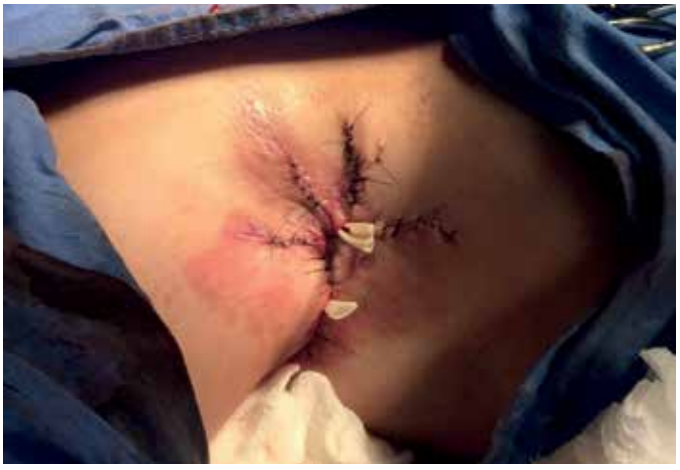

Figure 5: Surgical wound closure by primary suture with drain placement

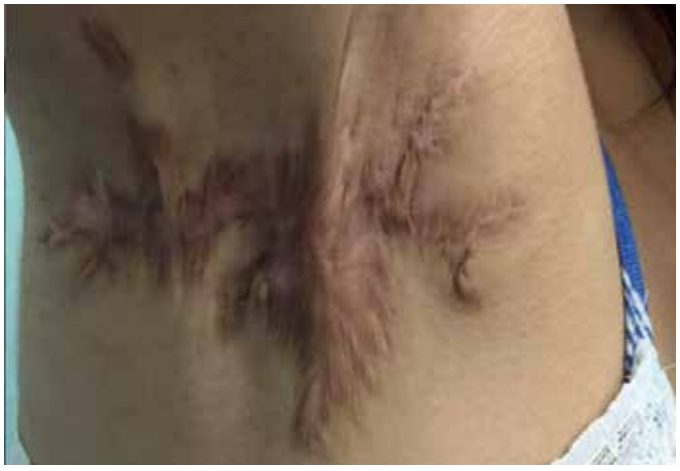

Figure 6: Late postoperative with the surgical scar restricted to the axillary region and satisfactory outcome resulting from the described technique

In the postoperative period, the patient had no intercurrences and enjoyed comfort, absence of secondary infection in the surgical site and healing of the surgical wound, all of which culminating in a good aesthetic outcome (Figure 6).

DISCUSSION

Hidradenitis suppurativa is recurrent and has a considerable impact on the patient's quality of life since its clinical picture is commonly associated with pain, secretion discharge and local aesthetic deformity impose a limit to the bearer's daily activities. These factors, coupled with an increase in cardiovascular risk and depressive disorders, mean HS management an important challenge.[1,9,10]

Patients with severe or refractory disease are indicated for surgical treatment. Among the techniques described are the locally limited or wide excisions, followed by primary or second intention closure, flaps (cutaneous, myocutaneous and fasciocutaneous) and grafts. Other therapeutic options are the CO_2 laser and the ablative Nd:YAG laser. Currently, radical excision is the treatment of choice for severe HS.

The V-Y plasty consists of performing a triangular incision and advancing the flap to cover the y-shaped defect. In this way, it was possible to observe a reduction in local tension, which contributed to the prevention of the cicatricial contracture and provided greater comfort for the patient, with a considerably favorable aesthetic outcome when compared to other techniques traditionally performed for the treatment by second intention and direct closure. It is a surgical technique that did not present complications in the immediate and late postoperative periods, and should be regarded as a therapeutic option, especially in cases of severe HS ●

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Case Reports

Merkel cell carcinoma with atypical immunophenotype: diagnostic challenge

Carcinoma de células de Merkel com imunofenótipo atípico: desafio diagnóstico

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ABSTRACT

The Merkel cell carcinoma is a rare tumor of neuroendocrine and epidermal origin and with poor prognosis. It is classically associated with immunosuppression, exposure to the sunlight and, more recently, with the polyomavirus. It is positive for epithelial and neuroendocrine markers. The combined expression of these markers confirms the diagnosis. Polyomavirus tumors have an unfavorable prognosis. The authors report a case of Merkel cell carcinoma with atypical immunophenotype (CK20 negative) and aggressive behavior. The present report is aimed at highlighting the importance of dermatologists having knowledge of different immunophenotypes that may be associated with the Merkel cell carcinoma.
Keywords: Carcinoma, Merkel Cell; Immunohistochemistry; Merkel cell polyomavirus

RESUMO

O carcinoma de células de Merkel (CCM) é um tumor raro de origem neuroendócrina e epidérmica, de mau prognóstico. Está classicamente associado à imunossupressão, exposição solar e, mais recentemente, ao poliomavírus (MCPyV). Caracteristicamente, o carcinoma de células de Merkel apresenta positividade para marcadores epiteliais e neuroendócrinos. A expressão combinada desses marcadores é o dado que corrobora o diagnóstico. Tumores MCPyV- possuem prognóstico desfavorável. Relata-se um caso de carcinoma de células de Merkel com imunofenótipo atípico (CK20 negativo) e comportamento agressivo. Este relato se justifica para reforçar a importância do conhecimento, pelos dermatologistas, de diferentes imunofenótipos que podem estar associados ao carcinoma de células de Merkel.
Palavras-chave: *Carcinoma de Célula de Merkel; Imuno-Histoquímica; Merkel cell polyomavirus*

INTRODUCTION

Initially described by Toker in 1972, Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous neoplasm, with a slight preference for males and higher incidence of Caucasians at a mean age of 65 years at diagnosis.[1] The most up to date evidence indicates that the neoplasia originates in cutaneous pluripotent stem cells, particularly those of epidermal lineage. This hypothesis supported by frequent association with other tumors originating in the epidermis, such as squamous cell carcinoma and Bowen's disease.[2]

Classically, MCC is associated with chronic exposure to sunlight and immunosuppression.[3,4] Transplanted patients, bearers of HIV infection and hematological malignancies constitute a risk group.

There are literature reports of regression of these tumors after reconstitution of the immune function in immunosuppressed patients, as well as descriptions of spontaneous regression, suggesting that prompt recognition of the lesions by the immune system may lead to the regression of the carcinoma.[4]

In 2008, a virus of the polyomavirus family (Merkel cell polyomavirus) was described, for which 80-90% of the CCMs cases were positive. Nevertheless, the real determinant of the oncogenic potential of this virus remains unclear.[2,4] Cases of MCCs associated with polyomavirus (MCPyV+), however, seem to have a better prognosis and longer disease-free survival time, possibly due to the virus' ability to stimulate the host's immune response.[4]

The present article reports a case of MCC with atypical immunophenotype and aggressive behavior, which corroborates with current literature data, showing that these cases present worse development and prognosis.

CASE REPORT

A 69-year-old white male patient reported an asymptomatic lesion of progressive growth in the left upper limb noticed six months before. He had systemic arterial hypertension, type 2 *diabetes mellitus*, heart failure, psoriasis and psoriatic arthritis. On physical examination, an erythematous-violaceous mass was observed on an infiltrate base, hardened and adhered to deep planes, of approximately 4 cm in diameter, with central ulceration surmounted by hyperkeratosis, on the anterior aspect of the left arm (Figure 1). There was absence of palpable lymph nodes. An excisional biopsy was performed, revealing an undifferentiated dermal neoplasm with subcutaneous infiltration, composed of blocks of small epithelioid tumor cells distributed in a trabecular pattern, with focal angiolymphatic invasion (Figure 2). The immunohistochemical study showed positivity for neuroendocrine markers (enolase, CD56 and synaptophysin) and epithelial markers (EMA and CK8/18), in addition to positive immunostaining for Ki-67, which indicates the intense mitotic activity of the neoplasia (Figure 3). The CK8/18 marker showed dot or perinuclear pattern reactivity, a fact that is representative of concomitant neuroendocrine and epithelial differentiation in a malignant small cell neoplasm. Immunostaining for cytokeratins 7 and 20 came out negative. The immunohistochemical panel is shown in Table 1. Excluding primary sites in other topographies, the final diagnosis was primary cutaneous neuroendocrine carcinoma, or MCC. Imaging studies were then performed for adequate staging and patient follow-up. Computerized tomography scans (CT) of the chest and abdomen showed images suggestive of secondary involvement in the mediastinum and liver (Figure 4a). Three months after the initial surgery, the patient presented a hardened mass of approximately 7cm in diameter in the infraclavicular region, on the left, which the CT examination evidenced as a lymph node megalia of probable metastatic origin (Figure 4b). In addition, considerable clinical signs and symptoms of consumptive disease, such as anorexia and weight loss, were observed. The patient died 3 months later, despite having been treated with systemic chemotherapy.

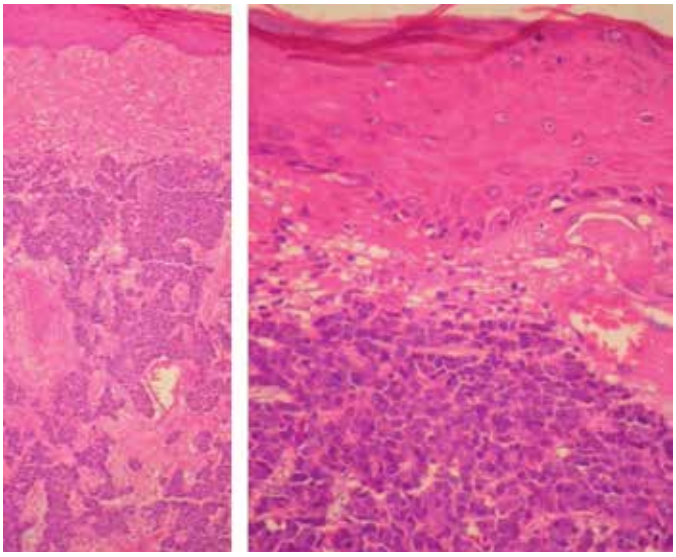

Figure 2: Anatomopathology: Undifferentiated dermal neoplasm with subcutaneous infiltration, composed by blocks of small epithelioid-like tumor cells distributed in trabecular pattern, with focal angiolymphatic invasion

