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c- Procedimentos: descrever as principais características das intervenções realizadas, detalhando a técnica e lembrando que o estudo de investigação deverá ser reprodutível.
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e- Inclusão da análise estatística descritiva e/ou comparativa com descrição do planejamento da amostra (representativa do universo a ser estudado), a análise e os testes estatísticos e apresentação dos níveis de significância adotados. A utilização de análises estatísticas não usuais é incentivada, porém neste caso, deve-se fazer uma descrição mais detalhada da mesma.
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Discussão: enfatizar os novos e importantes resultados encontrados pelo estudo e que farão parte da conclusão. Relatar observações de outros estudos relevantes. Mencionar as limitações dos achados e as implicações para pesquisas futuras.
Conclusões: devem ser concisas e responder apenas aos objetivos propostos. A mesma ênfase deve ser dada para estudos com resultados positivos ou negativos.

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Laser assisted drug delivery: a review

Drug delevery assistido por lasers: revisão

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ABSTRACT

The topical route for the delivery of drugs is essential in dermatology: it optimizes the penetration of medicaments, and when performed with the assistance of lasers, it takes place in a uniform and controlled manner. The degree of evidence of drug delivery is being investigated for many drugs. Moreover, the technique combines outstandingly with lasers for rejuvenation and treatment of skin diseases. It is therefore possible to conclude that the use of lasers for drug delivery is promising. While there are clinical studies on some substances that allow their indication and use, others require further controlled analyses, with longer follow-up periods, aimed at allowing thorough evaluations.

Keywords: *lasers; administration, cutaneous; skin absorption; drug delivery systems; drug administration routes*

RESUMO

A via tópica de entrega de medicamentos é essencial na dermatologia. O drug delivery otimiza a penetração de medicamentos e, realizado por lasers, ocorre de forma uniforme e controlada. O grau de evidência do drug delivery está em investigação para diversos medicamentos. Além disso, a técnica é excelente associação com a atuação dos lasers para rejuvenescimento e para tratamento de doenças dermatológicas. Conclusão: O uso de lasers para drug delivery é promissor: enquanto algumas substâncias possuem estudos clínicos que permitem indicar sua realização, outras necessitam de estudos controlados e com maior tempo de seguimento para sua avaliação.

Palavras-chave: *lasers; administração cutânea; absorção cutânea; sistemas de liberação de medicamentos; vias de administração de medicamentos*

Continuing Medical Education

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INTRODUCTION

Topical delivery of drugs is essential in dermatology. Moreover, it is of paramount importance that the drug applied on the skin be capable of penetrating cutaneous layers and reaching the target structure. It has many advantages over the oral, intramuscular and intravenous systemic routes, for there is absence of first-pass metabolism, and it reduces side effects present in the systemic use, increasing patient adherence to the treatment.[1] The epidermal barrier function is preserved by the stratum corneum's lipid bilayer, which is the main limiting factor for the use of drugs applied on the skin.[2] The penetration of drugs across an intact stratum corneum takes place by diffusion and, to a lesser extent, through the skin's appendages, and can occur by transcellular or intracellular pathway.[1] Only lipophilic and smaller than 500Da molecules are capable of penetrating an intact stratum corneum.[1] Furthermore, only 1% to 5% of the product applied to the skin is absorbed and becomes bioavailable to exert its therapeutic effect.

The technique termed *drug delivery* consists in finding methods to optimize the penetration of drugs into the skin, and this can be achieved using chemical, mechanical and physical methods.[1] The use of lasers as drug delivery agents was described in 1987 with the use of an ablative non-fractional device.[3] In 2004, Anderson introduced the concept of fractional photothermolysis, in which healthy skin areas are maintained among thermally damaged areas (micro thermal zones - MTZ) generated by the ablative fractional laser, transforming the use of ablative lasers.[4] The use of lasers allows the delivery of drugs in a uniform and controlled way.[5]

Lasers stimulate drug delivery by the means of three processes: 1- tissue ablation, which removes the stratum corneum and the most superficial layers of the epidermis; 2 - photomechanical waves, resulting from the conversion of light into mechanical energy; and 3 - non-ablative resurfacing, where thermal and physical injuries ruptures the skin barrier, promoting the delivery of medications.[6] The degree of evidence of the drug delivery technique has been investigated for many drugs, resulting in different degrees of recommendation, according to the substance studied. While some drugs have already been trialed in randomized clinical tests comparing the technique with traditional methods, some still need further assessment aimed at elucidating the degree of evidence and clinical indication.

Regarding the product used for drug delivery, there are some recommendations to be observed, according to the method employed. Ablative and Q-switched lasers should be preferred when hydrophilic vehicles are used. In contrast, non-ablative lasers and intense pulsed light (IPL) should be chosen for lipophilic active principles.[7] The more fluid is the used vehicle, the better the penetration of the active principles. The presence of cosolvents in the formulation significantly increases the penetration of the active principle with laser based drug delivery.[7] Anhydrous formulations hinder the proliferation of microorganisms and do not cause burning sensation, sensitivity or comedones during the application.[7]

Although controversial, the use of sterile products is questionable, for contamination with microorganisms located on the skin's surface can occur even after proper asepsis of the treated area and with the use of sterile formulations. In addition, most studies have used non-sterile products for drug delivery, with absence of descriptions of severe complications or side effects.

The present article is aimed at reviewing the current knowledge about the drug delivery technique assisted by lasers.

BIBLIOGRAPHIC RESEARCH

The bibliographic research was performed on the MEDLINE, Cochrane and Lilacs-Scielo data bases using the following keywords: *(fractional laser OR ablative fractional laser) AND (*drug delivery *OR transdermal delivery OR topical administration), (laser AND (*drug delivery *OR transdermal delivery OR topical administration)* and *(non ablative fractional laser) AND (*drug delivery *OR transdermal delivery OR topical administration)* and *(non ablative fractional laser) AND (*drug delivery *OR transdermal delivery OR topical administration)*.

After the selection of papers, the pieces were read based on their Titles and Abstracts, with those pertinent to the study being included. The *in vivo* studies were classified as randomized or non-randomized clinical trials.

EVIDENCE FROM STUDIES ON DRUG DELIVERY ASSISTED BY ABLATIVE FRACTIONAL LASER

The main ablative fractional lasers are 2,940nm Er:YAG and 10,600nm CO_2 laser, which operate in the infrared band and have water as chromophore.[6] The 2,940nm Er:YAG laser has a higher affinity for water, being therefore absorbed by the epidermis' water, allowing a more superficial penetration and minimum generations of heat. On the other hand, the 10,600nm CO_2 laser penetrates deeper and generates higher amounts of heat. Both lasers facilitate drug delivery both through MTZs and through thermal effect present on the tissue surrounding the MTZs.[8,9] Ablative fractional lasers characteristically act through tissular ablation columns surrounded by coagulation tissue (the MTZs), which can be modulated according to the used laser's type and energy. These channels penetrate the stratum corneum and grant direct access to lower layers, facilitating the drug delivery of medications applied on the skin. The MTZs can be adjusted using two parameters: density (i.e. the number of micropores per given area) and depth (which is controlled by choosing the level of fluence).[6] The adjustment of the wave type and pulse duration used in ablative fractional laser allow to modulate the ablation degree and the thickness of the coagulation column adjacent to the MTZ: if too thick, this coagulation column hampers the diffusion of the applied substance for drug delivery into the areas adjacent to the MTZ.[10] In addition, the use of excessively high energies results in deeper lesions, which can reach the vessels, thus entailing that the active principle in question may enter the bloodstream, an unwanted effect for drugs that act on the skin. When comparing the ablative fractional CO_2 laser with the 2,940nm Er:YAG, it is observed that the coagulation column is smaller in the latter due to its higher affinity for water, which favors the emergence of

bleeding points in the MTZ, decreasing the permeation of active principles applied in the area. This phenomenon can be minimized using lower energy levels, specific for drug delivery, as already made available in some laser devices.[10]

In vitro studies assessed the influence of the number and depths of pores for ablative fractional laser based drug delivery, observing that the delivery of the drug was dependent on the number of pores in the analyzed area.[11] Nevertheless, once a certain MTZ density is reached, subsequent increases in density do not promote increased permeation of the drug due to the excessive thermal damage inflicted to the tissue adjacent to the MTZ.[10] In general, substances containing hydrophilic molecules depend on the MTZ's depth to be absorbed – a phenomenon that does not occur with lipophilic molecules. [6]

Drug delivery of aminolevulinic acid (ala) and methyl-aminolevulinic acid (mal) assisted by ablative fractional laser

Drug delivery of ALA and MAL assisted by ablative fractional laser is one of the more intensely studied, with a great number of pre-clinical and clinical analyses comparing it with the traditional technique and with the use of other drug delivery methods. Its use has been described in actinic keratoses, Bowen's disease, basal cell carcinoma, actinic cheilitis and onychomycosis.[8,10,12-19]

The delivery of MAL after pre-treatment with ablative fractional CO_2 laser in pig skin was studied by Haederstal et al. in 2010.[10] The study's outcomes showed that pretreatment with lasers allowed a deep and uniform distribution of the drug due to radial diffusion of the product deposited on the MTZs. In 2014, the same authors evaluated the action of 10,600nm CO_2 laser followed by the application of ALA and MAL, describing an increase in the protoporphyrin IX's fluorescence of up to a depth of 1,8mm in the skin pretreated with laser. In addition, centrifuge radial diffusion of MAL was observed based on the uniform fluorescence of up to 1.5mm beyond the micropores inflicted by the laser.[12]

In 2013, Ko et al. evaluated the use of 2,940nm Er:YAG ablative fractional laser followed by the application of MAL in the treatment of 236 facial actinic keratoses of in 45 patients who were randomized to receive either only photodynamic therapy (PDT) or PDT after pre-treatment with laser. Photodynamic therapy assisted by laser was more effective for treating the lesions, especially hyperkeratotic ones ($p = 0.001$).[13]

In 2015, the use of 2,940nm Er:YAG ablative fractional laser followed by MAL application was evaluated for the treatment of actinic cheilitis in a randomized clinical trial. The study selected 33 patients with actinic cheilitis (confirmed by histology) who were randomized to receive either one pretreatment session of 2,940nm Er:YAG ablative fractional laser immediately followed by PDT or two sessions of traditional PDT with a seven-day interval between them. The group pretreated with laser had a more effective response both in the first 3 months of follow up (92% *versus* 59% of complete cure, $p = 0.04$) and after 12 months of follow up (85% *versus* 29%). In addition, the method including the pretreatment led to a lower recurrence rate in the 12 months after the procedure ($p = 0.029$).[14] Adverse effects ranged from mild to moderate, with absence of systemic effects reports. Using the same comparison techniques, the authors treated 440 facial and scalp actinic keratoses in 93 patients, in a follow on study.[16] In that study, the MAL's incubation time was modulated, which lasted 2 to 3 hours. The outcomes showed the superiority of the 3-hour incubation technique associated with the laser as compared to the others. Moreover, this superiority was maintained in the 12-month follow up with statistical significance.[16]

A 2016 *in vivo* study evaluated 5 patients regarding the absorption of ALA.[8] The drug was applied to each patient's arm in four areas: the first received an isolated topical application of the drug; the second received an application after pretreatment with fractional CO_2 laser; in the third area, the application was combined with high pressure; and the fourth area received the application of high pressure transdermal acoustic waves. The ALA was occluded for 30 minutes for incubation in the 4 areas. After this period, biopsies were performed in all areas. The best outcomes regarding the penetration depth and lateral diffusion of ALA were derived from the combination of the two techniques (fractional CO_2 laser combined with high pressure transdermal acoustic waves).

Drug delivery of diclofenac assisted by ablative fractional laser

In 2011, Bachhav et al. evaluated the use of 2,940nm Er:YAG laser applied on pig skin followed by the application of diclofenac in gel and in aqueous solution.[20] Both the aqueous and the gel forms of diclofenac had their delivery enhanced by 13 times with the use of laser. Furthermore, the laser's fluence influenced permeation, but not the deposition diclofenac in the skin.

Drug delivery of lidocaine assisted by ablative fractional laser

In 2010, Bachhav et al. evaluated the application of 2,940nm Er:YAG laser on pig and human skins for the delivery of lidocaine. The delivery of the drug was dependent on the number of pores, but was not influenced by the depth of these pores.[11]

Drug delivery of corticoids assisted by ablative fractional laser

In 2015, Li et al. deemed as symmetrical and stable the effect of CO2 laser as a promoter of drug delivery for topical corticosteroids aimed at treating vitiligo in the body's extremities. Twenty-five patients underwent a split-body treatment. In on side of the body, the lesions received the laser application followed by betamethasone solution and narrowband UVB phototherapy. The other side received laser followed by phototherapy (control). The side treated with betamethasone solution immediately after the laser procedure had higher re-pigmentation as compared to the control side, with proportions of 40% (*versus* 8%) for patients with re-pigmentation greater than 50% ($p < 0.05$).[21] Adverse effects were mild, and included edema, er-

ythema and burning sensation, being were well tolerated. None of the patients experienced worsening of the vitiligo, Koebner phenomenon or local infection.

The drug delivery of 0.05% clobetasol propionate cream immediately after the application of ablative fractional CO_2 laser associated with narrowband UVB phototherapy was also evaluated for the treatment of vitiligo in 26 patients.[22] The average improvement scores were significantly higher than when there was association of the phototherapy with drug delivery of clobetasol. No significant adverse effects, such as the Koebner phenomenon, cutaneous atrophy, telangiectasias or hypertrophic scars, were reported.

Figure 1 shows the outcomes obtained by the authors in the treatment of a patient with vitiligo. Three ablative fractional CO_2 laser sessions were carried out, followed by drug delivery of desonide.

In 2013, Waibel et al. treated 15 patients with hypertrophic scars in a case series.[23] Three to 5 sessions of ablative fractional CO_2 laser were performed in intervals of 2 to 3 months between the procedures. Drug delivery containing 10-20mg/ml triamcinolone acetonide was applied immediately after the laser. After six months assessing the overall improvement parameters, the improvement in the parameters *scars*, *atrophy*, *dischromia* and *contour* was 2.73, according to the Manchester modified scoring system, where the maximum score is 3. The parameter *texture* showed the best results, while the *dischromia* parameter obtained the lowest improvement scores.

Cavalié et al. assessed the drug delivery of betamethasone following the application of 2,940nm Er:YAG laser for treating 70 keloids, observing a mean improvement of 50% in the lesions, with a recurrence rate of 22% in 8 months.[24]

There is a case report of a dermatofibroma treated with fractional CO_2 laser and drug delivery of 0.05% fluocinolone ointment with good outcome.[25]

Figure 2 illustrates the treatment of keloids with ablative fractional 2,940nm Er:YAG laser associated with drug delivery of triamcinolone with good results after only one treatment session.