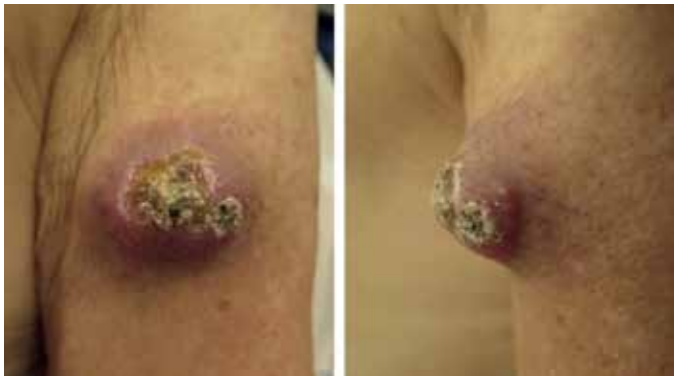

Figure 1: Clinical presentation: Erythematous-violaceous tumor with infiltrated base adhered to deep planes. Presence of central ulceration with keratotic surface

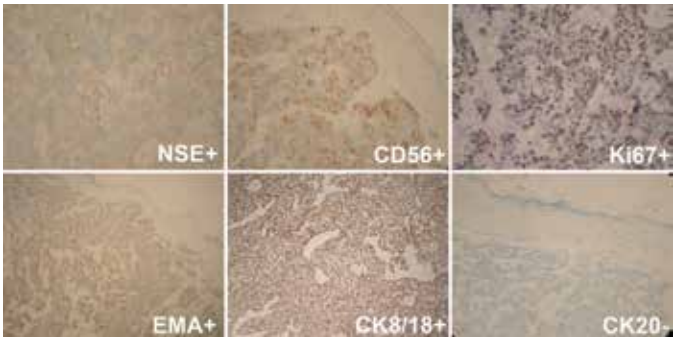

Figure 3: Immunohistochemistry: A study demonstrated positivity for neuroendocrine markers (enolase, CD56, synaptophysin) and epithelial markers (EMA, CK8 / 18), in addition to Ki67 positive immunostaining. Cytokeratin 20 came out negative

Table 1: Immunohistochemical panel of the patient

Marker(s)	Result	Meaning	Interpretation
Syn, NSE, CD56	+	Neuroendocrine differentiation	Neuroplasia of neuroendocrine origin
EMA	+	Epithelial differentiation	Reactivity in epithelial cells
AE1 / AE3	-	Epithelial differentiation	Epithelial differentiation Virtually positive in all carcinomas, for it is a pan-cytokeratin marker. May be negative in neuroendocrine carcinomas
CK8 / 18 (CAM5.2)	+(dot)	Epithelial and neuroendocrine differentiation	Reactivity of this marker in dot in malignant small-cell neoplasias is simultaneously a diagnostic of epithelial and neuroendocrine differentiation
CK20	-	Epithelial differentiation	Often positive in neuro-endocrine cutaneous carcinomas, but its negativity does not exclude this diagnosis
CK7	-	Epithelial Differentiation	Due to the more restricted distribution regarding CK8/18, it may be negative in some carcinomas
Ki-67	+	Cell proliferation	Intense mitotic activity of the neoplasia
Vimentin	-	Intermediate strand present in cells	In the context of an undifferentiated small-cell carcinoma, of several lineages it helps to rule out the diagnosis of PNETs, which are usually vimentin+
CD99	-	Membrane-cytoplasmic protein	Expressed in virtually all PNET cases, disfavoring the diagwith uncertain function nostic
CD45 LCA, CD3 and CD20	-	Lymphoid origin	The negativity for these markers disfavors the diagnostic of cutaneous lymphoma
S100, HMB-45	-	Melanocytic origin	Negativity for these markers disfavors the diagnostic of melanoma
TTF-1	-	Nuclear marker expressed in lung and thyroid carcinomas	Small-cell epidermoid lung and thyroid carcinoma represents the main differential histologic diagnosis of MCC, and usually has positivity for TTF-1
CD117 (c-kit)	-	Expressed in various human cell types	In this context it helps to rule out the hypothesis of neoplasm wit adnexal origin
CD31, CD34	-	Endothelial origin	Negativity for these markers disfavors the diagnosis of endothelial neoplasms, such as angiosarcoma
Desmina	-	Muscular origin	Negativity for this marker discards origin in muscle cells (e.g. rhabdomyosarcoma or leiomyosarcoma)

(Syn: synaptophysin; NSE: neuron-specific enolase; EMA: epithelial membrane antigen; CD45 LCA: common leukocyte antigen; HMB45: anti-glycoprotein melanosomal antibody; TTF-1: Thyroid transcription factor 1)

DISCUSSION

Clinically, MCC emerges as a solitary nodule or erythematous or violaceous plaque, of firm and rapid growth, usually painless, with eventual ulceration, in the head or neck regions. Trunk, extremities and photoprotected areas are less frequent locations. Due to the lack of specificity of its clinical appearance, Heath et al. proposed the AEIOU acronym, in an attempt to aid diagnosis (Asymptomatic, Expanding rapidly, Immune suppression, Older than 50, Ultraviolet exposed site).1 Lo-

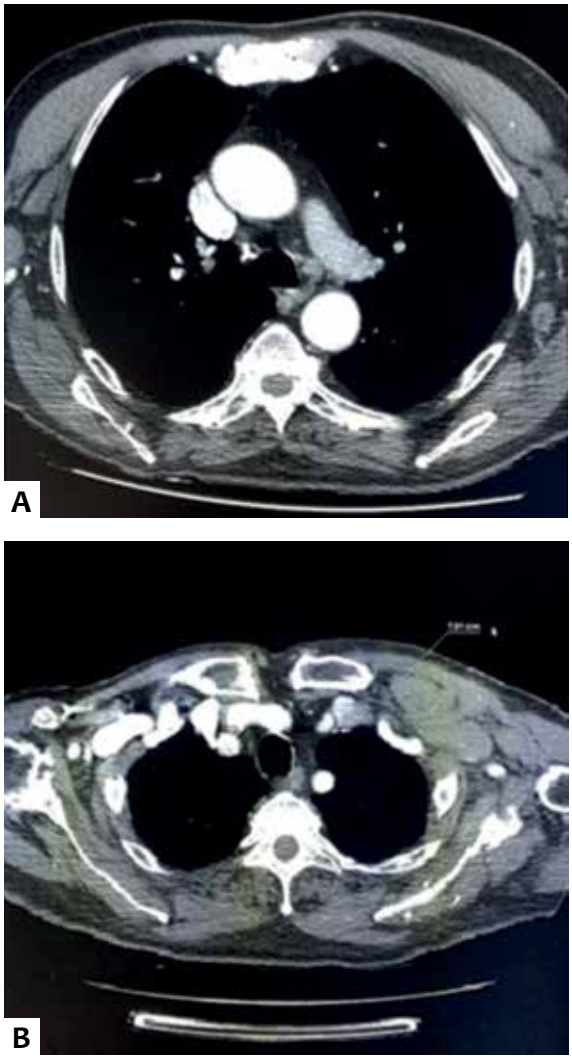

Figure 4: Tomography. **A -** Mediastinal involvement. **B -** Lymph node megalia of probable neoplastic origin

cal recurrence is very frequent, there is locoregional involvement in 17% to 76% of cases, and distant metastases occurs in approximately 50%, both hematogenously and lymphatically, with a lethality rate ranging from 20% to 55%. The most affected organs are (starting with the highest frequency): skin, lymph nodes, liver and lungs. Five-year survival rate is of 64% for localized disease, 39% for lymph node involvement, and 18% for distant metastases.[4]

Histology evidences the neoplasia as an poorly-defined dermal nodule that frequently infiltrates fat, fascia, and muscle.[5] The cell infiltrate is uniform and monotonous, composed of small round oval basal cells with vesicular ovoid nucleus and non-prominent nucleolus, in addition to scarce cytoplasm with numerous mitotic figures and apoptotic bodies.[6,7] Areas of extensive or focal necrosis are common. Three variants are described: trabecular, intermediate and small-cell, nonetheless mixed or transitional forms are more commonly found.3 The relationship between histologic type and prognosis is controversial. Histological findings are not characteristic and the main differential diagnoses include cutaneous metastasis from small-cell lung carcinoma, cutaneous lymphoma, melanoma, primitive neuroectodermal tumors (PNET), and squamous cell carcinoma (SCC). It is worth noting that, not infrequently, MCC occurs concomitantly with other lesions of epithelial origin, the most common being the association with invasive SCC. Bowen's disease, basal cell carcinoma (BCC), actinic keratosis and sebaceous carcinoma have also been reported.[2,5,6]

After the histological analysis, the immunohistochemical study becomes mandatory for diagnostic definition. Characteristically, MCC is positive for epithelial markers, such as cytokeratins 20 and 8/18, and neuroendocrine markers, such as chromogranin (CgA), synaptophysin (Syn) and neurospecific enolase (NSE). The combined expression of these markers is corroborated by the diagnosis.[1-7] Cytokeratin 20 is considered a standard marker in cases of MCC, since it is present in up to 95% of cases, often expressed as a perinuclear dot pattern.[2,3,4] CK20 expression is absent in most small-cell and round-cell neoplasms, except for MCC.

However, the absence of reactivity for CK20 does not exclude MCC as a diagnostic possibility. In these cases, it is necessary to analyze other cytokeratins such as AE1 / AE3 (pan-cytokeratin), CK8/18 or Cam5.2 and CK7, in addition to verifying the expression of other markers that are usually negative in Merkel cases. These markers are: thyroid transcription factor 1 (TTF-1), Melan-A, HMB45 (Human Melanoma Black), S-100, common leukocyte antigen (CLA), and CD99.[2-5,8] Table 2 depicts the main markers that should be evaluated after the histological diagnosis of small-cell, round-cell and small blue-cell, round and blue-cell neoplasms (Table 2).

The typical immunostaining of MCC is performed with CK20+ and CK7-, nevertheless any combination of the expression of these cytokeratins can be found (CK20+ / CK7+, CK20+ / CK7-, CK20- / CK7-, CK20- / CK7+) and the actual significance of these immunophenotypes still needs to be determined. In 2013, Ishida and Okabe reported 2 cases of MCC associated with Bowen's disease, one of which had a rather infrequent immunophenotype (CK20e TTF-1+). These authors concluded that collision tumors may have unusual immunophenotypes, and that atypical immunohistochemical patterns generally do not involve infection detectable by MCPyV.2

The breakthrough for the understanding of part of the MCC's pathogenesis took place in 2008 after the discovery of a polyomavirus, termed Merkel cell polyomavirus, for which positivity is observed in 80-90% of the Merkel tumors.[2,4,9] The polyomavirus could promote tumorigenesis through the oncogenic action of small and large T antigens (LT [large] and ST [small] -Ag) with subsequent integration of the viral genome into the host, which seems to occur early after infection by MCPyV.[4,8,9] Since its original description in 2008, epidemiological data have strongly supported the virus' correlation to MCC.

However, the real determinant of this virus' oncogenic potential remains unclear. Roughly 60%-80% of the normal population is positive for MCPyV infection, nevertheless only a minority develops the neoplasia.[9] A reported finding is that

Table 2: Markers used in the diagnosis of undifferentiated neoplasms of small-, round- and blue cells

	Merkel cell carcinoma	Small-cell lung carcinoma	Melanoma	Lymphoma	PNET	Basal cell carcinoma
CK 20	+/–	–/+	–	–	–	–
CEA	–	+	–	–	–	+
EMA	+	–	–	–	–	+
Crg A	+/–	+/–	–	–	+	–
Syn	+/–	+/–	–	–	+	–
NSE	+	+	–	–	+	–
TTF-1	–	+/–	–	–	–	–
Melan-A	–	–	+	–	–	–
HMB-45	–	–	+	–	–	–
S-100	–	–	+	–	+/–	–
CD-56	+	+	–/+	–	–	–
CD-99	–/+	–	–/+	–	+	–
LCA	–	–	–	+	–	–

(PNET: Primitive Neuroecdodermal Tumor; CEA: Carcinoembryonic Antigen; EMA: Epithelial Membrane Antigen; Crg A: Chromogranin; Syn: Sinaptophysin; NSE: Neuron-Specific Enolase; TTF-1: Thyroid Transcription Factor 1; HMB45: melanosomal anti-glycoprotein antibody; CD45 LCA: Common leukocyte antigen).

Table 3: TNM Staging

	Tumor
T1	Tumor ≤ 2cm
T2	Tumor> 2 cm and <5 cm
T3	Tumor> 5cm
T4	Invasion of bone, muscle, fascia or cartilage
	Lymph nodes
cN0	Negative lymph node based on clinical examination and image
pN0	Negative lymph node based on histopathological examination
N1	Regional lymph node metastasis
N1a	Micrometastasis (sentinel lymph node or elective lymphadenectomy)
N1b	Macrometastase (detected clinically and confirmed by surgery or aspirate)
N2	Transit metastasis
	Metastasis
M0	Absence of distant metastasis
M1	Metastases through regional lymph nodes
M1a	Cutaneous metastases, distant subcutaneous tissue or lymph nodes
M1b	Pulmonary metastasis
M1c	Metastasis to any other organ

Adapted source: Duprat JP et al. 20113. A Review of the epidemiology and treatment of Merkel cell carcinoma

patients infected with MCC have much higher levels of antibody to the virus than infected patients without the disease.[9] However, MCC cases associated with polyomavirus appear to have a better prognosis and longer disease-free survival, possibly related to the ability of the virus to stimulate the host's immune response.4,9 It is questioned whether immunosuppression would be the predisposing factor for the development of MCC in patients infected with the virus, since the neoplasia is much more frequent in this population. Notwithstanding, there is absence of studies demonstrating that MCCs with MCPyV positivity are more common in immunocompromised individuals.

It is believed that exposure to the virus and the resulting infection occurs in early childhood, being, however, clinically asymptomatic due to the fact it produces adequate humoral and cellular responses. Ultraviolet radiation and other potentially mutagenic environmental factors would be responsible for the integration of the viral genome into host DNA, with subsequent development of the neoplasm in adulthood. Concomitantly, systemic immunodepression, local or even induced by the own tumor would contribute to tumor proliferation. The disease's progression can be monitored by anti-T-Ag antibody levels and the outcome of the picture can be predicted by LTCD8+ levels in the tumor infiltrate (high levels of LTCD8+ correlate with a better prognosis). MCPyV tumors often associate with aggressive somatic mutations (RB1, Tp53 and PIK-3CA) and have an unfavorable prognosis, as they probably develop via a different oncogenic pathway. Knowledge of the biological behavior of polyomavirus-positive tumors seems to be considerably promising for the development of therapies specifically focusing on tumor-related proliferation targets.[4,8]

In 2015, Miner et al., from the University of Michigan, questioned the association of negativity to CK20 with the absence of polyomavirus infection, finding 10 cases without MCPyV positivity among the 13 studied CK20- (77%). Therefore, it was concluded that the CK20 MCCs are associated with a lower incidence of MCPyV positivity. Further studies are needed to establish whether the CK20 MCPyV MCC is genetically similar to other CK20 CCM, but MCPyV+ or whether this tumor subgroup has a single spectrum of mutations and would be a distinct class of CCM8 (Table 3).

Treatment is based on complete surgical excision associated with adjuvant treatments, such as chemo and radiotherapy, de-

pending on the extent of the disease. Postoperative radiotherapy of the tumor bed and regional lymph nodes is advocated aimed at better locally controlling the condition, due to the tumor's radiosensitivity, and lower recurrence rates. It presents proven and consensual application and benefits also in recurrent or unresectable tumors. Chemotherapy is a palliative option in advanced stages, with a positive response in two thirds of patients, however with recurrence within a few months. The proposed macroscopic margins range from 1cm to 3cm and the Mohs technique is well indicated for locations where this extension of margins may be impractical, such as in the face. Nonetheless, there remain controversies regarding the best therapeutic approach. Considering that there is subclinical lymph node disease in 25%-50% of cases, sentinel lymph node research is recommended. Moreover, lymphadenectomy is indicated in case of presence of clinical or histological lymph node involvement.3

The disease's prognosis is not good due to the high rates of local recurrence, lymph node and distant metastasis. The average 5 years survival rate is of 30%-75%, and usually ranges from 6 to 12 months. The factors most frequently associated with a worse prognosis include: male gender, large primary tumor, presence of lymph node or distant metastases at diagnosis, histological evidence of nuclear atypia, increased cell turnover and angiolymphatic invasion, MCPyV negativity, somatic mutations associated with CK20 (for instance Tp53 or PIK3CA), increased expression of markers such as Ki-67, and poor expression of other markers, such as CD34.4

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Case Reports

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Non-invasive treatment with transcutaneous non-focused ultrasound for the reduction of abdominal subcutaneous tissue

Tratamento não invasivo com ultrassom não focado transcutâneo na redução do tecido subcutâneo abdominal

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ABSTRACT

Introduction: Introduction: Not focused ultrasound is a noninvasive alternative to improve body contour.

Methods: It's reported five cases treated with eight weekly sessions of not focused ultrasound on the abdomen.

Results: The treatment did not affect the routine of patients; it was comfortable and safe for most. There was a reduction in the thickness of the fat layer evaluated by ultrasound and in the circumferential measures in all patients, with clinical improvement evidenced in the photographic documentation especially in patients with lesser thickness of subcutaneous.

Conclusion: The device was safe, and was shown clear reduction in abdominal subcutaneous tissue.

Keywords: adipose tissue; ultrasonic therapy; ultrasonography; abdominal subcutaneous fat

RESUMO

Introdução: O ultrassom não focado é alternativa não invasiva para melhora do contorno corporal.

Métodos: São relatados cinco casos tratados com oito sessões semanais de ultrassom não focado no abdômen.

Resultados: O tratamento não interferiu na rotina dos pacientes, tendo sido considerado confortável e seguro. Houve redução na espessura do subcutâneo avaliado por ultrassom e nas medidas circunferenciais em todos os pacientes, com melhora clínica evidenciada na documentação fotográfica principalmente nos pacientes com subcutâneo de baixa espessura.

Conclusão: O tratamento se mostrou seguro, com evidências de redução do tecido subcutâneo abdominal.

Palavras-chave: tecido adiposo; terapia por ultrassom; ultrassonografia; gordura subcutânea abdominal

INTRODUCTION

Although highly effective, surgical treatment of body remodeling requires anesthesia and a long recovery time.[1] Stimulated by an increasing demand for procedures with minimal recovery time and few side effects, several modalities of non-invasive treatment have arisen with the promise to improve the body's contour.[2,3]

A significant number of such devices are based on ultrasonic energy – including with focused and non-focused ultrasound devices, depending on how the energy is delivered to the tissues.[4] Focused ultrasound devices cause necrosis to fat cells in the treated area. Non-focused ultrasound devices act by altering the permeability of adipocytes, reducing their volume, with absence of cellular necrosis, leading to minimal discomfort.[4,6]

The MedContour® (General Project, Montespertoli, Italy) is a non-focused ultrasound device that has a handpiece equipped with two non-focused ultrasound angled transducers, aimed at treating adipose tissue (AT) between 1 and 5cm below the skin surface. Non-focused beams can create a weakly focused ultrasound field at the point where the beams overlap. The vacuum's action pulls the AT into the handpiece, allowing the ultrasonic beams to be directed exclusively to the treated area's AT, without exposing adjacent structures to risk. This mechanism alters the adipocyte's plasma membrane's permeability, releasing intracellular lipids into the interstitial fluid without evidence of cellular apoptosis.[1,4,6] The device also has a separate vacuum handpiece for lymph node stimulation and lymph drainage.

According to the scientific literature, non-invasive imaging, carried out with soft tissue ultrasound,[7] can evidence the reduction in the subcutaneous

The present study was aimed at describing the effect of transcutaneous, non-focused ultrasound on subcutaneous abdominal tissue of five patients.

METHODS

The present paper describes five cases of patients (Table 1) treated with eight 1-hour weekly sessions in the abdominal region (power = 2-3 watts, vacuum = 25mmHg, wave frequency = 1Mhz modulated between 20-50Khz), using the MedContour® (General Project, Montespertoli, Italy) device, from November to December 2014.

The objective and subjective parameters evaluated before and one week after the last session were: a) *circumferential measurements* b) ultrasound assisted measurements of the *abdominal subcutaneous tissue thickness* and c) *digital photographs* taken with a Sony Cyber-shot DSC-W380® digital camera (Sony, Tokyo, Japan). The patients were instructed not to change their eating habits and physical exercise routine.

Table 1: Patients' characteristics

Gender	Female	4	80%
	Male	1	20%
age (years)	Mean		28.4
	Median		28
	Minimum-maximum		27-32
	Standard deviation		2.1
Weight (kg)	Mean		60.1
	Median		64
	Minimum-maximum		52-66.5
	Standard deviation		7
Height (m)	Mean		1.63
	Median		1.62
	Minimum-maximum		1.57-1.71
	Standard deviation		0.05
Body mass index (kg / m2)	Mean		22.5
	Median		22.7
	Minimum-maximum		19.8-26.4
	Standard deviation		2.7

RESULTS

The treatment was described by patients as comfortable, with only burning sensation being reported when the handpiece was not well coupled to the treatment area. Only one patient reported burning sensation in the abdomen's lateral regions, which required several pauses for cooling.