Drug delivery of tranexamic acid assisted by ablative fractional laser

An *in vitro* study in pig skin evaluated the delivery of tranexamic acid after pretreatment with fractional or conventional CO_2 laser. The fractional variant was as effective as the traditional in delivering the drug, however it inflicted less damage to the epidermis.[26]

Drug delivery of methotrexate assisted by ablative fractional laser

In 2008, Lee et al. carried out an *in vitro* evaluation of the methotrexate's permeation assisted by either 2,940nm Er:YAG laser or electroporation in rodents' healthy skin (nude mouse), observing that the use of laser led to increased absorption of the drug by 3 to 80 times, the according to used fluence.[27] A later study – *in vitro*, in pig skin – demonstrated that 2,940nm Er:YAG laser treatment for delivering methotrexate depended upon the MTZ's depth: the absorption of the drug increased by 6, 9 and 11 times when the MTZ reached the epidermis, the superficial dermis and the medium dermis, respectively.[28]

Drug delivery of vitamin C assisted by ablative fractional laser

In vitro studies have evaluated the uses of 10,600nm CO_2 and 2,940nm Er:YAG lasers in the pretreatment of the skin, with different formulations containing vitamin C. Increases of up to 277 times were evidenced in the skin's permeation as compared to the to untreated skin.[29]

Hsiao et al. evaluated the permeation of ascorbic acid after the application of ablative fractional or conventional CO_2 laser, observing similar results irrespective of the laser used.[29] In 2013, a similar study was conducted by Huang et al., with three different forms of stabilized vitamin C.[30]

In 2016, in a split-face study co-authored by one of the present article's authors, Waibel et al., evaluated the use of CO_2 laser in the drug delivery of a non-sterile formulation containing vitamin 15% vitamin C, 1% vitamin E and 0.5% ferulic acid in serum vehicle, demonstrating acceleration in the healing of the hemiface that received the formula, despite the fact that this outcome was not statistically significantly different.[5] The molecular analysis of biopsy specimens harvested five days after the treatment showed the presence of increased fibroblast growth factor – which stimulates tissue repair – in the hemiface that underwent the drug delivery method. There were no descriptions of irritative effects resulting from the applied formulation.

Figure 3 shows the results obtained by the authors of the

Figure 1: Vitiligo treated with fractional CO_2 laser followed by the application of desonide: before (left) and after three sessions (right), excellent response.
Source: Authors' collection

present article in the rejuvenation treatment of a patient with one ablative fractional CO_2 laser session followed by *drug delivery* with vitamin C.

Drug delivery of 5-fluorouracil (5-FU) assisted by ablative fractional laser

Nguyen et al. evaluated the use of ablative fractional CO_2 laser associated with the drug delivery of 5% 5-fluorouracil (5-FU) under occlusion for the *in situ* treatment of in 30 lesions of superficial basal cell carcinoma and squamous cell carcinoma in the trunk and extremities. Five-fluorouracil was administered daily during the first seven days after the treatment, under occlusion. Biopsies of the treated area harvested from 4 to 8 weeks after the treatment confirmed histologic healing in 87% of the treated lesions. Adverse effects were mild and included erythema and erosion, with absence of local infections.[31]

The use of drug delivery in 5% 5-FU was also evaluated in the treatment of non-segmental vitiligo pretreated with ablative fractional 2,940nm Er:YAG laser, and post-treated (subsequently to the application of 5-FU) with narrow band UVB phototherapy, in a prospective right/left comparative study.[32] The association of laser assisted drug delivery with phototherapy resulted in repigmentation in 78% of the patients (*versus* 23.4% in the group that received only phototherapy).

Drug delivery of imiquimod assisted by ablative fractional laser

Lee et al. performed an *in vitro* study with 2,940nm Er:YAG and drug delivery of imiquimod, where there was an increase in the skin's permeability of imiquimod after pretreatment with laser, dependent upon the fluence and of number of passes in the treated area.[33]

Drug delivery of ingenol mebutate assisted by ablative fractional laser

According to an *in vitro* study, pretreatment of the skin with 2,940nm Er:YAG laser increased dermal permeation of ingenol mebutate. This penetration was influenced by the density set on the laser device, but not by the MTZ's depth.[34] Braun et al.

Figure 2: Keloid treated with one session of 2,940nm Er:YAG followed by the application of triamcinolone: before (left) and after (right), satisfactory outcomes.

Source: Authors' collection

Figure 3: Patient treated for facial rejuvenation with fractional CO2 laser followed by the drug delivery of vitamin C: before (left) and after (right), excellent results.

Source: Authors' collection

evaluated this finding in a case report based on a split-face study of field cancerization treatment. After pretreatment with 2,940nm Er:YAG, 0.015% ingenol mebutate was applied and maintained for three consecutive days. Despite the fact that both sides of the face showed an expected inflammatory reaction to the product, it was more intense on the side pretreated with laser.[35]

Drug delivery of tretinoin assisted by ablative fractional laser

An *in vitro* study evaluating the drug delivery of tretinoin evidenced that there was increased permeation after the application of ablative fractional laser. In addition, it demonstrated that this permeation was dependent upon the laser's fluence and density.[36]

Drug delivery of topical antifungals assisted by ablative fractional laser

Studies described the treatment of onychomycosis with an association of ablative fractional lasers and topical antifungals, such as terbinafine and amorolfine cream. The MTZs allowed the conformation of channels on the nail that removed the ungual tissue containing fungi and promote the drug delivery of products applied on the nail plate.[37-39]

A study by Yang et al. evaluating the use of ablative fractional laser for drug delivery on the nail plate employed optical coherence tomography aimed at identifying the optimal parameters in order not to damage the tissues located beneath the nail plate. They concluded that the use of tomography is effective in performing this analysis and ensures the procedure's safety.[40]

Drug delivery of polylactic acid assisted by ablative fractional lasers

Rkein et al. assessed the topical application of poly-L-lactic acid after fractional CO_2 laser for the treatment of atrophic scars in 10 patients.[41] Three months after, 95% of the scars received a improvement score of 2.18, on a scale ranging from 0 to 3.

Drug delivery of botulinum toxin assisted by ablative fractional laser

In 2015, Mahmoud et al. described the use of fractional CO2 laser followed by the application of topical botulinum toxin (drug delivery) in the periorbital area in a *split-face* study in 10 patients. The 30-day follow up evidenced significant improvement on the side associated with botulinum toxin ($p = 0.027$).[42] Similar results were reported by Zhu et al. in 2016, when the topical application of botulinum toxin (drug delivery) was compared to the application of saline solution, both after pretreatment with fractional CO_2 laser, in randomly chosen facial areas.[43] Twelve weeks after, the combined treatment received an improvement score of 2.70 in wrinkles, hydration and elasticity, on a scale ranging from 0 to 3 ($p \leq 0.05$).

Drug delivery of platelet-rich plasma (PRP) and adipose tissue stem cells assisted by ablative fractional laser

In a 2016 split-face study, Zhou et al. compared the effect of the application of stem cells from adipose tissue following pretreatment with ablative fractional CO_2 laser, to the isolated application of laser. The combined treatment increased the patient's satisfaction, improved the elasticity and hydration, and reduced the transepidermal water loss, rhytids and melanin index. These results were observed both in the group treated for rejuvenation and in the group treated for acne scars.[44]

An assessment of the use of PRP in drug delivery after ablative fractional laser was performed in 2012 by Shin et al. Platelet rich plasma combined with laser increased the elasticity and decreased the erythema index. Increased thickness of the dermal-epidermal junction, collagen content and number of fibroblasts were also observed.[45]

Drug delivery of minoxidil and diphencyprone assisted by ablative fractional laser

Ablative fractional Er:YAG laser was used to accelerate the topical permeation of minoxidil, diphencyprone and peptides in rat and pig skins. There was increased permeation of all active principles, including into hair follicles. Drug delivery was evidenced by micrography in the hair follicles and intercellular space.[46]

Drug delivery of growth factors assisted by ablative fractional laser

Figure 4 shows the outcome obtained by the authors of the present paper in the treatment of a patient bearing a single plaque of alopecia areata treated with 2,940nm Er:YAG lasr, followed by the application of a formula containing growth factors.

Other uses

Other uses of ablative lasers for drug delivery include the delivery of antibodies, vaccines, oligonucleotides and analgesics.

Ideal requirements for drug delivery formulations assisted by ablative fractional lasers.[7]

- Low viscosity vehicles are superior to emulsions, gels, or serums.

- The presence of cosolvents in the formulation promotes lateral diffusion (adjacent to MTZs) and increases deposition of the drug.

- Occlusion (which can be one of the vehicle's characteristics) increases the drug delivery effect.

- The permeation of hydrophilic active principles is facilitated by ablative fractional laser. The same is valid for active principles contained in nanocapsules, or those that are liposomed or vectorized.

- Avoid the use of propylene glycol and alcohol in the formulations, for they reduce the active principles' penetration.

- Permeation of active principles occurs continuously up until the skin's barrier function is completely restored, even though it decreases over this process of recovery. For this reason, the patient can use the drug delivery formulation for 2 or 3 days after the procedure.

- Vehicles of anhydrous nature or mineral origin that do not contain preservatives and dyes, reduce the risk of allergic reactions and do not generate discomfort (burning sensation)

during the immediate post-procedure application.

EVIDENCE FROM STUDIES ON DRUG DELIVERY ASSISTED BY NON-ABLATIVE LASER

Non-ablative laser promotes *drug delivery* via thermal effect – as in the cases of 1,064nm long-pulse Nd:YAG laser, non-ablative fractional Erbium laser, and intense pulsed light (IPL) – or via photomechanical waves due to the high magnitude of the transient pressure – as in the case of Q (quality)-switched lasers.[47] In 1998, Lee at al. demonstrated (in animal models) that even 40kDa macromolecules (dextran, for instance) could permeate into a cutaneous depth of 400μm, *in vivo.* Exposure of the skin to photomechanical waves leads to the expansion of the extracellular space up until the deeper layers of the stratum corneum, nevertheless the stratum granulosum remains unchanged. The addition of a cosolvent to the vehicle results in the large-scale expansion of the extracellular space, including intercellular ruptures in the stratum granulosum. The addition of a cosolvent to the vehicle used for drug delivery selectively acts on the lamellar lipids.[48]

Long-pulse lasers, non-ablative fractional Erbium laser and IPL increases the skin's temperature by up to 13°C, with transient disruption of keratin, making corneocytes to become brittle and exfoliative. In contrast, 532nm and 1,064nm Q-switched lasers completely rupture the keratin and corneocytes with minimal increases of temperature, generating micropores in the stratum corneum.[47] Q-switched lasers increase by 12 times the skin's permeability, which can remain at that level for up to one week, without risk of infection. In addition, it increases the permeation of hydrophilic molecules.[47] On the other hand, the order of magnitude of the increase in the skin's permeability promoted by long-pulse Nd:YAG laser, non-ablative fractional Erbium laser and IPL is roughly 6.8 times, which lasts for 15 to 30 minutes.[7]

Different sources of light were studied in diverse doses as drug delivery promoters. The results demonstrated that all methods used to increase permeation of glycerol – lasers, such as CO2, 532nm and 1,064nm Nd:YAG; and 400-700nmn and 560-950nm IPL – significantly increased the transdermal delivery of the studied active principle as compared to the control group.[49] The increase in transepidermal water loss (TEWL) after the treatment with non-ablative fractional laser demonstrates that the use of this type of device induced an increase in the skin's permeability. [50]

Non-ablative fractional laser promotes dermal heating in a columns layout similar to the MTZs, however without causing significant damage to the overlying epidermis, being therefore associated with less discomfort and shorter recovery time than that of ablative fractional laser.[51,52]

Drug delivery of aminolevulinic acid (ALA) and methyl-aminolevulinic acid (MAL) assisted by non-ablative laser

Lim et al. evaluated 10 patients pretreated with non-ablative fractional 1,550nm Er:glass laser followed by PDT with ALA, left to incubate for 30, 60 or 180 minutes under occlusion. Each patient was treated in 12 areas in his or her dorsum. The study's results demonstrated increased penetration of ALA in the areas laser pretreated with laser. In addition, viewed under fluorescence, ALA absorption was proportional to the incubation's duration.[51] In 2016, Lee et al. showed an increase of up to 1,200 times in the skin's permeability to ALA after pretreatment non-ablative fractional 1,550nm Er:Glass laser, as compared with the untouched skin.[50]

Drug delivery of topical antifungals assisted by non-ablative lasers

Kim et al. assessed the efficacy of 1,064nm Nd:YAG in the treatment of onychomycosis dividing the patients into 3 groups: Group 1 (treated only with laser); Group 2 (treated with laser and topical antifungal); Group 3 (treated only with antifun-

Figure 4: Single plaque of alopecia areata treated with 2,940nm Er:YAG followed by the application of formulation containing growth factors: before (left) and after (right), with regrowth of the hair in the affected area.

Source: Authors' collection

gal). Laser was performed monthly, in a total of 3 or 4 sessions. Clinical and mycological outcomes demonstrated superiority of results in the laser treatment, isolated or combined with topical treatment, as compared to the treatment with topical antifungals. Furthermore, the addition of topical antifungal seemed to be capable of preventing reinfection in patients who received the combination treatment.[53]

Drug delivery of tretinoin assisted by non-ablative lasers

In 2016, Lee et al. evaluated *in vitro* the permeation of tretinoin into the skin pretreated with non-ablative fractional 1,550nm Er:glass laser. They observed a two-fold increase in the permeation of the active principle as compared with the untouched skin.[50]

Drug delivery of 5-fluorouracil (5-FU) assisted by Q-switched laser

The use of 1,064nm Q-switched Nd:YAG laser for drug delivery of 5-FU was effective in promote the permeation of the active principle in a study with animals.[54]

Drug delivery of vitamin C assisted by Q-switched laser

Zhou et al. evaluated the use of 694nm Q-switched ruby laser associated with sonophoresis and drug delivery of vitamin C lotion, for the treatment of melasma in 26 patients. They observed an initial reduction of 35% in the MASI Index (Melasma Area and Severity Index) after 3 months of follow up.[55] In 2013, Lee at al. also evaluated the use 20% vitamin C with ultrasound after pretreatment with Q-switched laser. The results showed a significant improvement in the hemiface where the drug delivery was performed, according to the visual analog scale for the treatment of melasma.[56]

Drug delivery of cosmeceuticals assisted by Q-switched lasers (laser toning)

Kalil et al. reported improvement of acne, spots, pores, texture and UV index using a formula containing Hyaxel®, Hidroxiprolisilane®, DMAE Pidolato®, Nano Vit C® and Matrixyl 3000® as compared to a placebo group.[57]

Drug delivery of cosmeceuticals assisted by non-ablative laser

The authors of the present paper experienced excellent outcomes using non-ablative fractional 1,340nm Er:YAG laser associated with drug delivery containing growth factors (IGF – insulin growth factor, and EGF – epidermal growth factor) for the treatment of perioral scarring (Figure 5).