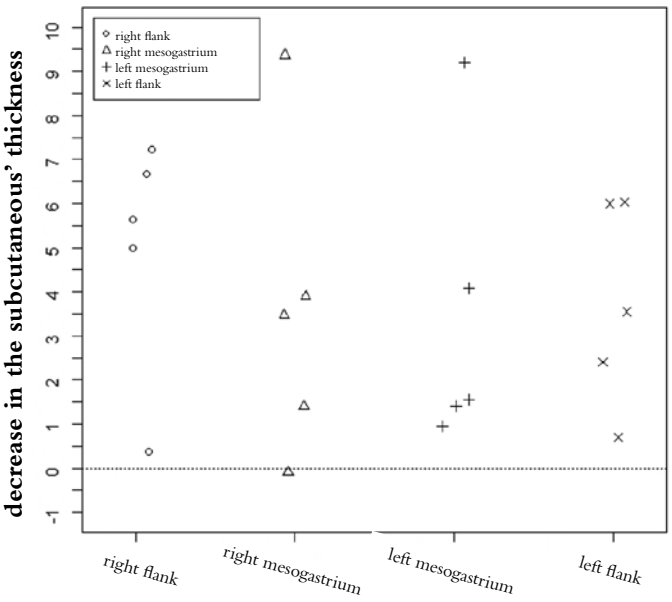
There was erythema and heat sensation immediately after the session, which resolved within hours without intervention. Ecchymosis occurred in one patient, with complete remission after two weeks. The treatment did not interfere in the patients' routine, and there were no reports of other adverse events.

There was a significant reduction in the subcutaneous tissue's thickness, measured by ultrasonography (Table 2, Graph 1), with a maximum decrease of 9.4 mm. In the circumferential measurements (Table 3, Graph 2), a patient had an increase of the circumference of up to 1cm in two of the measurements (Graph 2), which, however, was not confirmed on ultrasonography (Graph 1).

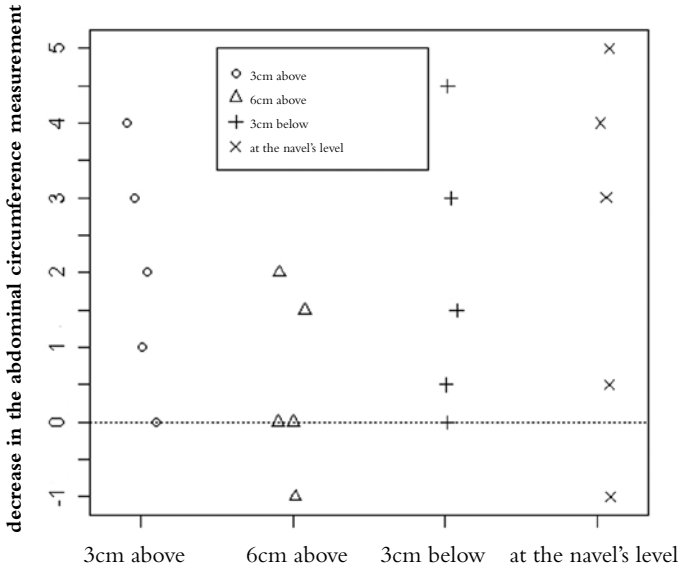
Table 2: Summary of measurements of the patients subcutaneous' thickness in the mesogastrium and right and left flank regions at baseline and one week after the last session

	Subcutaneous thickness (mm)			
	before	after	decrease	p
Right flank (n = 5)				
mean	24.17	19.,18	4.98	0.015[a]
median	23.10	18.10	5.65	
min	14.77	9.12	0.37	
max	34.57	34.20	7.23	
standard deviation	7.64	9.57	2.72	
Right mesogastrium (n = 5)				
mean	23.01	19.40	3.61	0.088a
median	23.40	19.50	3.47	
mínimo	7.92	8.01	-0.09	
máximo	39.67	30.30	9.37	
standard deviation	11.99	8.58	3.60	
Mesogástrio esquerdo (n=5)				
mean	22.43	18.99	3.44	0.090[a]
median	22.27	18.20	1.56	
min	8.10	7.15	0.95	
max	38.10	28.90	9.20	
standard deviation	11.74	9.29	3.44	
flanco esquerdo (n=5)				
mean	23.38	19.64	3.74	0.023[a]
median	19.50	17.10	3.55	
min	12.17	8.62	0.70	
max	35.10	34.40	6.03	
standard deviation	9.35	10.16	2.31	

[a]*t-Student for paired samples*



Graph 1: One-dimensional dispersion diagram of the decrease in the thickness of the patients' subcutaneous, according to the body site (mm)



Graph 2: One-dimensional dispersion diagram of the decrease in the patients' abdominal circumference, according to the body site (cm)

The graphs show the distribution of the decrease in the patients' abdominal circumference measurements between Week 1 and the final experimental timepoint. The points above the dashed line correspond to patients who experienced a decrease in the measurements (positive decrease), and the points below that line correspond to patients who had an increase in the measurements (negative decrease). Dashed line = zero decrease.

Table 3: Summary of measurements of the patients' abdominal circumference (cm) and weight (kg), according to the body site

		Week 1	final	decrease	p
3cm above the) navel (n=5	mean	76.8	74.8	2	0.047[a]
	median	79	78	2	
	min-max	67-89	65-86	0-4	
	standard deviation	9	9.4	1.6	
6cm above the navel (n=5)	mean	74,5	74	0.5	0.413[a]
	median	76	74	0	
	min-max	66-85	66-86	-1-2	
	standard deviation	8.4	8.5	1.2	
3cm below the navel (n=5)	mean	84.1	82.2	1.9	0.083[a]
	median	81	81	1.5	
	min-max	76-94.5	73-94	0-4.5	
	standard deviation	7.3	8.5	1.9	
at the level of the navel (n=5)	mean	80.3	78	2.3	0.108[a]
	median	81.5	81	3	
	min-max	70-92	66-89	-1-5	
	standard deviation	8.2	9.3	2.5	
weight (kg)	mean	60.1	60.3	-0.2	0.601[a]
	median	64	64.2	-0.2	
	mínimo-máximo	52-66.5	52-67.9	-1.4-1	
	standard deviation	7	7.7	0.9	

[a] *t-Student for paired samples*

The majority of the patients had a slight clinical improvement (Figures 1).

DISCUSSION

Although most modalities of noninvasive treatments for the improvement of the body's contour are safe, there is little scientific proof of the efficacy of the various modalities. In addition, most of the published studies use subjective parameters or circumferential measurements with little standardization.[1,8]

Ultrasound has been used in studies on cryolipolysis due to the fact that it is capable to objectively evidence the thickness of the subcutaneous tissue.[3,9] Using ultrasonography, Coleman *et al.*[9] verified a mean reduction of 20.4% in the subcutaneous tissue that was not correlated with body weight, after two months of treatment. The authors of the present study also observed a reduction of the subcutaneous weight that was not associated with body weight.

All individuals presented circumferential reduction in at least one measurement. Two patients presented a reduction greater than 4cm (Graph 2), a decrease similar to that of the focused ultrasound study.[10] The authors of the present study emphasize that, although objective, circumferential measurement is subject to many sources of possible imprecision, such as adequate positioning, greater or lesser compression during measurement, and even interference from breathing.

In a controlled study by Jewell *et al.*[8] with high intensity focused ultrasound, there was a significant reduction of the abdominal circumferential measures. However, 7.6% (9/118) reported severe pain during the procedure, and 22.2% required analgesia before, during and after the procedure. Alterations in

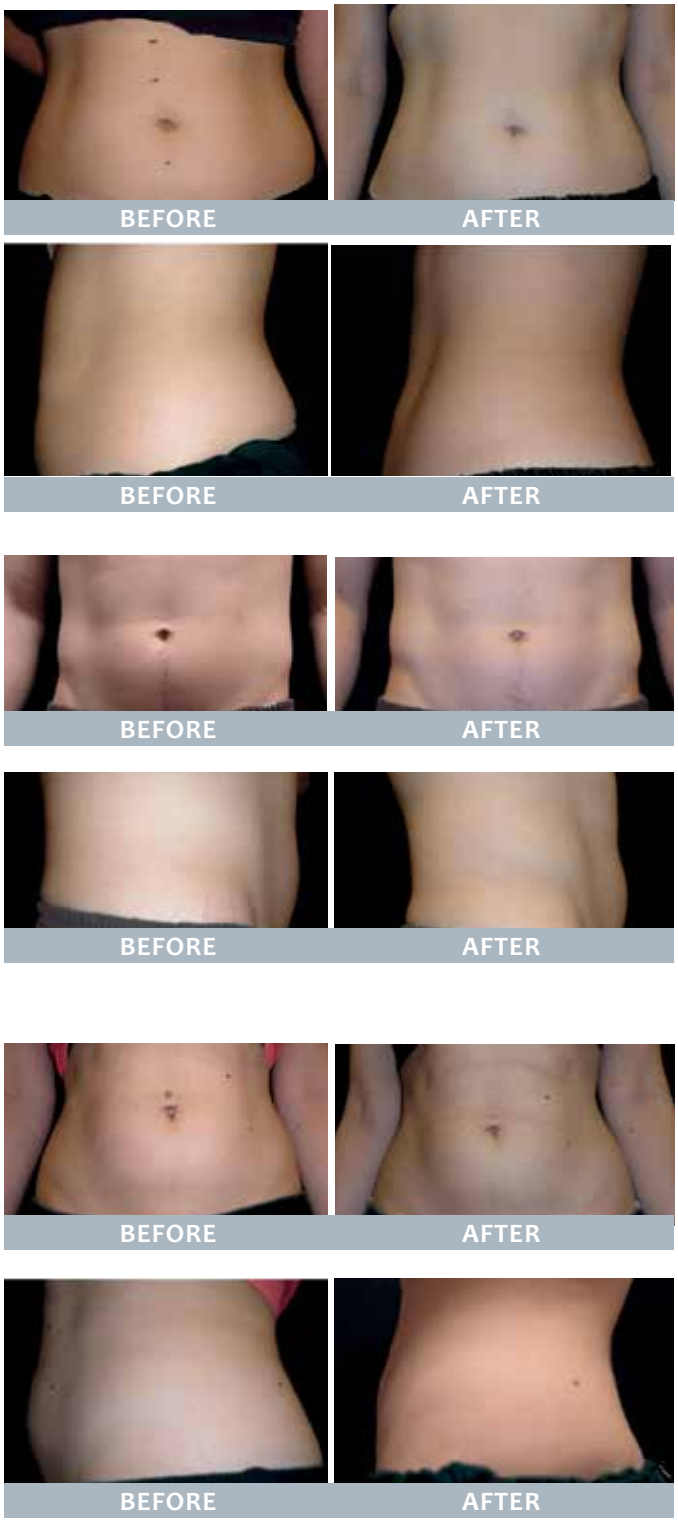


Figure 1: Before and one week after the last session

the sensitivity for up to six weeks are described in cold-based therapies.9 In contrast, in the present study, tolerability was excellent and there was no need for any analgesia, and absence of alterations in sensitivity. It is worth noting that the mechanism of action of the device in question is the alteration of the adipocyte's permeability, with absence of apoptosis (as is the case with cryolipolysis) or fat cell necrosis (as is the case with focused ultrasound). In this way, the authors of the present study believe that, in face of the fact that no long term follow up has been carried out aimed at verifying whether the decrease in measurements would be sustained, results may be less durable.

Of all presented measurements, the most reliable was the thickness of the subcutaneous abdominal region taken via ultrasonography. In this evaluation, the five patients experienced reduction, which although millimetric, is significant, especially in lean individuals, since it corresponds to the AT's thickness and not to the circumferential measurement. As for the clinical photographs, standardization was flawed, which may have interfered with the evaluation of clinical improvement.

The fact that reductions of up to 9mm in the thickness of the subcutaneous tissue were found is promising. Nevertheless, in individuals with great subcutaneous' thickness, this reduction leads to limited benefits. In these cases, even if there is a 9mm reduction in thickness, most of the AT remains in place. This might justify the limited improvement seen in the photographic records of patients with voluminous abdomens.

The major complication of all these noninvasive technologies used for improving the body's contour is the patient's dissatisfaction due to unreal expectation with the outcomes of the procedures.[2] In line with this, most patients in the present study were dissatisfied with the final results because they expected better outcomes. Many patients believe they will experience outcomes similar to those obtained with liposuction, entailing that and it is crucial to educate them about what to expect from the treatment.

Patients who desire non-invasive body contouring need to be carefully selected, and the best candidates are those who are likely to accept modest results and those who do not want to undergo surgery.

Cryolipolysis presents robust results, for instance a 30-50% reduction in the thickness of the fat layer.[3,9] Although safe, most often there is discomfort during the procedure, ecchymosis, and temporary dysesthesia in up to 20% of patients 9 with risk of paradoxical hypertrophy of the subcutaneous. In addition, outcomes can only be observed after several months.[3]

A lower cost (there is absence of consumables) and probably faster initial results are some of the advantages of non-focused ultrasound for improving the body's contour in patients with small localized increases in the AT, as compared to cryolipolysis.

CONCLUSION

The present study shows that the non-focused ultrasound is able to offer localized reductions of the AT. Studies with larger, randomized and controlled samples are however necessary to better evaluate the percentage of the reduction in the AT. The authors also suggest that other studies should be performed with longer follow-up periods and that ultrasound based subcutaneous measurement be used, in this manner allowing uniformity of methods and better scientific evidence. ●

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Treatment of the Hailey-Hailey disease with fractional CO2 laser: a three-case series

Tratamento da doença de Hailey-Hailey com laser de CO2 fracionado: uma série de três casos

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RESUMO

A doença de Hailey-Hailey ou pênfigo familiar benigno é condição rara, que se caracteriza por lesões vesiculares e erosões, associadas a dor e queimação, que comprometem a qualidade de vida dos pacientes. Existem vários tratamentos tópicos e sistêmicos que podem promover temporariamente a remissão das lesões, não existindo tratamento curativo. Algumas opções de tratamento com resultados duradouros abrangem a dermoabrasão e a vaporização com laser de Erbium YAG ou CO2. Relatamos três casos de pacientes com lesões recorrentes e respostas limitadas aos tratamentos clássicos, que apresentaram melhora clínica importante e alívio sintomático após terapia com laser de CO2 fracionado.

Palavras-chave: pênfigo familiar benigno; terapia a laser; dióxido de carbono

ABSTRACT

The Hailey-Hailey disease or familial benign pemphigus is a rare condition, characterized by vesicular lesions and erosions with a predilection for intertriginous areas associated with pain and burning sensation that affect the quality of life of patients. There are many topical and systemic treatments for the injuries that can temporarily promote partial or complete remission, but there is no curative treatment. Some treatment options with lasting results include dermabrasion and Erbium laser resurfacing (YAG or CO2). We report three cases of patients with recurrent lesions and limited responses to classical treatments, which showed significant clinical improvement after fractional CO_2 laser therapy.

Keywords: *pemphigus, benign familial; laser therapy; carbon dioxide*

INTRODUCTION

The Hailey-Hailey disease or familial benign pemphigus is a rare condition that affects the keratinocytes' adhesion. It has an dominant autosomal inheritance and is characterized by vesicular lesions and erosions, with a predilection for intertriginous areas, such as the armpits, groins, and inframammary region.[1] The lesions appear around the second and third decades of life and can manifest up to the fifth decade.[1,2]

Its has an indeterminate course, usually with periods of outbreaks and remissions. Eruptions can be triggered by factors such as friction, sweating, heat, emotional stress and ultraviolet radiation. The lesions may have spontaneous remission or worsen with painful fissures or bad odor vegetating lesions, compromising the quality of life in a significant manner.[1,2]

Several therapeutic options have been described, the most common being antibiotic therapy and oral or topical cor-

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ticosteroid therapy, with varying remission and recurrence rates. Retinoids, systemic methotrexate and cyclosporine, topical tacrolimus, botulinum toxin and photodynamic therapy also led to variable rates of therapeutic success.[2] The long-term treatment options comprise surgical excision associated with cutaneous graft, and dermabrasion. These therapies yield good results, however with significant rates of complications (i.e. infections and retractions) due to their more invasive character. In contrast, laser therapy is less invasive and has been reported as safe and effective, leading to long-lasting results.[3]

The authors of the present paper describe three cases of patients who had limited response to classic treatments, nevertheless showed significant clinical improvement, symptomatic relief and absence of recurrence after fractional CO_2 laser therapy.

METHODS

The procedures were performed in an ambulatorial setting, under topical anesthesia (7% lidocaine + 7% tetracaine) (Pliaglis® Galderma, São Paulo, Brazil). The laser device used was the DUAL DEEP® (Lutronics - South Korea), set at the static mode, with a 12mm spot and fluence between 80 and 100 Joules/cm2. Two passes (exceeding by 1cm the lesion's visibly active borders) were performed in each of the sessions.

In all cases, it was possible to observe hyperpigmentation sequelae resulting from chronic lesions.

Case reports

Case 1

A 58-year-old female patient had a 6-year history of recurrent Hailey-Hailey disease. She had fissured, hyperkeratotic painful plaques on the dorsum and cervical region. The patient had previously undergone conservative treatment with topical corticosteroids and oral antibiotics, without significant improvement. Multiple areas of the dorsum were treated – one per session – with an average of four sessions in each of the affected areas, over a total period of two years (Figure 1). During a four-year clinical follow up period, the patient did not show recurrence of the lesions in the treated areas.

Case 2

A 39-year-old female patient had experienced recurrent Hailey-Hailey disease in the axillae for about 10 years. Antimicrobial therapy and oral isotretinoin had been ineffective. Three CO2 laser sessions were performed in each axilla with monthly intervals (Figure 2). The patient did not present recurrence after 2 years of clinical follow-up.

Case 3

A 46-year-old male patient had been diagnosed with the Hailey-Hailey disease in the adolescence (predominantly in the axillae). There were reports of partial improvement of the lesions with oral antibiotics and topical corticosteroids, however with frequent recurrence. The axillae were then treated monthly with CO2 laser sessions, in a total of four sessions in each axilla. There was a significant improvement in the lesions, without recurrence after a one year follow-up (Figure 3).

DISCUSSION

Familial benign pemphigus is a disease that courses with recalcitrant erosive plaques and can be debilitating. First-line therapies are generally medicament-based and only promote temporary suppression of the lesions.[1] Dermabrasion and ablative laser, which have been resulting in the long-term remission of the condition, are the most advanced techniques for the treatment of the Hailey-Hailey disease. Dermabrasion is effective, nonetheless limited due to its complications and the impossibility of being performed in certain body sites.[2]

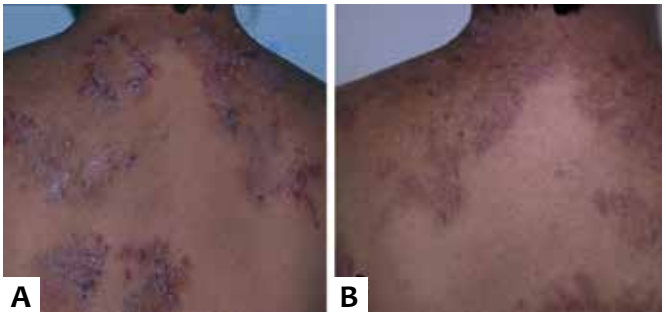

Figure 1: A – Pre-treatment appearance; **B –** Two months after the end of the treatment

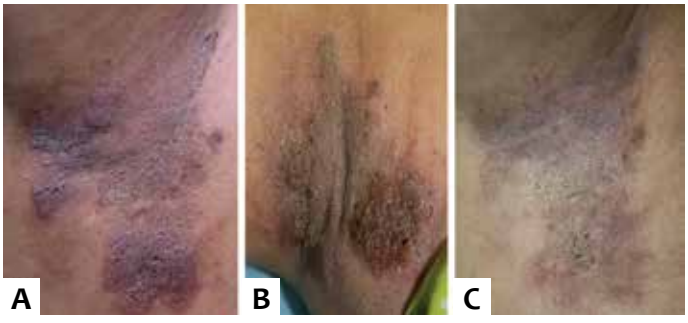

Figure 2: A – Before treatment; **B –** Immediate post-treatment; **C –** Two months after the treatment

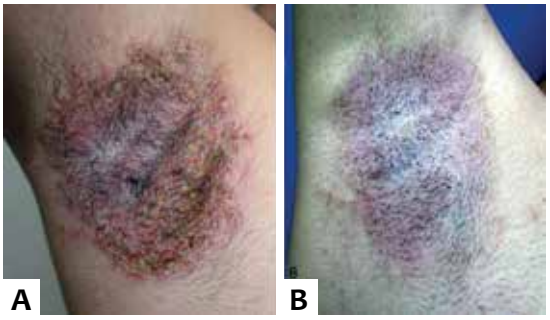

Figure 3: A – Pre-treatment appearance; **B –** Two months after the end of the treatment

On the other hand, laser therapy has several advantages over other therapies: it can be used to treat a large area in a short period of time; it causes less intraoperative pain and less postoperative bleeding; it offers better control of the procedure's depth and decreased probability of scarring as compared to dermabrasion; and it can be performed ambulatorially under local anesthesia.[2, 3] Therefore, it is a promising therapy with the possibility of becoming the method of choice for the treatment of recurrent Hailey-Hailey disease.