Drug delivery of minoxidil assisted by non-ablative laser

The authors of the present paper experienced excellent outcomes using non-ablative fractional 1,340nm Er:YAG laser associated with drug delivery of minoxidil for the treatment of androgenetic alopecia (Figure 6).

Ideal requirements for drug delivery formulations assisted by Q-switched lasers. 7, 48

- Vehicles with low viscosity and of hydrophilic nature are better than emulsions, gels, or serums.

- The presence of co-solvents in the formulation promotes the extracellular space dilation by increasing the diffusion of active principles throughout the skin. It also increases the skin barrier's restoration time.

- Hydrophilic active principles have their permeation facilitated by Q-switched lasers.

- The use of propylene glycol and alcohol in the formulations should be avoided for they reduce the active principle's penetration.

- The active principles' permeation is increased by at least 12 times, and this effect lasts for up to 1 week. In this manner, the drug delivery formulation can be used by the patient throughout this period.

Ideal requirements for drug delivery formulations assisted by non-ablative fractional lasers and IPL. 7, 49

- Low viscosity vehicles are better than emulsions, gels, or serums.

- The presence of co-solvents in the formulation promotes greater transient disruption of keratin and increases intercellular spaces.

- Lipophilic active principles have their permeation facilitated by long-pulse Nd:YAG laser, non-ablative fractional Erbium laser and IPL.

- The use of propylene glycol and alcohol in the formulations should be avoided for they reduce the active principle's penetration.

- The active principles' permeation is increased by at least 6.8 times, nevertheless this effect is ephemeral and lasts for roughly a 15 to 30 minutes, entailing that the drug delivery should be performed immediately after the procedure.

ADVERSE EFFECTS RELATED TO DRUG DELIVERY PROCESSES

To date, there has been absence of descriptions of infections secondary to drug delivery procedure performed with lasers.

Soltani-Arabshahi et al. described two cases of foreign body reaction after microneedling and drug delivery with a commercial product for use at home containing vitamin C (Vita C Serum, Sanitas Skincare, PAÍS), confirmed by biopsy and with negative cultures for the biopsied sample.[58] Another study described foreign body reactions after electroporation.[59] Although the reports did not describe the use of lasers, attention should be given to the formula employed for drug delivery; some ready-made formulas for daily use at home contain preservatives and dyes, which may be related to the observed adverse effects.

In a 2016 study, Lee et al. evaluated the risk of permeation of the bacteria *Staphylococcus aureus* and *Pseudomonas aeruginosa* after treatment of the skin with non-ablative fractional 1,550nm Er:glass laser observing absence of increase in the risk of bacterial infection after the laser application , as compared to the untouched skin.[50]

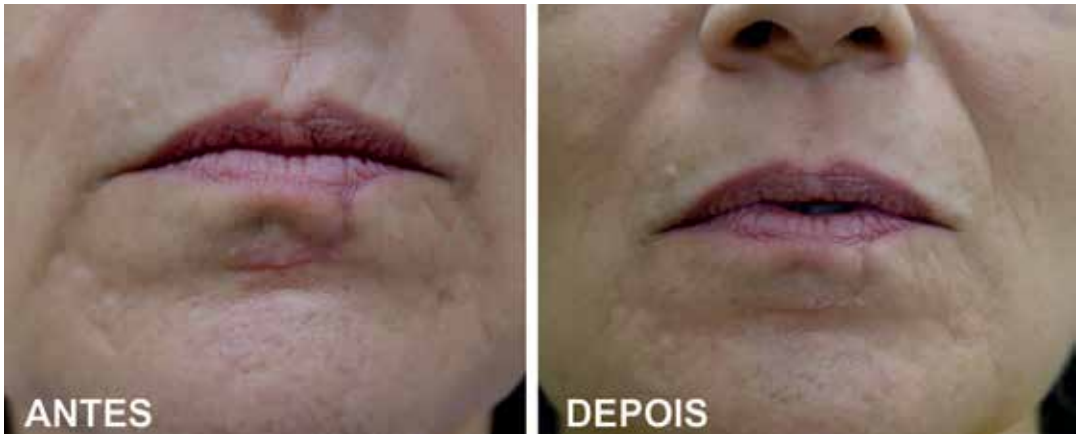

Figure 5: Perioral scar treated with 6 sessions of 1,340nm Er:YAG and drug delivery of growth factors: before (left) and after (right), excellent response.
Source: Authors' collection

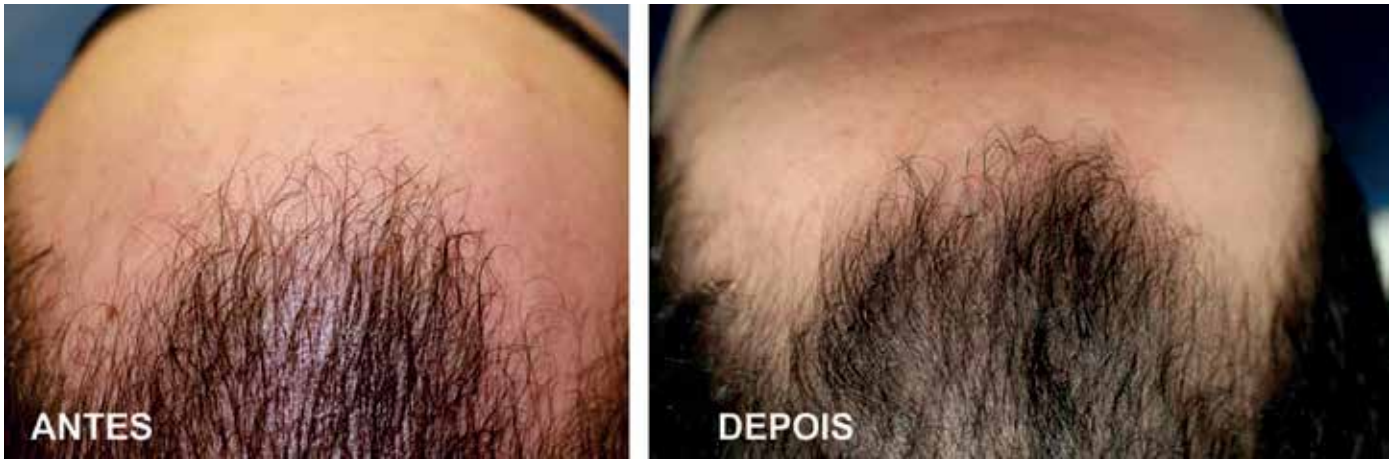

Figure 6: Androgenic alopecia treated with 6 sessions of 1,340nm Er:YAG laser with drug delivery of minoxidil: before (left) and after (right), good response.
Source: Authors' collection

CONCLUSION

The use of lasers for promoting drug delivery is promising, however a greater number of controlled studies with longer follow-up periods are necessary in order to allow the evaluation some of the studied substances, which still do not have the adequate degree of evidence for indication. The standardization of the energy and density used in the laser applications, as well as the standardization of the concentration of each substance to be applied via drug delivery processes, call for a greater number of studies, since many articles discuss the use of lower concentrations of the active principles since there is increased permeability.[6,9] The use of lower concentrations of active principles increases the safety of the procedure and reduces the risk of side effects.

Notwithstanding, issues linked to the procedure's safety, such as the potential risk of adverse effects secondary to the systemic absorption of the drugs and the risk of infection and immune sensitization, require a greater number of studies aimed at clarifying whether the use of sterile formulas for drug delivery is necessary, although a 2016 study by Lee et al. has demonstrated that the use of non-sterile formulas with non-ablative fractional laser is safe.[50] Despite the fact that there are many topical formulations, it is necessary to determine which are appropriate or not for use in drug delivery.[6] The cost of the procedure represents a constraint for its implementation in the daily practice, and it is necessary to discuss the cost/benefit of the procedure with the patient.[9]

The knowledge currently available demonstrated that the substances studied for the combined use of lasers are safe in the promotion of drug delivery, provided that the procedures are performed in medical environment, according to appropriate pre-procedure antisepsis protocols. The technique is promising and promotes a new application for lasers, allowing to expand its use not only in rejuvenation treatments, but also in the treatment of dermatological diseases, reducing the toxicity of the active principle and the costs of more expensive drugs, and increasing the therapeutic response.

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Questions for Continued Medical Education - CME

1) Regarding the drug delivery technique, the below are all correct except for:

a) The stratum corneum is the major limiting factor for the delivery of drugs applied on the skin.
b) Hydrophilic molecules or those exceeding 500Da are capable of penetrating more easily the intact stratum corneum.
c) The penetration of drugs through the intact stratum corneum occurs by diffusion and, to a lesser extent, via the skin's appendages.
d) The penetration of drugs across the stratum corneum can be achieved via transcellular or intracellular route.
e) Only 1% to 5% of the concentration of active principles applied on the skin are absorbed, becoming bioavailable.

2. Regarding the use of lasers for promoting drug delivery, which of the below is correct?

a) Only ablative fractional lasers are capable of promoting drug delivery effectively.
b) The depth of the MTZs (thermal microzones) created does not interfere in the penetration of either hydrophilic or lipophilic active principles used for drug delivery.
c) Both ablative and non-ablative fractional lasers are capable of promoting drug delivery effectively.
d) Lasers can only promote drug delivery through photomechanical waves.
e) The use of lasers does not allow drug delivery in a uniform and controlled manner.

3. Regarding the characteristics of the products used for drug delivery assisted by lasers, which of the below is incorrect?

a) The cosolvents present in the formulation enhance the penetration of the active principles involved in the drug delivery process.
b) Preventing the proliferation of microorganisms in the formulations is desirable. In order to achieve that, anhydrous formulations are chosen for drug delivery.
c) More viscous vehicles allow better penetration of the active principles involved in the laser-assisted drug delivery process.
d) Occlusion increases the effectiveness of drug delivery.
e) The use of propylene glycol and alcohol should be avoided in the formulations, for they reduce the active principles' penetration.

4. Regarding ablative fractional laser-assisted drug delivery, read the statements below:

I - The energy used allows modulating the degree of ablation and the thickness of the coagulation column adjacent to the MTZs (thermal microzones).
II - If the coagulation column adjacent to the MTZ is too thick, it may hamper the diffusion of the active principles involved in the drug delivery process to the areas adjacent to the MTZs.
III - The use of excessively high energies leads to deeper lesions, which may reach blood vessels, entailing that the involved active principle may penetrate the circulatory system.
IV - The delivery of active principles based on ablative fractional laser-assisted drug delivery is dependent on the number of pores formed per area (density).

Which of the above is (are) correct?

a) Only I.
b) Only I and II.
c) Only II, III, IV.
d) Only III and IV.
e) All of them.

5. Regarding laser-assisted drug delivery, it is correct to state that:

a) Studies on photodynamic therapy using MAL (methyl-aminolevulinic acid) and ALA (aminolevulinic acid), indicate that these substances are the most studied – both in vitro and in vivo – for laser-assisted drug delivery.
b) Studies evaluating the use of vitamins C and E, and ferulic acid for drug delivery, demonstrated increased fibroblast growth factor, which stimulates neocollagenesis.
c) The treatment of onychomycosis was described as an association of ablative fractional lasers with topical antifungals, such as terbinafine and amorolfine cream, that has therapeutic success.
d) The permeation of the active principles occurs only on the day of the laser application.
e) Vehicles of anhydrous nature and mineral origin that do not contain preservatives and dyes reduce the risk of allergic reactions.

6. Research on photodynamic therapy using MAL and ALA in laser-assisted drug delivery describe treatments for all conditions below, except for:

a) Actinic keratosis.
b) Basal cell carcinoma.
c) Bowen's disease.
d) Onychomycosis.
e) Psoriasis.

7. Regarding the adverse effects linked to the drug delivery techniques, it is correct to state that:

a) Two cases of foreign body reaction after laser-assisted drug delivery were described with the use of a formulation containing vitamin C to be used at home.
b) The studies describing foreign body reaction linked to drug delivery occurred when it was assisted by microneedling and electroporation.
c) The use of ready made formulas indicated for daily use at home that contain preservatives and dyes is recommended for drug delivery, for they may be related to the onset of adverse effects.
d) A study evaluating the risk of permeation of bacteria following the treatment of the skin with non-ablative fractional laser observed that there was indeed increased risk of bacterial infection after the laser application.
e) Infections secondary to laser-assisted drug delivery have been reported in in vivo studies.

8. Regarding non-ablative laser-assisted drug delivery, which of the statements below are (is) correct?

I - Non-ablative lasers promote drug delivery through thermal effect or photomechanical waves.
II - The exposure of the skin to photomechanical waves leads to the expansion of the stratum corneum's extracellular space, however the stratum granulosum remains unchanged.
III - The addition of a cosolvent to the drug delivery's vehicle dilates the extracellular space and causes intercellular ruptures in the stratum granulosum.

a) Only I.
b) Only II.
c) Only II and III.
d) Only I and III.
e) All of them.

9. What type of light/laser increases the permeation of hydrophilic active principles?

a) Intense Pulsed Light.
b) 1,340nm Er:YAG.
c) 1,550nm Er:glass.
d) 2,940nm Er:YAG.
e) Long-pulse Nd:YAG laser.

10. What is the advantage of using nanoencapsulated active principles in laser-assisted drug delivery?

a) Their permeation does not depend on the used laser's type and parameters.
b) They minimize the risk of allergic reactions.
c) They do not cause post-procedural burning sensation.
d) They decrease the transepidermal water loss and increase the skin's hydration.
e) They protect the devices' tips.

Key

Use of bleomycin in keloids and hypertrophic scars: a literature review. 2016;8(2):97-102.

1D, 2E, 3B, 4E, 56, 6C, 7E, 8E, 9C, 10E

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Referências bibliográficas: 1. Ferreira CM, et al. Cicatrizes hipertróficas e queloides. Rev Soc Bras Cir Plást. 2006;21(1):40-8. **2.** Data on file. Avaliação da segurança e eficácia clínica do uso imediato e prolongado do gel de silicone C-kaderm na cicatrização cutânea. 2014. **3.** Newman JP, et al. Review of closed dressings after laser resurfacing. Dermatol Surg. 2000;26(6):562-71.

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Original Articles

Treatment of the orbicularis oculi muscle's lower portion with microdoses of botulinum toxin: a 300 cases series

Tratamento da porção inferior do músculo orbicular dos olhos com microdoses de toxina botulínica: série de 300 casos

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ABSTRACT

Introduction: The use of botulinum toxin in the periorbital muscles is aimed at reducing expression lines in that site, correcting the eyebrows' height and treating blepharospasm. However, the application of botulinum toxin in this area can lead to undesirable side effects, such as ptosis, edema in the lower eyelids, artificial appearance of the demarcation area between the orbicularis muscle's treated area and the malar region, ectropion and hematomas.

Objective: To treat the dynamic wrinkles in the lower portion of the orbicularis oculi muscle through injections of microdoses of botulinum toxin.

Methods: A prospective monocentric study with the analytical longitudinal observation of 300 patients undergoing treatment with botulinum toxin microdoses in the lower eyelids' rhytids was carried out. Sociodemographic data, patient satisfaction, dose quantification and complications were analyzed.

Results: Sixty-six percent of the patients showed a total improvement of the wrinkles after the first session. The other required an additional session. Eighty-six percent preferred the treatment with this therapeutic modality.

Conclusions: Despite the great benefit offered by the classic injection points for the treatment of periorbital rhytids types I to III, the authors observed the need to treat rhytids type B (presence of wrinkles on the lower eyelid). Due to the high rate of complications in this region, microdoses of botulinum toxin were proven to be effective and safe.

Keywords: *botulinum toxins, type A; esthetics; dermatology*

RESUMO

Introdução: *A aplicação da toxina botulínica nos músculos periorbitais é utilizada para reduzir linhas de expressão na região, corrigir a altura das sobrancelhas e tratar o blefaroespasmo. Essa área de aplicação pode gerar efeitos colaterais indesejáveis como ptose palpebral, edema das pálpebras inferiores, linha de demarcação com aspecto artificial entre a área tratada do músculo orbicular e a região malar, ectrópio e hematomas.*

Objetivo: *Tratamento de rugas dinâmicas da porção inferior do músculo orbicular dos olhos por meio de injeções de microdoses de toxina botulínica.*

Métodos: *Estudo prospectivo e unicêntrico de observação longitudinal analítica de 300 pacientes submetidos ao tratamento com microdoses de toxina botulínica das rítides de pálpebras inferiores. Foram analisados dados sociodemográficos, nível de satisfação, quantificação de dose e complicações.*

Resultados: *66% dos pacientes apresentaram melhora total das rugas após a primeira sessão. Os demais necessitaram de mais uma sessão. 86% preferiram o tratamento com essa modalidade terapêutica.*

Conclusões: *Mesmo com o grande benefício trazido pelos pontos clássicos para o tratamento das rítides periorbitais do Tipo I a III, verificamos a necessidade do tratamento das rítides do tipo B (presença de rugas na pálpebra inferior). Devido ao grande índice de complicações na região, microdoses de toxina botulínica mostraram-se eficazes e seguras.*

Palavras-chave: *toxinas botulínicas tipo A; estética; dermatologia*

INTRODUCTION

Botulinum toxin (BT) is a neurotoxin produced by *Clostridium botulinum* bacteria, usually found in plants, soil, and water, and in the intestinal tract of animals.[1] This toxin is used to treat expression lines, and spasticity, strabismus, nystagmus and blepharospasm disorders.[1,2]

Botulinum toxin interferes with neural transmission, blocking the release of extracellular acetylcholine, which is the main neuromuscular junction's neurotransmitter, stimulating muscle contraction.[1,3,4]

Botulinum toxin Type A is the most powerful and the first BT type to be made available and used in the United States for clinical purposes. It is deemed the most powerful biological toxin to human beings.[2,5]

The application of BT in the periorbital muscles is used to reduce fine lines in that region, correct the height of the eyebrows and treat blepharospasm.[4] This application area can develop undesirable side effects, such as ptosis, edema of the lower eyelids, artificial demarcation line between the treated area of the orbicularis muscle and the malar region, xerophthalmia, ectropion, strabismus and hematoma.[4]

The present study was aimed at demonstrating the treatment of the lower portion of the orbicularis oculi muscle with microdoses of BT.

METHODS

A prospective, monocentric, longitudinal analytical observational study was carried out with 300 patients who underwent treatment with microdoses of botulinum toxin (Onabotulinumtoxina A - BoNT/A, Botox®, Allergan Inc., USA) in the periorbital rhytids located in lower third of the orbicular muscle of the eyes (i.e. below the zygomatic arch) at a private practice. The patients treated during this period underwent standardized digital photographs and were followed up using the private practice's proprietary medical records system.

A) Patient selection - Inclusion criteria

The patients selected for the study should mandatorily have periorbital dynamic wrinkles as their main complaint. Cases where there was presence of rhytids located in the lower third of the orbicularis oculi muscle were included.

All patients in the study should already have undergone the treatment of the periorbital dynamic rhytids with conventional application of BT, for more than six months. This criterion was important to allow the comparison of the degree of patient satisfaction between the two treatment methods (conventional x microdoses). Patients who had never undergone previous treatment in the area with BT were not included in the study.

B) Exclusion criteria

Patients with contraindication for the use of BT – such as the presence of neuromuscular diseases, including myasthenia gravis, active autoimmune conditions, pregnancy, breastfeeding, allergic reaction to the product and local infection were excluded from the study.

In addition, patients who had never undergone treatment with BT, or had been treated with BT less than six months before or who had already undergone treatment in the studied region with BT microdoses, were not selected. This exclusion criterion was important in allowing the comparison of the degree of patient satisfaction between the two methods.

c) Dilution technique

Dilution of BT for microdosing starts with the dilution of one 100 IU botulinum toxin vial (Botox®) into 2ml 0.9% saline. Two IU (0,04ml) are removed from this solution, and 10 IU (0,40ml) 0.9% saline are added, in BD Ultra Fine II® short 1ml syringe and 8mm needle, reaching a total volume of 0,48ml (12 IU). This is the final dilution, with each 0,04ml being considered one unit, which can be termed a BT *microdose unit* (BTMDUn).

Studied body site

The lower third of the orbicularis oculi muscle region was defined as the region below an imaginary line originating in the lateral canthus (Figure 1). The region above this line and the remaining of the upper third of the face were treated with classic injection points.

The following classification of periorbital wrinkles,[6] was used for the study:

TYPE I - wrinkles located laterally to the outer corner of the eye (lateral canthus), extending from the eyebrow up until the zygomatic arch.

TYPE II - wrinkles located laterally to the outer corner of the eye (lateral canthus), extending from the outer corner of the eye's line up until the zygomatic arch (absence of wrinkles in the upper lateral region).

TYPE III - wrinkles present only on the lateral canthus' line.

These three types of wrinkles can arise with:

A - absence of wrinkles on the lower eyelid;

B – presence of wrinkles on the lower eyelid, according to the following sub-classification (Figure 1):

B1 - lateral wrinkles,

B2 - medial wrinkles,

B3 - wrinkles in the medial canthus.

All patients selected for the study had been classified as "B" according to the above classification, with the wrinkles being sub-classified for the calculation of the number of BTMDUns needed for treating the region.

Application method and chosen dose

The number of micro doses used in each patient was computed according to the region's muscular strength and the formation of dynamic rhytids. After the patients were classified into types (B1, B2, B3 and B1+B2+B3 – the last classification meaning patients who had rhytids in all locations), the extent of the area with dynamic rhytids (i.e. the area to be treated, which corresponded to the whole of the region that formed rhytids

resulting from movement) was determined. There were no anatomical restrictions for this study, therefore the initial points were the rhytids located closest to the orbital margin, with the inferior points respecting the last inferior rhytid. The points were marked every 0.5cm in parallel horizontal lines, marked in the craniocaudal direction.

The initial marking was of 6 to 24 points in the case of type B1 patients, 6 to 12 in the case of type B2, and 3 to 6 in type B3 (Figure 2). On the second visit (15 days after the initial application) if it was still possible to identify wrinkles in the region, additional BT micro doses were applied, according to the same pattern of distribution of points, as described above. One BTMDUn was applied in each point with a 1ml BD Ultra Fine II® short syringe and a 8mm needle. The application was carried out via intradermal route.

D) Statistical analysis

The included sociodemographic variables were *gender*, *age*, *ethnicity*, *periorbital rhytids classification*, *BT micro doses used in the initial and second applications*, *duration*, *patient satisfaction compared to the previous treatment* (B: better, S: similar, W: worse) and *complications*. The study complied with the ethical standards set out by the Helsinki declaration.

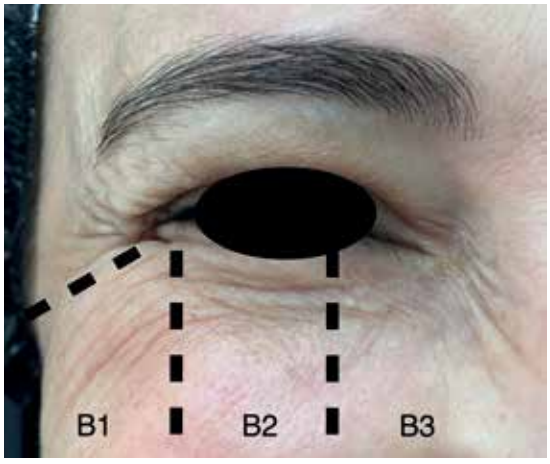


Figure 1: Classification of wrinkles in the lower eyelid - **B1:** lateral; **B2:** medial; **B3:** medial canthus

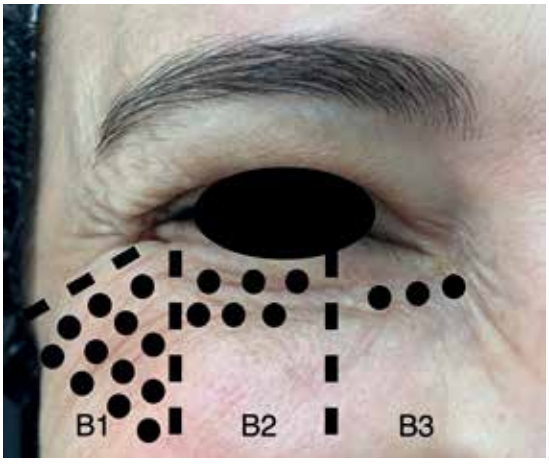


Figure 2: Marking of the points for the micro diluted toxin - "microbotox"

RESULTS

Three hundred patients were selected for the study (average age = 45, min =18, max = 72). Eighty-five percent of the study patients were female. Regarding ethnicity, 96% were Caucasian, 0.5% African-Brazilian, and 3.5% Asian. The distribution of the periorbital rhytids in the lower third of the orbicularis oculi muscle was as follows: 82% = B1, 10% = B1 + B2 + B3), 5% = B2 and 3% = B3.

The average number of BT MD used per session for each rhytid type (for the first and second sessions) is depicted in Table 1. Thirty-four percent of the patients required a second session. The average duration of the treatment was 125 days.

The level of patient satisfaction can be observed in Graph 1. The final outcome was recorded in digital photographs (Figure 3). Among the complications linked to the application of BT in the studied region, local pain and ecchymosis (14% and 4% of cases, respectively) were described.

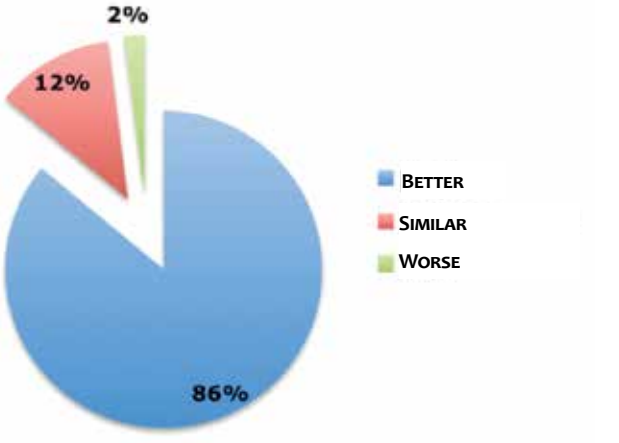
DISCUSSION

The study included 300 selected patients (youngest = 18 years old, oldest = 72 years old, average patient age = 45 years). Eighty-five percent of patients were female, 96% Caucasian, 0.5% African-Brazilian, and 3.5% Asian.

The predominance of female patients in the present study is explained by the women's greater interest for cosmet-

Table 1: Average BTMDUns used per session for each rhytid type

	Rhytid B1	Rhytid B2	Rhytid B3	Total (B1+B2+ B3)
1st Session	15	9	4	22
2nd Session	9	8	4	15



Graph 1: Patients' satisfaction level as compared to the previous treatment

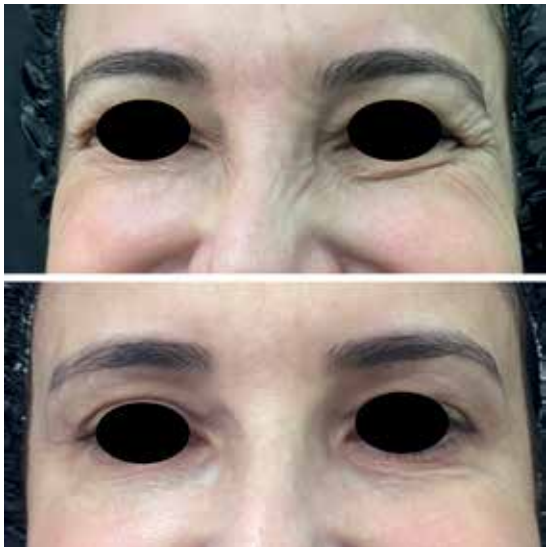


Figure 3: Digital photography for the comparison of outcomes - Above: before the treatment; Below: after the treatment

ic procedures, as compared to men. There are other studies in the literature demonstrating this predominance of female patients regarding similar procedures.[7,8] In Brazil, the Caucasian population has greater purchasing power on average, which can be correlated with the greater demand of these patients for the treatment of rhytids in the periorbital region.[7,8]

The classic points for BT injection are located in the orbicularis muscle's lateral portion, having been described by Carruthers in 1998, however these points become occasionally insufficient, triggering a search for better outcomes.[9] There are several published classifications for dynamic wrinkles in different facial regions, suggesting he presence of a constant search for improvement of results resulting from BT applications.[10-12]

The present study showed a high rate of efficacy based on the degree of patient satisfaction, with 86% of cases reporting better outcomes derived from the application of BT microdoses as compared to those achieved in previous treatments using only classic points. The analysis of complications indicated that 14% of cases had local pain while 4% had ecchymosis, converging with literature data.[11] The authors highlight that in none of the 300 cases there was demarcation of an aesthetically unacceptable line between the lower eyelid and the malar region.

In line with the values found in the literature, the average treatment duration was 125 days. In his work, Costa presented an average duration of 84.5 ± 38.8 days for patients who received Toxin 1 (Botox®) and 89.9 ± 41.1 days for patients who received Toxin 2 (Prosigne®, Cristália, SP, Brazil), with absence of statistically significant difference. For the researchers, those values were 76.8 ± 46.6 and 88.1 ± 43.6 days, for Toxin 1 and Toxin 2, respectively, also with no statistically significant difference between the groups.[13]

CONCLUSION

The lower third of the orbicularis oculi muscle is a delicate area for treatment with BT as there is potential for many undesirable side effects, such as palpebral edema, ectropion, xerophthalmia and, in special, the formation of a demarcation line with artificial aspect between the treated area of the orbicularis muscle and the malar region, with unsightly aesthetic outcome. Even with the great benefit lent by the classic points in the treatment of types I to III periorbital rhytids, the authors verified the need for the treatment of type B rhytids. Due to the high rate of complications intrinsic to the studied region, BT microdoses were effective and safe for the treatment of that body site.