The main side effects of CO_2 laser are transient edema and erythema, scarring and depigmentation. A common problem is the recurrence of the disease at the treated lesion's periphery. In order to avoid this situation, Kruppa et al. have suggested that the application of laser should cover an area that exceeds that of the clinically visible disease.[4,5]

The exact mechanism of action of the ablative laser in this pathology remains uncertain. One theory is that the epidermis and keratinocytes expressing the molecular defect are destroyed, leaving the adnexa intact, allowing the regeneration of the normal epidermis without the adhesion defect. The adnexa have the mutation however they do not express them, being therefore unaffected by the acantholytic process.5 Another theory is that dermal fibrosis leads to better support of the unhealthy epidermis and decreases the risk of ulceration and fissure formation.[6]

The three cases reported in the present paper had an excellent response to fractional CO_2 laser, with minimal side effects (erythema, edema and transient pain). They were followed for up to four years with absence of recurrence of the lesions in the treated sites.

Evidence describing the treatment of familial benign pemphigus with CO_2 laser is encouraging in cases such as those described here. Nevertheless, more encompassing studies are necessary to consolidate the status of this method in the therapeutic armamentarium available to treat the Hailey-Hailey disease. ●

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Case Reports

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Frontal edema after application of 5% minoxidil and biotin in intradermal injections

Edema frontal após aplicação de minoxidil 5% e biotina em injeções intradérmicas

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RESUMO

A intradermoterapia, ou mesoterapia, é procedimento não cirúrgico, minimamente invasivo, que consiste em múltiplas aplicações de substâncias farmacológicas diluídas por via intradérmica ou subcutânea. Já foram relatados vários efeitos adversos posteriores a esse procedimento: alopecia, erupção liquenoide, oleoma, indução de psoríase e infecções cutâneas. A informação científica sobre o tema é escassa, e há poucos estudos com metodologia rigorosa acerca da eficácia e do mecanismo de ação da via intradérmica. Relata-se caso de edema frontal após intradermoterapia com minoxidil e biotina.

Palavras-chave: mesoterapia; alopecia; doenças do cabelo

ABSTRACT

Intradermotherapy, also known as mesotherapy, is a non-surgical procedure, minimally invasive consisting of multiple applications of pharmacological substances diluted by intradermally or subcutaneously. Adversities already been reported after treatment mesoterápico as alopecia, lichenoid rash, oleoma, psoriasis induction and skin infections. There is scant scientific information on the subject, and few studies with more rigorous methodology of the efficacy and mechanism of action of intradermally. Knowing this, there was this article having a complicating account of this method in a patient of our service, and elucidate some of its benefits and other complications.

Keywords: *mesotherapy; alopecia; hair diseases*

INTRODUCTION

Intradermal therapy, also known as mesotherapy, is a non-surgical, minimally invasive procedure consisting of applications of diluted pharmacological substances intradermally or subcutaneously, at multiple points in the area to be treated. The technique was introduced in 1958 by Pistor, a French physician who initially used the procedure as a new analgesic therapeutic method for rheumatologic diseases.[1] Nowadays – 50 years on – this practice has been adopted in many European countries and the United States of America. It has been recently introduced in Brazil and is indicated for the treatment of fat deposits, skin rejuvenation and hair growth.[2]

Regarding hair growth, the technique is used as an alternative therapy in the treatment of female androgenetic alopecia. In theory, its advantage would comprise a faster therapeutic response and a greater stimulus to hair regrowth. Despite this, sufficient scientific evidence could not be found in support of this approach.[3,4]

In this manner, the present report's proposal is to describe a complication after treatment with capillary mesotherapy.

CASE REPORT

A 36-year-old female patient diagnosed with androgenetic alopecia experienced non-inflammatory frontal edema 24 hours after undergoing mesotherapy with 5% minoxidil and biotin on the scalp (Figures 1 and 2). The edema emerged after the patient worked for 8 hours looking down at a computer monitor. She was then instructed to massage and apply compresses on the edema's site, with spontaneous remission of the condition one day after the onset of the picture.

DISCUSSION

The scarce publication of articles and reports on the complications of intradermotherapy in the treatment of androgenetic alopecia validates the importance of the present study. One of the few reports found describes the presence of frontal edema after biotin intradermal therapy and topical application of 5% minoxidil. In this paper, published in 2015, the authors report that after discontinuation of the topical therapy, the edema receded. According to the article, the reason for this side effect was the mechanism of vasodilation, triggered by minoxidil. The great number of drug injection points would have been responsible for the greater absorption of the substance, leading to edema in the frontal region.[5]

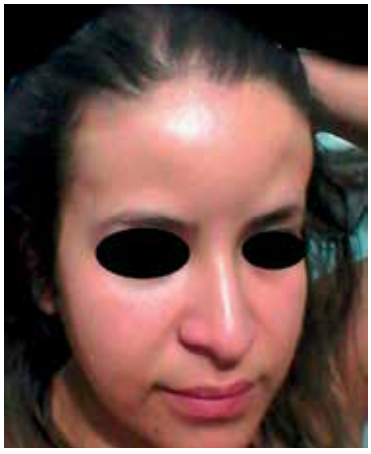

Figure 1: Depressible and non-inflammatory edema on the forehead

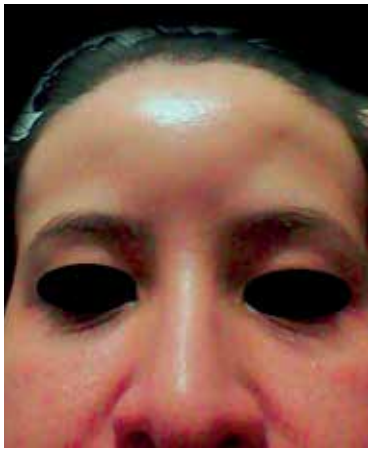

Figure 2: Frontal edema in greater detail

In 2009, another type of complication caused by intradermal therapy was reported by Duque-Estrada *et al.*, who described two cases of presence of irregular alopecia after the treatment for androgenetic alopecia. In the first case, the patient developed areas of residual cicatricial alopecia after injections of the heparinoid vasodilator mesoglycan, while in the second case, the patient presented reversible alopecia after multiple injections of homeopathic agents.6 Another complication caused by this procedure was reported in 2008 by Kadry, Hamadah, Al-Issa , Field and Alrabiah, with the emergence of multiple abscesses on the scalp, with fat necrosis, resulting from mesotherapy in the scalp, using a mixture of flavonoids, vitamins (B1, B3, B5, B6, C), procaine and saline solution.[7] Surgical repair was necessary due to that side effect.

It is believed that the fact that the present report's patient had edema in the frontal region 24 hours after the procedure, after having remained with the head positioned down for a considerably long time, has contributed to the development of the complication.

Although described as a minimally invasive procedure, intradermal therapy has potential for several types of complications. Special attention should be given to rigorous asepsis and antisepsis, as well as to the origin of the material to be used. In addition, patients should be provided with guidance on appropriate posture measures after the sessions.

Because of the scarcity of standardized studies and the reports of side effects resulting from intradermal therapy, caution is truly required when choosing this therapeutic method. Further research is therefore needed aimed at elucidating the precise mechanism of hair mesotherapy. The present case was described with a view to expanding the literature available on mesotherapy.

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Case Reports

Microneedling: a case series associated with drug delivery

Microagulhamento: série de casos associados drug delivery

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ABSTRACT

Six patients underwent two sessions of microneedling associated to drug delivery on the face, hands or stretch marks, at three-week interval between sessions. Patients were evaluated using clinical analysis and objective measures. Compared to baseline, objective face analysis showed decrease in acne lesions and improvement in the skin texture. The evaluation of stretch marks showed great improvement, and face and hands presented excellent results compared to baseline. The association of microneedling to drug delivery for rejuvenation of the face and hands, and for the treatment of stretch marks presented promising results in our study.

Keywords: administration, cutaneous; hyaluronic acid; rejuvenation; striae distensae; tranexamic acid; hydroxyproline

RESUMO

A associação do microagulhamento com o drug delivery tem-se mostrado benéfica pois potencializa os resultados de ambas as técnicas. Seis pacientes foram submetidas a duas sessões dessa associação de técnicas no tratamento da face, mãos e estrias, com intervalo de 20 dias.

As avaliações foram realizadas por fotografias comparativas padronizadas. Os resultados revelaram redução da acne e melhora das manchas e textura da pele na face, melhora das manchas e textura da pele das mãos, e redução das dimensões e visibilidade das estrias. O presente estudo apresentou resultados promissores associando microagulhamento e drug delivery para tratamentos dermatológicos em face, mãos e estrias.

Palavras-chave: *administração cutânea; ácido hialurônico; rejuvenescimento; estrias de distensão; ácido tranexâmico; hidroxiprolina*

INTRODUCTION

Microneedling has a range of clinical indications, and is performed with a polyethylene cylinder provided with sterile stainless steel microneedles. Among the objectives that can be achieved with this technique are cutaneous rejuvenation, the treatment of scars and spots, and the penetration of active principles in the skin. Several studies have been conducted to demonstrate that microneedling effects drug delivery, promoting increased skin permeability by creating microchannels, which stimulate the transepidermal/transdermal conveyance of drugs.[1] In the case series presented in this paper, the authors describe the use of microneedling associated to drug delivery in the treatment of stretch marks and skin rejuvenation of the face and hands.