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Original Articles

Reduction of body measures after a nine-session protocol with Low Level Laser Therapy

Redução de medidas corporais após nove sessões de tratamento com laser de baixa intensidade

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The present study was conducted at the Centro Brasileiro de Estudos em Dermatologia. - Porto Alegre (RS), Brazil.

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ABSTRACT

Introduction: Low level laser therapy has been considered a non-invasive treatment alternative to body remodeling and fat tissue reduction.
Objective: To evaluate the efficacy of low level laser therapy in reducing body circumference measures and subcutaneous adipose tissue of the abdomen and hips areas.
Methods: An open, prospective, monocentric study was performed including 25 women with localized fat on the hips and abdomen. Nine sessions of low level laser therapy were performed over 3 weeks. The participants were assessed at baseline and at 1, 4 and 12 weeks after treatment. Assessment of weight and body circumferences, lipid profile tests and MRI were performed.
Results: The abdominal circumference measurements showed a significant reduction up to 12 weeks after the treatment. Participants showed a more marked reduction in the hips region one week after the last session. Also one week after the completion of the treatment, 80% of the participants considered that the treatment improved their body contour. There was absence of reports of adverse events related to the treatment.
Conclusion: Low level laser therapy is safe and effective in reducing the circumference measurements, particularly in the abdominal region.
Keywords: low-level light therapy; subcutaneous fat; magnetic resonance imaging; laser therapy; abdominal subcutaneous fat

RESUMO

Introdução: *A terapia com laser de baixa intensidade tem sido considerada alternativa não invasiva para remodelamento corporal e redução do tecido subcutâneo.*
Objetivo: *Avaliar a eficácia do laser de baixa intensidade na redução de medidas corporais e do tecido adiposo subcutâneo da região do abdômen e do quadril.*
Métodos: *Estudo aberto, prospectivo, unicêntrico incluiu 25 mulheres com acúmulo de gordura localizada na região do quadril e abdômen. Nove sessões de low level laser therapy foram realizadas ao longo de três semanas. As participantes foram avaliadas no basal e em 1, 4 e 12 semanas após o tratamento. Aferição de peso e medidas de circunferência corporal, exames de perfil lipídico e de ressonância magnética foram realizados.*
Resultados: *As medidas de circunferência abdominal apresentaram redução significativa até 12 semanas após o tratamento. Na região do quadril, as participantes apresentaram redução mais marcante uma semana após a última sessão. Também uma semana após a finalização do tratamento, 80% das participantes consideraram que o tratamento melhorou o contorno do seu corpo. Nenhum evento adverso relacionado ao tratamento foi relatado.*
Conclusões: *O tratamento com a low level laser therapy é seguro e eficaz na redução das medidas de circunferência, principalmente na região abdominal.*
Palavras-chave: *terapia a laser de baixa intensidade; gordura subcutânea; imagem por ressonância magnética; terapia a laser; gordura subcutânea abdominal*

INTRODUCTION

The search for non-invasive cosmetic treatments for body remodeling has increased in recent years, due to the fact that these treatments are associated with low frequency of adverse events and complications. Many lasers have been used to treat localized fat and, more recently, low level laser therapy (LLLT) has been reported as an alternative to reduce the body's measures, by reducing the hip's, thigh's and waist's circumferences.

The mechanism of action of LLLT was the object of some studies, however it is deemed as controversial.[1] The main hypothesis is linked to the formation of pores in the plasma membrane of adipocytes previously irradiated with LLLT, as demonstrated by Neira *et al.* [2] in an *in vitro* study. Electron microscopy images showed particles of fat coming out of adipocytes, while cells in the interstitial space remained untouched.[2] Corroborating this hypothesis of Neira, the *in vitro* results obtained by Caruso-Davis *et al.* [3] showed that there is not lysis of adipocytes and that there is extravasation of whole triglycerides from the adipocytes' interior. Jankowski *et al.* [4] have questioned these hypotheses recently, suggesting an effect on lipid metabolism, possibly involving some autocrine systemic action.

Results obtained from different studies have reported LLLT's effectiveness in the reduction of body measures,[3,5-8] which supports the use of this technology as a non-invasive alternative to body remodeling and reduction of subcutaneous tissue. However, up until now few studies used objective methods for determining the subcutaneous tissue's thickness before and after treatment with LLLT[4,9,10] In addition to the effects in the body's circumference, authors suggest that LLLT is able to improve the lipid profile, reducing the levels of serum cholesterol.[11,12]

The objective of the present study was to evaluate the effectiveness of a 635nm LLLT device (Zerona®, Erchonia Medical Inc., Melbourne, USA) in the reduction of the body's measures and subcutaneous adipose tissue in the abdomen and hips of women. Moreover, the studied individual's lipid profile was also evaluated before and after treatment with LLLT.

METHODOLOGY

An open, prospective, single-center study was carried out at the Centro Brasileiro de Estudos em Dermatologia (*Brazilian Center for Research in Dermatology*), Porto Alegre (RS), Brazil, having been previously approved by the Research Ethics Committee of the Associação Hospitalar Moinhos de Vento. The main inclusion criteria were: female gender, aged between 18 and 60 years, body mass index (BMI) between 18.5 and 29.9kg /m^2, fat accumulation located in the hip region and abdomen, and availability to maintain stable weight throughout the study period with a maximum acceptable variation of ± 5% of the total body weight. The main exclusion criteria were: pregnancy, lactation or intention to become pregnant during the study period; to have undergone other treatments to reduce body measures in the 30 days preceding the study and during the study; tanned skin or intention to expose the studied body site to the sunlight, to undergo artificial tanning or use tanning creams and / or self-tanning products during the study; to begin intensive practice of sport during the study or to go through a major change regarding the practice of sports during the study, or in the three months prior to the start of the participation in the study.

The treatment was performed in the hip and abdomen region of all patients included in the study with the device Zerona® (Erchonia Medical Inc., Melbourne, USA). This device has been approved for cosmetic use in 2010 by the Food and Drug Administration (FDA) and in 2013 by the Agência Nacional de Vigilância Sanitária – ANVISA (the Brazilian *National Health Surveillance Agency*). It is composed of two fixed (central) heads and four movable (lateral) heads, each containing a source diode laser (Figure 1). The emitted wavelength is 635nm, with a potency of 17,5mW per head. The adopted protocol was three sessions per week for three weeks, totaling nine sessions. The protocol allowed the possibility of missing only one session. In each session, the patients received the laser application in the supine position for 20 minutes and in the prone position for 20 minutes. The fixed diode sources were positioned on the line of the umbilicus, while the mobile sources were positioned on the body's side: two in the flanks' region and two in the hip's region, with all being positioned parallel to the patients' body's surface.

Each participant attended four evaluation visits: a selection visit (baseline), and at 1, 4, and 12 weeks after treatment (W1, W4 and W12). In the selection visit, after obtaining the participant's consent, the researchers carried out a physical examination, including measurement of weight, clinical evaluation and checking of inclusion and exclusion criteria. The patients were then scheduled to undergo examination of lipid profile and MRI. Clinical evaluations with body circumference measurements were performed in all visits. Lipid profile tests were performed at baseline and at S1.

The MRI was performed at baseline and 12 weeks after treatment (W12).

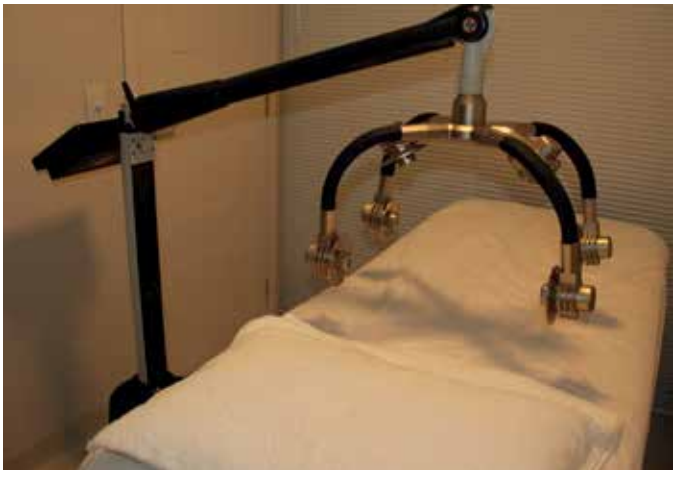


Figure 1: Low level laser Zerona® (Erchonia Medical Inc., Melbourne, USA)

Abdomen and hip circumferences measurement

Three circumference measurements were performed in the hip: one at the point of greatest circumference and the other two 10 and 15cm below the iliac crest. Two circumference measurements were performed in the abdomen: one at the point of greatest circumference and the other at the umbilicus' height. In order to standardize the measures at the points of greatest circumference, it was decided that the point's height to the ground should be measured and recorded in the medical records at baseline, and used as a parameter in the subsequent visits.

Adipose tissue's thickness

Ten of the 25 patients were invited to sequentially undergo the MRI, with five undergoing the scan in the abdominal region and the other five, in the hip region. The device 1.5 Tesla closed bore scanner (Magnetom Essenza, Siemens, Erlangen, Germany) was used to obtain the MRI images in T1. The measurement of the subcutaneous adipose tissue's thickness was performed on the images with the assistance of pre-defined anatomical markers. In the hip region, the anatomical point defined for the reproduction of images was the femur's head at its greatest circumference. In the abdomen, the chosen point was the umbilicus.

The thickness of the subcutaneous adipose tissue was measured on the right and left sides, in millimeters (mm), using the Syngo software (Siemens, Erlangen, Germany). An independent radiologist physician performed the evaluations before and after the treatment.

Statistical analysis

Demographic descriptive data for the population with intention to treat were analyzed.

The results obtained with the evaluations regarded the population from a protocol standpoint. The categorical variables were expressed as percentages, while the quantitative variables were expressed in mean ± standard deviation. The differences between cholesterol and triglyceride levels pre and post-treatment were tested with the t-test for paired samples, while the differences in body weight and corporal circumference measurements were tested with ANOVA for repeated measurements.

RESULTS

Having signed the Consent Term, 32 patients were evaluated, and 25 were included. Twenty patients completed the study, with 4 having dropped out due to lack of availability to attend all visits, and 1 participant was excluded for exceeding the limit of the allowed body weight variation (± 5%).

Demographic data of the included patients are described in Table 1. The patients' average age was 42 ± 10.4 years [variation: 22-59] while their BMI was 24.1 ± 2.5kg /m^2. Most of the patients had Fitzpatrick skin phototype III (60%) and reported the use of hormonal contraception (68%). On average, the weight of the patients who completed the study remained stable over the assessment timepoints, with a maximum variation of 0.4kg between the baseline and the last evaluation (p> 0.05).

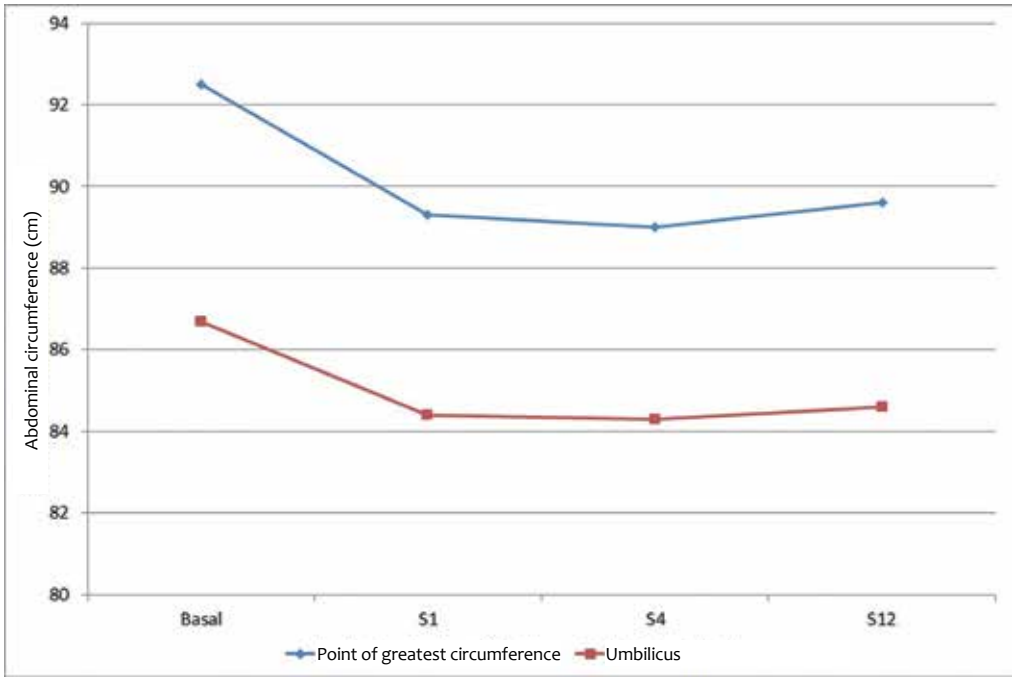
The abdominal circumference measurements at the greatest circumference and the umbilicus' height were significantly reduced in up to 12 weeks after the treatment (p = 0.001 and p <0.001, respectively), as shown in Graph 1. In addition to the statistical improvement, clinical and aesthetics improvement with visually perceptible reduction of measures, was observed in W12 as compared to the baseline (Figures 2 and 3). Nevertheless, analyzing the hip's measures, it was possible to observe a reduction trend in the body circumference at the points located at 10cm and 15cm below the iliac crest, only between the baseline and S1 (Figure 2). This reduction was not maintained throughout the study period.

The 4 patients whom had their hip regions evaluated by MRI and have completed the study showed a decrease in the subcutaneous adipose tissue's thickness in the point measured on the right side. On the left side, 2 patients showed a decrease in the subcutaneous adipose tissue's thickness and other 2 presented the same measurements pre- and post-treatment (Table 2). In

Table 1: Demographic data

	N = 25
Mean age (years; mean ± SD)	42 ± 10,4
BMI (kg/m²; mean ± SD)	24,1 ± 2,5
Fitzpatrick's phototype n (%)	
II	7 (28)
III	15 (60)
IV	3 (12)
Smoking n (%)	
Yes	1 (4)
No	24 (96)
Contraceptive method n (%)	
Hormonal	17 (68)
Vasectomized partner	1 (4)
Surgically sterile	2 (8)
Sexually inactive	1 (4)
Not applicable (menopause)	4
(16)	
Previous pregnancy n (%)	
0	12 (48)
1	3 (12)
2	4 (16)
3	4 (16)
4	2 (8)
Lipid profile (mg/dL)	
Total Cholesterol	196,6 ± 31,6
HDL Cholesterol	62,2 ± 16,1
LDL cholesterol	119 ± 28,6
Triglycerides	77,1 ± 38,3

***DP:** desvio-padrão; **IMC**: índice de massa corporal = **DP**: standard deviation; **BMI**: body mass index*



Graph 1: Abdominal circumference measurements (cm) throughout the study. Measurements of the abdominal circumference were taken in two points in all patients

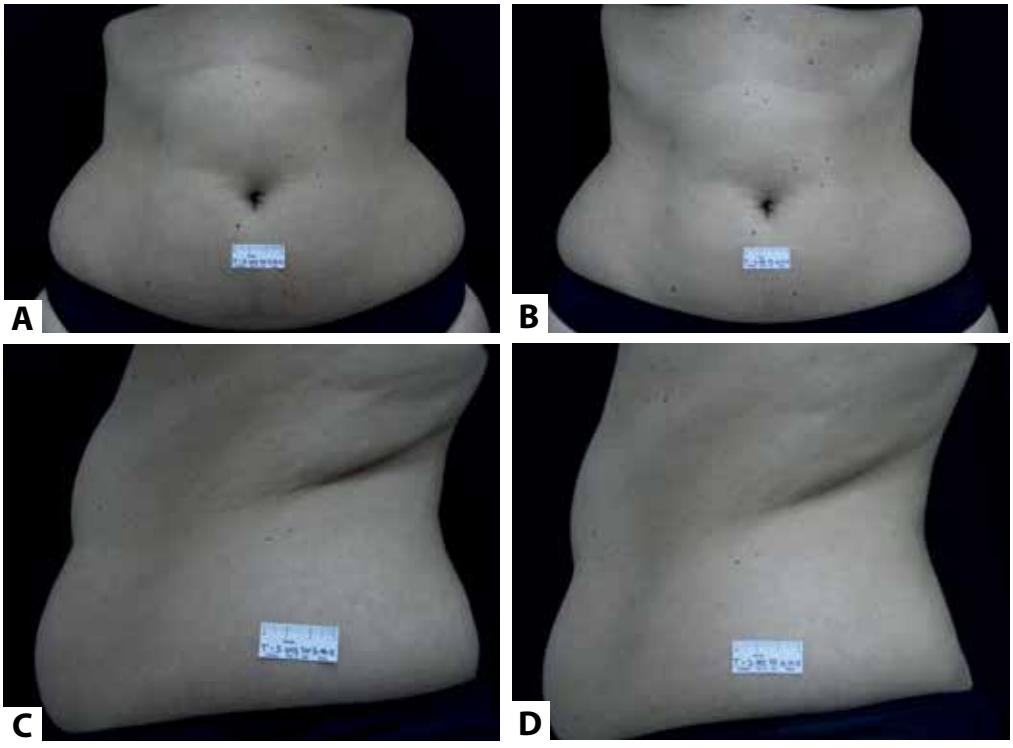


Figure 2: Abdominal region of 36 year-old patient before the treatment **(a, c)** and 12 weeks after end of treatment **(b, d)**. There is improvement in the body contour and reduction of measures. The patient's body weight remained stable throughout the study (BMIbaseline = 22.4 kg/m2, BMIS12 = 22.3 kg/m2)

the abdomen region, 3 of the 5 patients evaluated had a decrease in the thickness of the subcutaneous adipose tissue in both sides (Table 3). There was absence of reports of adverse events linked to the treatment by the patients, whose lipid profile did not significantly change after the treatment (Table 4).

A week after the completion of the treatment, 80% of the patients felt that it improved their body contour, 75% noticed reductions in their measures and would undergo the treatment again, and 65% said they were satisfied. Twelve weeks after the end of the treatment, 55% of the patients noticed improvement in their body contour, 50% observed a reduction in the measures and were satisfied with the treatment, and 75% would undergo it again.

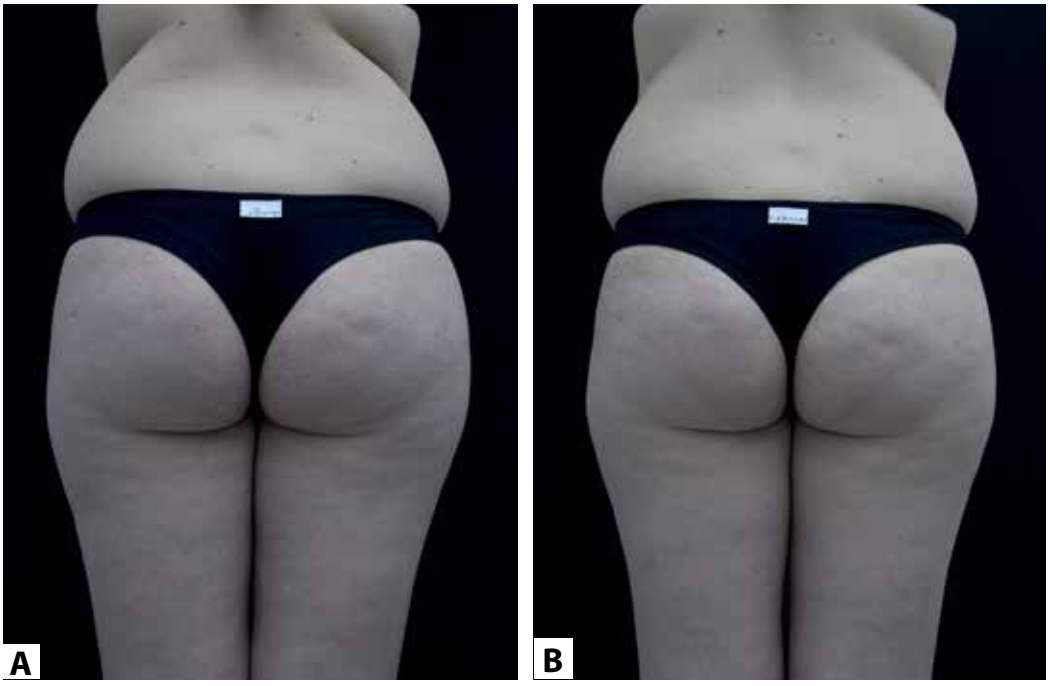
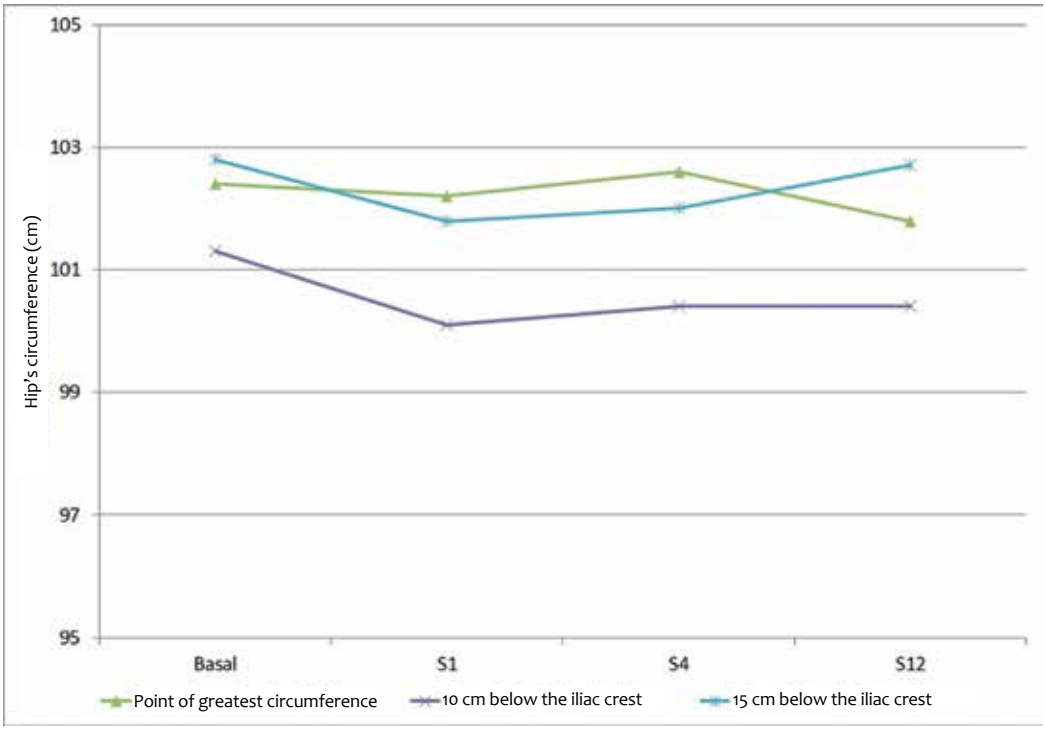


Figure 3: Dorsal view photographs of a 22 year-old patient before the treatment **(a)** and 12 weeks after completion of the treatment **(b).** There is improvement in the body contour and reduction measures. The patient's body weight remained stable throughout the study (BMIbaseline = 27.3 kg / m², BMIS12 = 26.9 kg / m²)



Graph 2: Measurements of the hip's circumference (cm) throughout the study. Measurements were taken in three anatomical points throughout the study in all patients

DISCUSSION

The present study evaluated the effects of a LLLT nine-session protocol for improving the body contour, reducing measures and the fat thickness in the abdominal and hip regions. The patients showed a significant decrease in abdominal measures after the treatment, with permanence of the outcome for up to 12 weeks after the last session. In the hip region, however, it was not possible to observe the same pattern in the reduction of measures: the patients had a more marked reduction one week after the last session, maintaining it throughout the study period.

Reductions in the body's circumference measurements have already been described by other researchers.[3,5–8,13] Most authors have reported the use of the treatment in question in the abdominal region[3,5,6,8] with significant effects in up to 2 weeks after its completion. In the present study, the outcomes were main-

Table 2: Subcutaneous adipose tissue's thickness measurements taken by MRI in the hip region, described by patient

Patient	Right side Baseline N = 5	S_{12} N = 5	Left side Baseline N = 5	S_{12} N = 5
001	5.6	5.3	5	5
005	4	3.9	3.9	3.9
007	6.7	6.5	6.2	6.1
013	5.5	5.2	5.5	5.1

Results expressed in cm

Table 3: Subcutaneous adipose tissue's thickness measurements taken by MRI in the abdominal region, described by patient

Patient	Right side Baseline N = 5	S_{12} N = 5	Left side Baseline N = 5	S_{12} N = 5
002	2.5	2	2.3	1.9
006	3.1	3.1	3	3.4
009	1.6	1.5	1.4	1.2
015	2.6	2	2.3	2
016	3.6	3.4	3.3	3.3

Results expressed in cm

Table 4: Lipid profile of patients before and after treatment with LLLT

	Baseline N = 20	S1 N = 20	P*
Total cholesterol	203,9 ± 28,4	199,9 ± 31,6	> 0,05
HDL cholesterol	65,7 ± 15,8	62,2 ± 12,1	> 0,05
LDL cholesterol	121,9 ± 28,1	121,8 ± 34,0	> 0,05
Triglycerides	81,6 ± 40,6	79,6 ± 28,4	> 0,05

Results Expressed in mg / dL

tained for a considerably longer period in the abdominal region than previously described, while results in the hip region was similar to those found in the literature. Previous publications[3,5,6,8,13] describe the use of protocols with fewer treatment sessions.

McRae and Boris assessed the correlation of weight variation with decreases in body circumference measurements. Although the reduction in weight was significant, the authors describe a weak correlation between changes in weight and body circumference measurements.[13] In the present study, the weight variation observed in the evaluated patients was not statistically significant.

The decrease in the thickness of subcutaneous adipose tissue measured by MRI was observed in most of the evaluated anatomical points in both the abdominal and hip regions. Due to the small number of patients assessed, these data were not statistically evaluated. Magnetic resonance imaging is a safe, effective and reproducible method for the evaluation and quantification of body fat.[14-16] This technique creates a good contrast between the body's diverse soft tissues, providing accurate images for measuring the adipose tissue's thickness.

Jankowski *et al.*[4] carried out a double-blind randomized study, which included the assessment of the subcutaneous adipose tissue's thickness after treatment with LLLT (6 sessions over 2 weeks). Nonetheless, these authors used ultrasonography as the assessment methodology. The found data suggest that the decrease in the tissue's thickness would be related to the patients' different physical activity habits, however the study is inconclusive since this factor was not controled.[4] In addition, the presence of physical activity was not controlled in the present study, where the criterion established for patients was that changes in health habits should not occur.

In line with the data reported by other authors[3,6,7,13,] the occurrence of adverse events linked to the treatment was not verified in the present study. Like Savoia *et al.*[10] observed, there were not significant changes in serum cholesterol and triglycerides in the present study. Savoia *et al.* suggest that the combination of LLLT with vibration therapy can have led to an increase in the basal metabolism and ensuing consumption of the lipids mobilized from the adipose tissue.[10] In the present study, however, LLLT was not associated with any other procedure or therapy. The results obtained reinforce the hypothesis that mobilization of LLLT activated fat does not result in higher cholesterol levels. Likewise, the treatment did not result in the reduction of these levels, as suggested by different autores.[11,12]

CONCLUSIONS

In the present study, it was possible to observe that LLLT was effective in reducing the body's circumference measurements, particularly in the abdominal region. The treatment was proven safe according to the used protocol, without changes in the cholesterol and triglyceride levels, with absence of other adverse events linked to the treatment. Other studies with controlled parameters – including the daily practice of physical activity – are needed to confirm the effectiveness of LLLT in reducing body measures.

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Mohs micrographic surgery: analysis of 39 cases

Cirurgia micrográfica de Mohs: análise de 39 casos

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ABSTRACT

Introduction: Mohs micrographic surgery is a technique that offers high cure rates for non-melanoma skin cancer.

Objective: To describe the clinical and epidemiological profile of patients who underwent Mohs micrographic surgery in a reference center in dermatologic surgery.

Methods: Medical records of patients who underwent Mohs micrographic surgery in the period 2014-2015 at a dermatology reference center, in the city of Mogi das Cruzes (SP, Brazil), were analyzed.

Results: The patients' ages ranged from 38 to 87 years; of these 54% were women. The most affected topography was the nose (54% of patients). Previous history of skin cancer was positive in 62% of cases. The indication driver for micrographic surgery was the lesion's location in 67% of the patients, followed by the size (23%) and tumor recurrence (10%). The most prevalent intraoperative diagnosis was basal cell carcinoma (90%).

Conclusions: Mohs micrographic surgery is an excellent therapeutic option in cases of tumors of aggressive nature, large diameter and high-risk location. This study is in line with the current literature regarding the epidemiological data linked to the occurrence of nonmelanoma skin cancer.