MATERIALS AND METHODS

The treatment protocols of six female patients, aged between 30 and 50 years, are described below. Two patients underwent microneedling for the treatment of stretch marks, two for treating melanosis and rejuvenate the hands' skin, and two for treating melanosis and rejuvenate the facial skin. The device used was the Dr. Roller® (Moohan Enterprise, South Korea), with needle with lengths of 2 mm (for facial procedures), 1.5 mm (hands) and 2.5 mm (stretch marks). The topical anesthetic Dermomax® (Aché Laboratory, São Paulo, Brazil) was applied 30 minutes before the procedure and removed using 0.2% aqueous chlorhexidine. Two sessions were performed in each region observing a 20-day interval. The procedure was performed by rolling the device on the patient's skin surface in "back and forth" movements up until a uniform pattern of petechiae emerged – after 10 to 15 passes in the same direction plus four transversal passes on the same area, inflicting 250-300 punctures /cm². [2,3] Once the procedure was performed, cleansing was carried out with 0.9% saline followed by the application of the formulation prepared for *drug delivery.*

On the face and hands a serum containing the association of 0.4% tranexamic acid, 1.5% 4-hexylresorcinol, 1% alpha bisabolol, 2% Belides and 2% peptide TGP-2 was applied. Another serum containing 4% hydroxyprolisilane, 5% active omega, 2% regestril, 2% matrixyl 3000, and 1.5% IGF serum was applied in the stretch marks. For 30 days the patients used at home the same formulations, which were dispensed by Farmatec Farmácia de Manipulação Ltda. (Porto Alegre, RS, Brazil).

The assessments were performed based on the clinical analysis of photographs taken before and 30 days after the second session for all patients. Patients who underwent facial microneedling were also objectively evaluated using the FOCCO Facial® device (Fabinject Technology, Taubaté, SP, Brazil), outfitted with three types of lighting, used to carry out the photographic records: daylight (RGB), ultraviolet light (emulates the use of a Wood's lamp), and polarized light. By analyzing baseline and follow up photographs, the device evaluates the parameters *spots* (visible to the naked eye and under ultraviolet light), *wrinkles*, *texture*, *pores*, *skin hydration level*, *reddish areas* and *porphyrin* (acne lesions), comparing the findings between experimental timepoints.

RESULTS

According to the data obtained with assistance of the FOCCO Facial® device, both patients who underwent facial procedures experienced reduction of *acne* (52% and 69%) and improvement in *skin texture* (16.2% and 10.7%). One of the patients also had improvement in the number of *pores* (28.5%), decrease in the number of *spots* (20.3%) and improvement in the *skin's sensitivity* (25%). The clinical evaluation, based on photographs taken before and 30 days after the last procedure and carried out on the stretch marks evidenced satisfactory improvement in all the parameters evaluated (*texture*, *thickness of stretch marks* and *visibility* in the photos - Figure 1). A similar outcome was clinically observed in the evaluation of *spots*, *texture* and *skin quality* in patients who underwent the procedure in the hands (Figure 2). In the evaluation performed on the face, the parameters *redness*, *acne* and *pores* were rated with reasonable results, while the other variables (*texture*, *spots*, *skin quality*, *wrinkles* and *rhytids* - Figure 3) yielded a high degree of improvement.

DISCUSSION

The association of microneedling with drug delivery has proven beneficial because it enhances the outcomes of both techniques. According to a study by Kalil *et al.*, the association of a cosmetic formula with microneedling enhances the result of skin rejuvenation by 28%. [4] Microneedling results in the loss of cutaneous integrity, which triggers the healing process and culminates with the formation of type I collagen, which influences skin rejuvenation and scar improvement.[2] For the remodeling of collagen, the needles need to reach a depth of 1 to 3mm, so that the dermis is reached; However, only 50% to 70% of the needles penetrate during the rolling process, meaning that the needles used for collagen remodeling must be at least 1.5mm long. Microneedling increases the skin's permeability for approximately 48 hours; this lapse can be expanded with the assistance of occlusion, which delays the stratum corneum's restoration, also taking into consideration that the combination of used substances is anhydrous and water repellent.[1] Other factors that affect the skin's permeability are the properties of drugs (ionization, concentration, liposomes or nanoparticles), the presence of co-solvents, pH, viscosity and the presence of permeators.[2,5-8] In addition to the vehicle's hydrophobicity characteristics, the formula used in the present study had low viscosity – which increases the drug delivery capacity – and contained hyaluronic acid in its composition – which delays the closure of the pores – and active principles with modified permeation systems aimed at achieving greater penetration.[5,6] According to a study by Milewski *et al.*, liposomal, nanoencapsulated, vectorized and lipophilic active principles reach higher tissue concentration than hydrophilic macromolecules.[5] In addition to the fact that the physicochemical characteristics of the active substances aided permeation – consequently boosting outcomes – the specific mechanism of action of each particular active principle may have contributed positively for the observed results.

Figure 1: Stretch marks before and 30 days after the last microneedling session: decrease in the thickness and number of striae

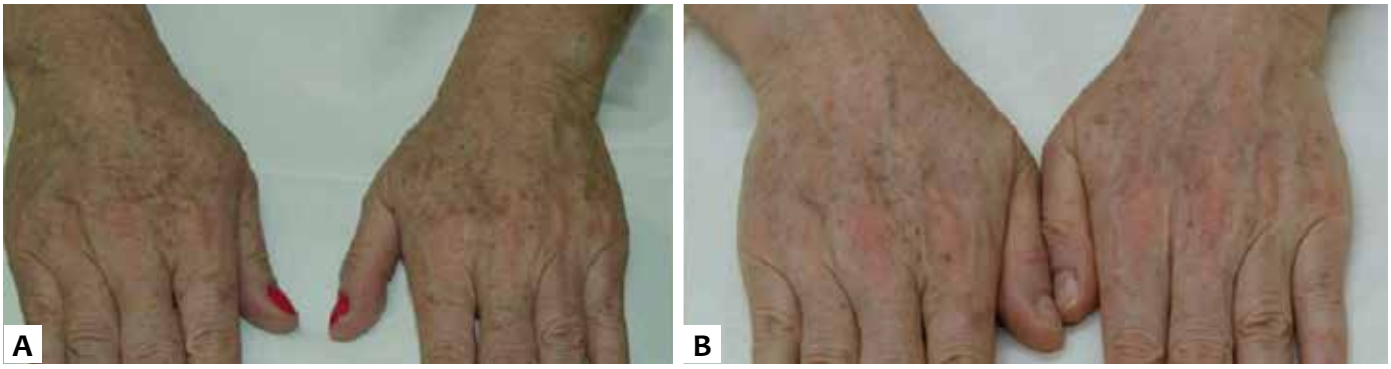

Figure 2: Hands before (**2a**) and 30 days after (**2b**) the last microneedling session performed with a roller with 1.5mm long needles. In addition to the whitening of the region, it is possible to observe improvement of the texture and quality of the skin

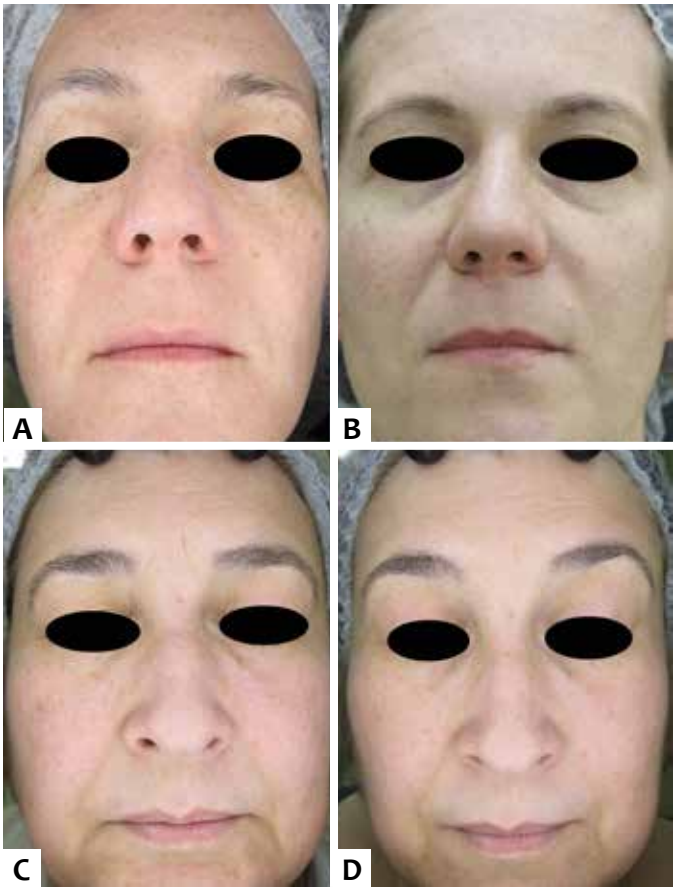

Figure 3: Photographs of the face at baseline (**3a and 3c**) and 30 days after the second session (**3b and 3d**) using a roller with 2.0mm long needles: improvement in spots, texture, skin quality, wrinkles and rhytids

In the formula for the photorejuvenation of the hands and face, active principles were used to inhibit tyrosinase (tranexamic acid and 4-hexyl resorcinol), endothelin-1 / modulator of melanocytes' response to ultraviolet radiation (belides), α-MSH hormone / melanin production activator (alpha bisabolol for both its anti-inflammatory and inhibitory activity) and TGP-2 peptide as an inhibitor of melanosome formation.[9] The set of active principles, each of which with different mechanisms of action on the synthesis of melanin, may have been responsible for the whitening observed on the hands and face (Figures 2 and 3). In addition, it was possible to observe excellent results in the microneedling and drug delivery technique applied to stretch marks largely due to a set of active principles that act on the synthesis of collagen and elastin – such as hydroxyprolisilane and matrixyl 3000 – or that inhibit collagenase – such as regestril and active omega. All these active principles act synergistically to increase the skin's hydration and reduce the stretch marks' thickness by acting on several mechanisms of action.[9]

CONCLUSION

The present study showed promising results with the technique that associates microneedling to specific formulas for drug delivery for treating the face, hands and stretch marks. The drug delivery technique deserves emphasis due to the fact it optimizes the outcomes of microneedling, calling attention to the benefit of the association of procedures, leading to more promising results provided by the stratum corneum's increased permeability. Due to the fact it is an innovative technique with a short recovery time – not precluding the patient from carrying out daily activities – and that can be applied in high skin phototypes with minimal risk of adverse effects as compared to other techniques that are, for instance, contraindicated in melasma, the studied method deserves further investigation aimed at confirming the findings of the present report. Published studies exploring the use of microneedling for drug delivery are fewer than those linked to the use of ablative lasers – either fractional or not –therefore calling for new studies aimed at clarifying the doubts that persist about the subject. ●

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Case Reports

Basal cell carcinoma growth over a nevus sebaceous: treatment of the field cancerization with photodynamic therapy

Carcinoma basocelular desenvolvido sobre nevo sebáceo: tratamento com terapia fotodinâmica abordando campo de cancerização

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RESUMO

Nevo sebáceo de Jadassohn é hamartoma congênito que pode apresentar evolução para neoplasia cutânea maligna. A terapia fotodinâmica é utilizada para tratamento de ceratoses actínicas e carcinomas basocelulares superficiais ou nodulares, podendo-se observar o campo de cancerização cutâneo através da lâmpada de Wood, durante a realização da técnica. Relata-se um caso do uso da terapia fotodinâmica para o tratamento de um carcinoma basocelular, que se desenvolveu sobre nevo sebáceo, demonstrando-se o campo cancerizável através do uso da lâmpada de Wood. O procedimento consistiu em alternativa de tratamento não cirúrgico para o carcinoma basocelular, com excelente resultado estético. A paciente encontra-se em seguimento clínico, não apresentando recidiva da neoplasia 18 meses após o tratamento.