Keywords: Mohs surgery; skin neoplasms; dermatologic surgical procedures

RESUMO

Introdução: *A cirurgia micrográfica de Mohs é técnica que oferece altos índices de cura para câncer de pele não melanoma.*

Objetivo: *Traçar o perfil clínico e epidemiológico dos pacientes submetidos à cirurgia micrográfica de Mohs em um centro de referência em cirurgia dermatológica.*

Métodos: *Foram analisados os prontuários dos pacientes submetidos a cirurgia micrográfica de Mohs no período de 2014 a 2015 em serviço de referência de dermatologia na cidade de Mogi das Cruzes (SP).*

Resultados: *A idade dos pacientes variou de 38 a 87 anos; desses 54% eram do sexo feminino. A topografia mais acometida foi o nariz (54% dos pacientes). História pessoal prévia para câncer de pele foi positiva em 62%. A indicação da cirurgia micrográfica foi a localização em 67% dos pacientes, as dimensões em 23% e a recidiva do tumor em 10%. O diagnóstico intraoperatório mais prevalente foi o de carcinoma basocelular (90%).*

Conclusões: *A cirurgia micrográfica de Mohs é excelente opção terapêutica em casos de tumores agressivos, de grande diâmetro e localizados em áreas de risco. O presente estudo está de acordo com a literatura atual, quanto aos dados epidemiológicos de acometimento por neoplasias cutâneas não melanoma.*

Palavras-chave: *cirurgia de Mohs; neoplasias cutâneas; procedimentos cirúrgicos dermatológicos*

Original Articles

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INTRODUCTION

Mohs micrographic surgery (MMS) is the technique used to treat non melanoma cutaneous malignant neoplasias that leads to the best cure rates and is today regarded as the gold standard.[1,2] In this procedure, the dermatologic surgeon performs the mapping of the neoplasia, and the removal and histological analysis of the tumor and its margins.[1]

Frederic Mohs developed the first concepts of micrographic surgery in 1930, studying the potential curative effect of various substances injected into different neoplasms. During an experiment, there was tissue necrosis after the injection of 20% zinc chloride solution. Microscopic analysis evidenced that the tissue maintained its microscopic structure, as if it had been excised and processed for routine histological examination. With this, Dr. Mohs observed that the *in situ* fixation was effective,[1] enabling the development of a surgical technique in which the tumor could be removed in a staged way. After undergoing *in situ* fixation, the tumor was excised and then cut into tangential sections, which allowed the analysis of both the epidermis and the deep tumoral region.[3] In contrast with the traditional section, which evaluates only 0.001% of the total sample's surface, the horizontal sections used in this technique allowed analysis of 100% of the sample's margins.[1]

Mohs tested many substances for *in situ* fixation, and zinc chloride was chosen due to the facts that it preserved the microscopic characteristics for analysis, had good penetration in the tissues with precise control of the fixation's depth, did not interfere with the healing of the exeresis' site by secondary intention, did not cause systemic toxicity, was safe during use and had no smell.[1]

Initially, Mohs named the technique as microsurgery, however this term was already employed to describe the dissection of small structures using a microscope; the term chemosurgery was then chosen, since skin tumors were chemically fixed *in situ* before excision.[4]

Although this technique had a higher healing rate than that of the traditional excision technique, it had some drawbacks: it could take days to complete, it could cause pain, fever, lymphadenopathy in tumors of large diameter, and the detachment of the fixed tissue could take days to complete, which delayed the surgical wound reconstruction.[1]

Due to these drawbacks, the *in situ* fixation was gradually replaced by the fresh tissue technique, with the use of freezing after the tumor's excision, which has been described by Theodore Tromovitch and Samuel Stegman. As a result, Mohs also adhered to it.[1,4]

The fresh tissue technique eliminated the need for zinc chloride, allowing the tumor's removal and reconstruction to be performed on the same day, without having to wait for the crust caused by the zinc chloride to detach from the viable underlying tissue. Thus, *in situ* fixation (chemosurgery) fell into disuse, giving way to the currently used technique based on fresh tissue (Mohs micrographic surgery - MMS).

The conventional excision technique usually leaves a margin of 3 to 6mm beyond the tumor. The histological margins are then evaluated by the pathologist by sampling, which can lead to evaluation flaws. In MMS, the superficial and deep margins are fully evaluated.[5]

The five-year recurrence rates of primary and recurrent basal cell carcinomas (BCCs) treated with conventional surgery are 10% and 17%, respectively. When treated using MMS, those rates drop to 1% and 6%; [6] another significant advantage is that the technique allows greater conservation of normal tissue. In this manner, it is clearly indicated for tumors that are large in diameter, recurrent, have aggressive histological subtypes or are located in critical areas (periocular, periauricular and nasal regions).

In order to perform the MMS, the following pieces of surgical material are needed: dieresis, hemostasis and synthesis materials (the same used for conventional excision), pen for marking the surgical margins, histological stains, specimen processing material, a cryostat, a microscope and, in addition, the assistance of a laboratory technician to stain and perform the cuts in the specimen.

The technique has five steps:

1) Marking of the area to be excised: delineate the clinical margins of the tumor with a pen and then the surgical margins with a distance varying from 2 to 5mm from the clinical margins. Perform the markings transversally to the incision line, which will allow to locate the position of the removed fragments in the tissue surrounding the surgical wound.

2) Excision of the tumor: it is performed using a scalpel at a 45°-degree angle, which allows the epidermis and dermis to be cut straight in the cryostat, allowing microscopic analysis in the same plane.

3) Mapping of the specimen: can be carried out using a sheet of paper or digitally on devices that take photographs and allow drawing on that image (e.g. tablets). The surgical specimen and its location should be drawn in the area of the surgical defect. Its divisions and the ink markings should also be outlined. This map is crucial for the dermatologic surgeon's directing during the analysis of the tissue using the microscope and for the exeresis of the areas compromised with the tumor.

4) Processing and histological analysis of the specimen: in this phase, the specimen's marking with ink, flattening, freezing, cutting and staining must be performed.

The division of the specimen, when necessary, as well as the marking with ink must always be indicated on the map. The most frequently used ink for the specimen's marking is nankin, which comes in several colors, allowing highlighting each region.

The flattening of the surgical specimen can be performed using mechanical pressure on it, while cuts with a scalpel are required in some cases. The flattening on the slide is critical so that the whole of the epidermis and dermis can be cut in a single plane in the cryostat.

The tissue is then frozen and sectioned in the cryostat, with the slides being prepared with hematoxylin-eosin for histological evaluation.[5]

The surgeon evaluates the slides in order to determine

whether the margins are compromised. If the tumor is completely excised, the surgical defect can be immediately reconstructed. Nevertheless, if the tumor is still present, the corresponding location is marked on the map.

5) Selective excision of the areas with residual tumor: it is necessary to go through this step in case there is compromise of any portion of the margin. If the lateral margin is compromised, a 1-2mm excision should be performed at this site. If the deep margin is compromised, an excision should be performed along the defect's interior, removing tissue from the deep base of the wound.

The tissues of the compromised areas must undergo histological analysis. These steps are repeated until the margins are considered free of tumor and the reconstruction can be performed.[5]

The objective of the present study was to describe the clinical and epidemiological profile of the patients who underwent MMS at a dermatological surgery referral center.

METHODS

The present study was approved by the Universidade de Mogi das Cruzes – UMC (SP, Brazil) Research Ethics Committee on 22/06/2016 under the protocol number 55945216.8.0000.5497.

A retrospective, descriptive, observational cross-sectional study analyzed medical records of all patients who underwent MMS at the dermatology referral service in the city of Mogi das Cruzes, São Paulo, Brazil, in the years of 2014 and 2015.

The sampling method was non-probabilistic for convenience, and included all patients who underwent MMS during the study period.

Aimed at grouping the study data into clinical, epidemiologic and histologic categories, the following items were analyzed for each case: gender, age, preoperative biopsy diagnosis, intraoperative biopsy diagnosis, MMS indication, tumor location, previous history of skin cancer, photodamage degree (mild, moderate or severe), Fitzpatrick phototype (I, II, III, IV, V, VI), number of phases in each surgery, number of fragments of each tumor excised during surgery, and final surgical defect reconstruction type.

The obtained data were recorded on Microsoft Excel® spreadsheets, with descriptive analysis of percentages and graphs.

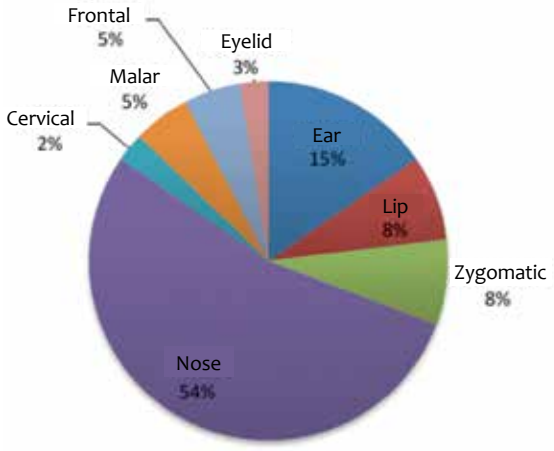
RESULTS

During the study period, 39 patients were treated and operated using MMS, and had their medical records analyzed. Of these, 54% were female. The participants' ages ranged from 38 years to 87 years, with an average of 60.8 years.

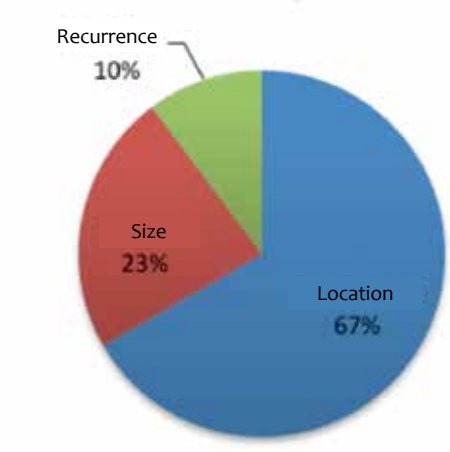
Regarding the lesion's topography, the most affected body sites were the nose (54%) and the ear (15%), as depicted in Graph 1. Previous personal history of skin cancer was present in 62% of the patients. The indication for MMS was due to the lesion's location in 67% of patients, as shown in Graph 2. The degree of photodamage was classified as moderate or severe in most patients, as shown in Graph 3. Graph 4 illustrates the treated patients' phototypes' percentages, according to the Fitzpatrick Scale. Most of the sample's individuals had phototypes I and II (i.e. fair skin).

Thirty-nine lesions – one of each studied patient – were excised. Of these, 92% were diagnosed with preoperative BCC biopsy; squamous cell carcinoma (SCC) and actinic keratosis (AK) were present in a much lower proportion (Graph 5). In the intraoperative diagnosis, 90% of the lesions were confirmed as BCCs, 8% SCC and 2% were trichoepitheliomas (Graph 6), indicating diagnostic disagreement in 2 lesions of the 39 evaluated. A lesion preoperatively diagnosed as an AK was proven a clearly differentiated SCC in the intraoperative biopsy. Another initially diagnosed as a BCC, was proven a trichoepithelioma in the intraoperative biopsy.

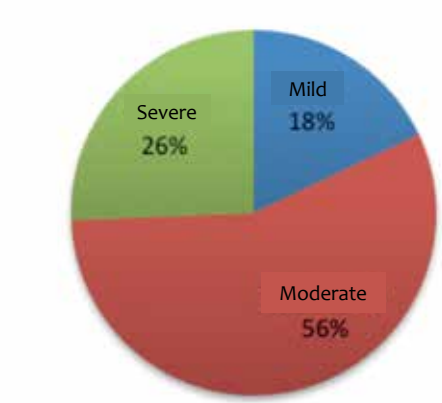
Surgeries had one, two or a maximum of three operative phases, with an average of three phases. Each surgery yielded on average 4.4 tissue fragments during the excisions, having been prepared and analyzed intraoperatively.



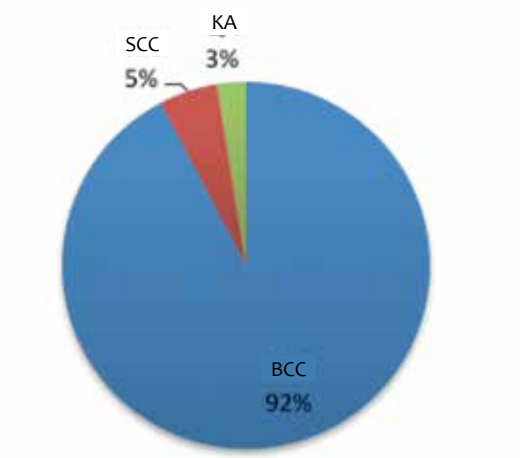
GRAPH 1: Tumor locations



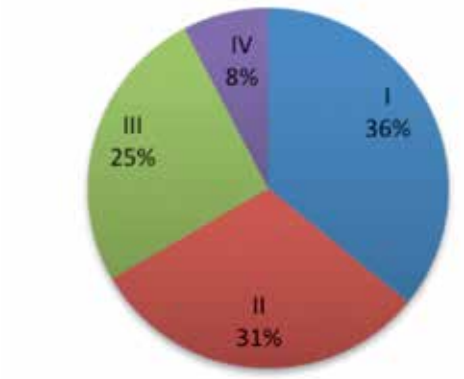
GRAPH 2: Indication for MMS



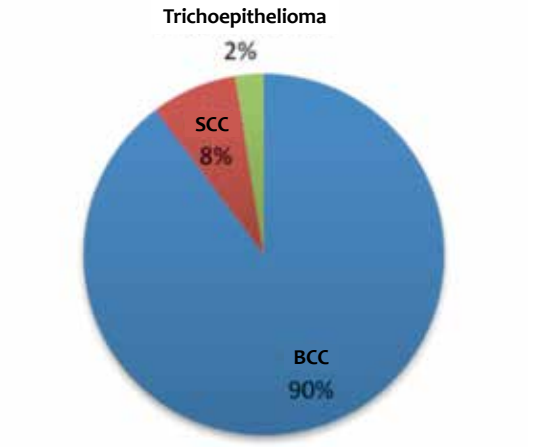
Graph 3: Degree of photodamage



Graph 5: Preoperative biopsy diagnosis



Graph 4: Phototype



Graph 6: Intraoperative biopsy diagnosis

In the nose region, 90% of the tumors were BCCs, 5% SCCs, and 5% trichoepitheliomas (Graph 7), and most reconstructions in this area were performed with transposition flaps (Graph 8).

In the zygomatic region, 67% of the tumors were SCCs and 33% were BCCs; 34% of the reconstructions were performed with transposition flaps, and edge-to-edge closures and advancement flaps were performed in 33% of the cases in this area (Graph 9).