Palavras-chave: carcinoma basocelular; nevo sebáceo de Jadassohn; fotoquimioterapia

ABSTRACT

The sebaceous nevus of Jadassohn is a congenital hamartoma that may develop into a malignant cutaneous neoplasia. Photodynamic therapy is used to treat actinic keratoses and superficial or nodular basal cell carcinomas, and the cutaneous field cancerization can be observed using the Wood's lamp during the performance of the technique. This article describes a case of photodynamic therapy used in the treatment of a basal cell carcinoma, which developed on a sebaceous nevus, where the field cancerization was demonstrated through the use of Wood's lamp. The procedure is a non-surgical alternative for the treatment of the basal cell carcinoma, with excellent aesthetic outcome. The patient is on clinical follow-up, with absence of recurrence of the neoplasia 18 months after the treatment.

Keywords: *carcinoma, basal cell; nevus, sebaceous of Jadassohn; photochemotherapy*

INTRODUCTION

The sebaceous nevus of Jadassohn is a congenital hamartoma [1] commonly located on the scalp and face, being found in 0.5 to 1% of the population. Its etiology is unknown, however recent studies suggest a possible link with the human papilloma virus or mutations in the patched gene (PTCH).[2] The development of malignant neoplasms in this lesion is rare, and typically involves basal and squamous cell carcinomas.[3]

Photodynamic therapy (PDT) is currently used for the treatment of actinic keratoses on the face and scalp and as an alternative to surgical treatment of superficial or nodular basal cell carcinomas (BCCs).[4] The visualization of the cancerization field in PDT is possible with the assistance of a Wood's lamp three hours after the use of methyl aminolevulinate (MAL) photosensitizing cream, followed by occlusion with clear plastic film and aluminum foil.

On examination, a reddish fluorescence is observed in the areas corresponding to the actinic keratoses visible on dermatological examination or in subclinical lesions [5] (Figure 1). In BCC lesions, it is possible to delimit the margins of poorly defined lesions, which helps in future surgical procedures.[6] The authors describe a clinical case of a patient who underwent PDT for the visualization of the cancerization field and treatment of nodular BCC that developed over a sebaceous nevus.

CASE REPORT

A 28-year-old female patient (Fitzpatrick phototype IV) with history of congenital lesion in the right temporal region sought medical advice. Irritation and pruritus had emerged at the site six months before, with biopsies having been performed in two points: one at the lesion's upper border – whose anatomopathological study confirmed the presence of a sebaceous nevus – and the other at the lesion's lower third – which indicated the presence of a nodular BCC, with compromised margins (Figure 2). The proposed treatment comprised two sessions of PDT using MAL cream, with an interval of one week. Curettage of crusty and rough areas of the nevus was performed on the day of the first procedure, with the subsequent application of MAL cream and occlusion with plastic film and aluminum foil for three hours. The dressing and product were removed after that period, when the field cancerization could be visualized

Figure 1: Reddish fluorescence in areas of visible actinic keratoses

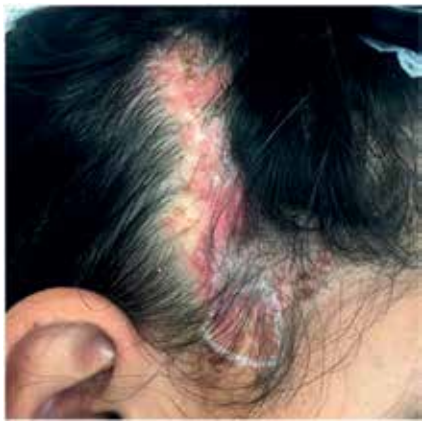

Figure 2: Sebaceous nevus with area marked at the site of anatomopathology compatible with BCC

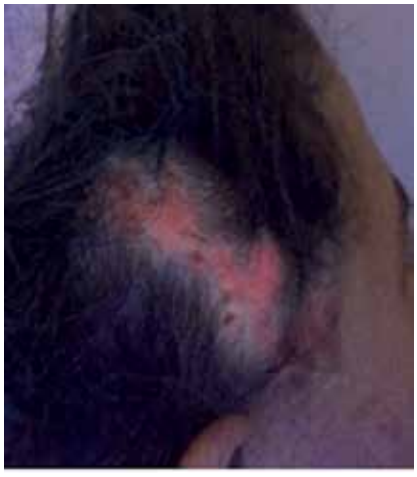

Figure 3: Visualization of areas with risk of malignization on a sebaceous nevus

Figure 4: Minimum fluorescence after the second session of PDT

through fluorescence with the assistance of a Wood's lamp (Figure 3). Irradiation with red light was then applied for eight minutes with a diode light emitting equipment whose wavelength ranged between 631 and 637nm, at a fluence of 37 J/cm². After a one-week interval, the procedure was repeated. Re-examination with Wood's lamp did not show fluorescence, evidencing the therapeutic effect of the photosensitizing agent in the neoplastic areas or at risk of malignization (Figure 4). A new biopsy was then performed in two points in the lower third of the sebaceous nevus, where a BCC lesion had been identified. Both specimens showed absence of signs of neoplasia (Figure 5). The cutaneous lesion histopathological images obtained before and after the therapy are shown in Figure 6.

The patient remains under clinical follow-up, with no signs of neoplasia recurrence 18 months after the treatment.

DISCUSSION

Sebaceous nevi have the clinical appearance of yellow or orange plaques with a well-circumscribed verrucous surface.[7] Dermoscopic observation reveals isolated or grouped yellow-whitish rounded structures, which correspond to mature superficialized sebaceous glands.8 From the histological perspective, there are a series of abnormalities in the sebaceous and sweat glands, and in hair follicles, which are not well differentiated.[2] The lesion's size increases proportionally to the patient's age, presenting velvety appearance, small protrusions and verrucous surface at puberty.[7] Some neoplasms can arise over sebaceous nevi, especially after puberty: [1] benign tumors (trichoblastoma and syringocystadenoma papilliferum) and malignant tumors, among which BCC is the most common,[7] arising in approximately 0.8% of patients with this type of lesion.[1] There is no consensus regarding an ideal therapy. Some authors recommend early surgical excision in order to prevent malignant and aesthetically disfiguring transformations. Nevertheless, others advocate a more conservative approach. Future research should identify molecular markers or genetic alterations that might indicate a greater risk of neoplastic transformation, in this manner avoiding unnecessary surgical interventions.1 Lasers and PDT are currently being explored for the treatment of sebaceous nevi, with different degrees of response.[2]

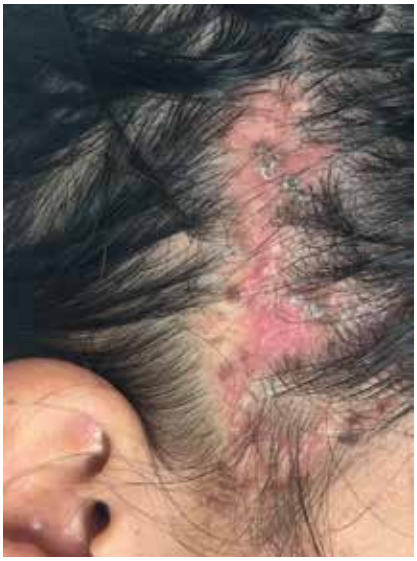

Figure 5: Sebaceous nevus after clinical treatment of the BCC with PDT

Photodynamic therapy with MAL has been used in the treatment of superficial or nodular BCC with varying rates of efficacy and recurrence depending on the lesion's characteristics, namely dimensions, periorificial location and recurrent nature. It is also effective for the mapping of actinic keratoses in the field cancerization.[9,10]

In this way, in the case in question, it was possible to show: i) the efficacy of PDT-MAL as an alternative to surgery in patients with BCC growth over sebaceous nevi, and ii) the usefulness of the Wood's lamp as a tool for observing subclinical malignant lesions on hamartomas.

CONCLUSION

Photodynamic therapy is an effective treatment option for BCC as a non-surgical alternative and also useful for visualizing areas of risk of cancerization in a sebaceous nevus, as observed in the present case. ●

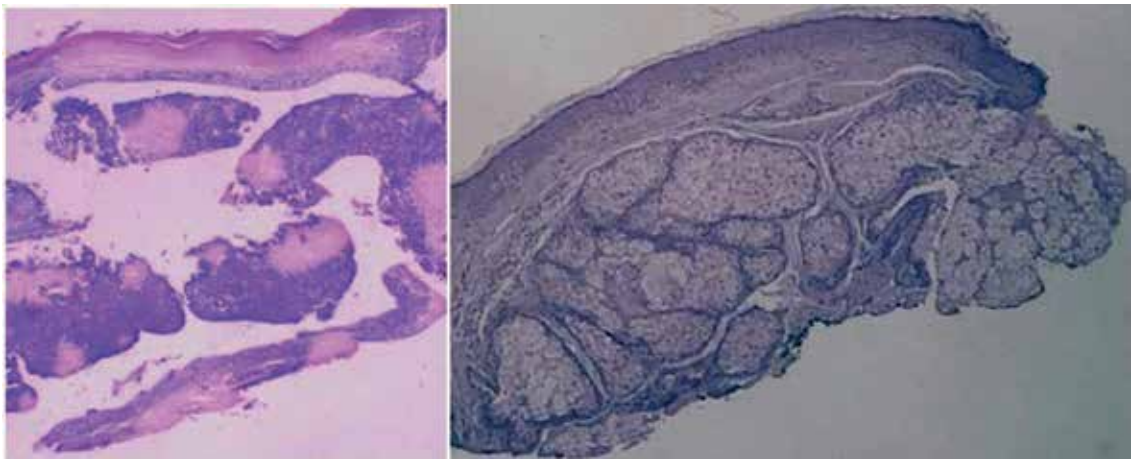

Figure 6: Histopathology evidencing a nodular basal cell carcinoma and absence of signs of neoplasia

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