In the ear region, 83% were BCCs, and 17% SCCs, with edge-to-edge reconstruction and transposition flaps being the most frequent, each performed in 33% of cases in this area (Graph 10).

In the cervical and malar regions, all cases were BCCs, with edge-to-edge reconstructions.

In the palpebral and labial regions, all cases were also diagnosed as BCCs, with the advancement flap being the most commonly used reconstruction method.

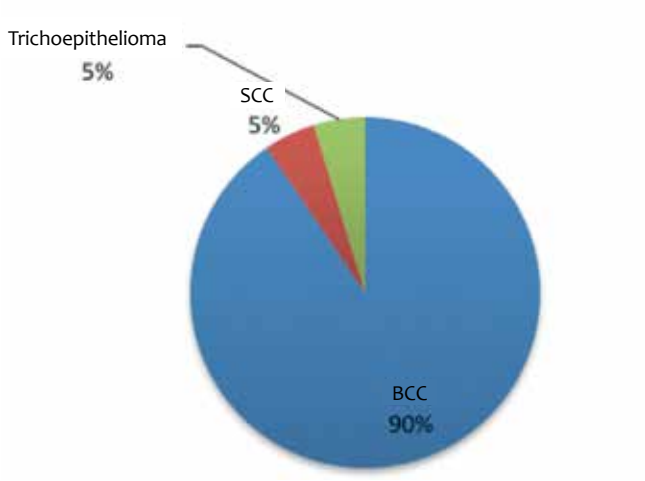
DISCUSSION

Non-melanoma skin tumors in advanced stages have high morbidity. Prevention, early diagnosis and an effective treatment that leads to a decreased risk of recurrence – such as MMS – are crucial for the reduction of morbidity.

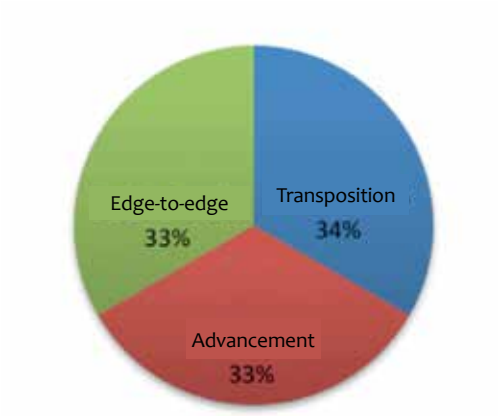
According to a recent publication on MMS in Brazil, the technique has been performed in the country for at least 30 years, and is restricted to less than 1% of dermatologists, being mainly concentrated in the Southeast Region. Training in this technique takes about one year and is offered by only six accredited services.[7]

The lack of data on the epidemiology of non-melanoma skin cancer in the Brazilian population also justifies the present study.

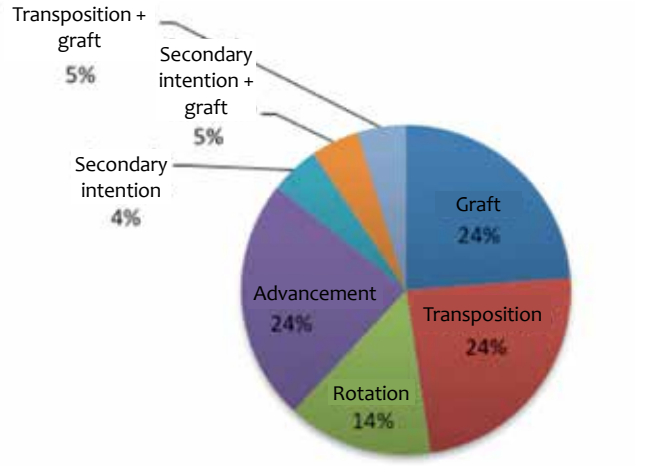
There was a greater involvement of women as compared to men, while most of the literature suggests men are more affected by skin cancer.[8-10] Recent studies, however, have demonstrated this change in the disease's profile.[11-13]



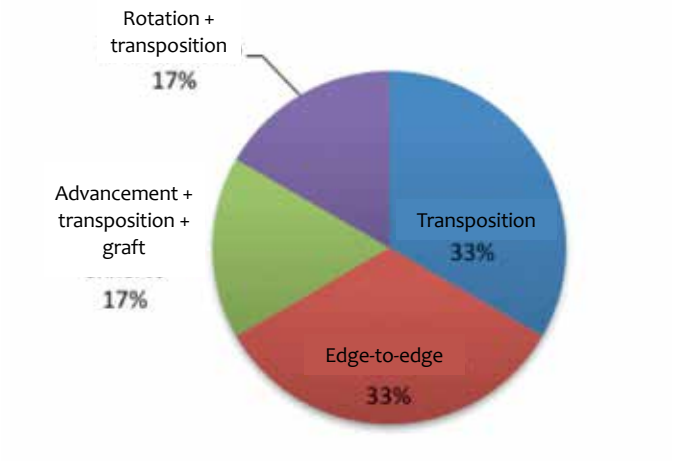
Graph 7: Diagnosis in the nose region



Graph 9: Types of reconstruction in the zygomatic region



Graph 8: Types of reconstruction in the nose region



Graph 10: Types of reconstruction in the ear region

The literature indicates that lower phototypes, advanced age and photodamage are risk factors for skin cancer such as BCC and SCC,[8,9] a fact that was confirmed by the present study, in which 67% of the patients had Fitzpatrick phototypes I or II. The mean age was 60.8 years, and 82% of the patients bore important photodamage (moderate or severe).

Regarding the location, it is known that lesions are more aggressive in the centrofacial region,[13] which is a common area of recurrence. Among the tumors analyzed in the present study, 72% were located in an area of risk (nose, eyelid and ear), confirming their indication for MMS. Previous history of skin cancer was present in 62% of patients and, according to the literature, patients who have had skin cancer are at increased risk of new cutaneous neoplasms.[14,15] This data also includes patients who had recurrence of a tumor previously removed with the traditional surgical method, having later been referred for MMS, which constituted 10% of the cases. Rowe .. presented data regarding recurrences of BCCs that had been treated with traditional therapies and had cure rates of roughly 82% after surgical excision, and 60% with electrocoagulation and curettage. The use of cryotherapy resulted in an 87% cure rate in time series of less than five years. The application of MMS in recurrent BCCs increased these cure rates to 94.4%.[14]

Other indications for MMS are extensive dimensions and tumor location aiming at preserving healthy tissue that is free of the neoplasia, which would not be possible with the conventional excision. In the present study, the tumor's large size and its location led to indication for MMS in 23% and 67% of the cases, respectively.

In the present study, BCCs and SCCs represented 90% and 8% of the tumors, respectively. The literature describes BCC as the most common type of skin cancer.[8,9] In addition, BCCs that are extensive or recurred, or are located in areas with increased risk, is the main indication for MMS, justifying its high prevalence in the studied sample.

There was also one case of trichoepithelioma that was initially diagnosed as BCC, being correctly diagnosed during intraoperative biopsy. Trichoepithelioma is a benign skin tumor that differentiates from the hair follicle and arises as a usually solitary, erythematous, usually facial tumor that resembles BCC both clinically and histologically, constituting an important differential diagnosis.

In the present study, the authors observed an average number of three operative phases per surgery, demonstrating the prevalence of aggressive tumors, given that the actual invasion was more extensive than that detected clinically.

The studied patients did not experience recurrence of the operated tumors, with the majority being followed up for more than one year (6 to 18 months). Although the follow-up duration can still be deemed as short, these data show the effectiveness of the MMS technique.

The study has some limitations (i.e. small number of patients and short follow-up time), which are justified by the fact that the sampling method was based on convenience, using a technique that still not largely performed in Brazil, at a dermatologic surgery referral service that has only been using the MMS technique for two years.

CONCLUSION

The data analyzed allow indicating MMS as an excellent therapeutic option in cases of tumors that are aggressive, have large dimensions, and are located in areas of high risk or recurrence. When performed by professionals with adequate training, this technique is safe and reliable, with a tendency to become increasingly frequent in the practice of the dermatologist physician. The present study is in line with most of the current literature regarding the epidemiological data of non-melanoma skin cancer.

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Importance of texture and sensorial profile in cosmetic formulations development

Importância do perfil de textura e sensorial no desenvolvimento de formulações cosméticas

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ABSTRACT

Introduction: The evaluation of the clinical efficacy of cosmetic formulations in real conditions of use is indispensable and the correlation of these results with texture and sensory profile analyses is necessary because impacts directly in the continuity of cosmetic treatment.
Objective: The evaluation and correlation of the texture and sensorial profile, and clinical efficacy of cosmetic formulations containing alfafa oligosaccharides, cassava polysaccharides and sunscreens.
Methods: It was evaluated the texture and sensorial profile, and clinical efficacy of formulations through biophysical and imaging analysis techniques.
Results: The methods presented a good correlation, because formulation added with suncreens and active ingredients provided better spreadability and sensorial properties. The assessment of clinical efficacy was coherent with the sensory analysis once the "skin smoothness" parameter could be proven with the increase of hydration and improvement of skin microrelief.
Conclusions: The application and correlation of the used techniques enabled the definition and obtainment of a formulation with sensory acceptance and proven clinical efficacy in the improvement of texture and skin hydration. Thus, this study provides contribution in dermatological area, once an appropriate sensory favors the adhesion to the use of the product and the consequent treatment success.
Keywords: efficacy; cosmetics; biophysics; polysaccharides; oligosaccharides

RESUMO

Introdução: *Assim como a avaliação da eficácia clínica de formulações cosméticas nas reais condições de uso é imprescindível, a correlação destes resultados com análises do perfil de textura e sensorial faz-se necessária, pois impactam diretamente na continuidade do tratamento cosmético.*
Objetivo: *Avaliar e correlacionar o perfil de textura, características sensoriais e eficácia clínica de formulações cosméticas contendo oligossacarídeos da alfafa, polissacarídeos da mandioca e filtros solares.*
Métodos: *Foram avaliados o perfil de textura, características sensoriais e a eficácia clínica de formulações, por meio de técnicas de biofísica e análise de imagem.*
Resultados: *Os métodos empregados apresentaram correlação, pois, a formulação acrescida de filtros e ativos proporcionou melhores espalhabilidade e características sensoriais. A avaliação da eficácia clínica se mostrou coerente com a análise sensorial uma vez que o parâmetro "pele macia" pode ser comprovado com o aumento da hidratação e melhora do microrrelevo da pele.*
Conclusões: *A aplicação e correlação das técnicas empregadas possibilitaram a definição e obtenção de formulações com aceitação sensorial e eficácia clínica comprovadas na melhora da textura e hidratação da pele. Assim, este estudo apresenta contribuição na área dermatológica, uma vez que o sensorial adequado favorece a adesão ao uso do produto e o consequente sucesso do tratamento.*
Palavras-chave: *eficácia; cosméticos; biofísica; polissacarídeos; oligossacarídeos*

Original Articles

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INTRODUCTION

The aging process brings the loss of structural integrity to the skin, that occurs due to a decreased in cell renewal, vascularization, number of keratinocytes, fibroblasts, collagen and elastin fibers, in addition to the flattening of the dermal-epidermal junction, and a reduction in the immune response, which leads to change in functions such as cutaneous protection, absorption, thermoregulation and sensory perception. Moreover, exposure to exogenous factors – air humidity, ultraviolet radiation – as well as endogenous factors – hormones – possibly alters the balance between the stratum corneum and the lipid layer.[1-3]

Whereas there are still no means to prevent the occurrence of genetic aging processes, cosmetic products with anti-aging properties are only able to prevent, delay and alleviate the effects caused by extrinsic factors.[4] Furthermore, the cosmetic industry has been committed to developing formulations that meet current consumer needs, integrating many benefits to the skin in a single product.[5]

Among cosmetic active principles used for anti-aging and cutaneous health general improvement purposes, research on Alfalfa extract *(Medicago sativa)* evidenced a mechanism of action similar to that of Retinol ("retinol like"), which has the potential to stimulate cell activity, favoring the renewal of the epidermis and regulating the differentiation of keratinocytes. In addition, it promotes stimulation of type I collagen synthesis and reduction in the activity of the metalloproteinases, the latter responsible for the destruction of elastin fibers.[6,7]

Apart from active principles that act in the long term, the use of principles with immediate tightening effect, such as the cassava's bio polymerized sugar *(Manihot esculenta),* can contribute to the perceived efficacy of cosmetic formulations, since after application of the product on the skin, this active is capable of forming a three-dimensional mesh composed of high molecular weight polysaccharides, lending resistance and cohesiveness, allowing a significantly rapid tightening effect.[8,9]

Nonetheless, for the verification of the potential effects described, it is necessary to conduct clinical effectiveness studies under actual use conditions. For this end, *in vivo* non-invasive methods are employed, including biophysical and skin imaging analysis techniques using multiple devices with different physical and/or physicochemical principles that facilitate the interpretation of the outcomes regarding the performance of a particular cosmetic product on the skin.[10]

In this manner, it is possible to evaluate parameters linked to the stratum corneum's water content, transepidermal water loss and cutaneous microrelief, among others, using the Tewameter®, Corneometer® and Visioscan® devices.[10,11]

It is important to note that in order for the cosmetic formulations to be in fact effective, choosing good active principles and showing evidence of clinical effectiveness are only two of a series of important steps to be considered during the development of these formulations. For example, it is also imperative that the formulation offers enjoyable sensory characteristics and good spreadability on the skin, aimed at providing consumers' wellbeing and conditions for continuity of the cosmetic treatment.[12,13]

For that end, conducting texture and spreadability trials using the TA.XT plus texturometer device are crucial because they allow analyzing the influence of the components' mechanical properties, and comparing these results with sensory analyses. This supports the development of formulations with different sensory characteristics, which in turn promote the continuity of their use.[13,14]

In this context, innovative methods such as texture analysis combined with clinical effectiveness can mean a great contribution to the development of cosmetic products with proven efficacy and differentiated sensory characteristics.

OBJECTIVE

The present study was aimed at evaluating and correlating the texture, sensory characteristics and clinical effectiveness profiles of cosmetic formulations containing alfalfa's oligosaccharides, cassava's polysaccharides and sunscreens.

MATERIALS AND METHODS

Assessed formulations

A multifunctional cream gel formulation was developed based on Polyacrylamide (and) C13-14 Isoparaffin (and) Laureth-7 (Sepic), Ethylhexyl Palmitate (Croda), Bis-ethylhexyloxyphenol methoxyphenyl triazine (Basf), Octocrylene (Symrise), Methylene bis-benzotriazolyl tetramethylbutylphenol (Basf), Glycerin (Mapric), Propylene glycol (Mapric), Cyclomethicone (Dow Corning), Cyclopentasiloxane (and) Dimethicone crosspolymer (Dow Corning), Polyglyceryl-10 myristate, Triethylhexanoin, Glycerin, Water (Nikko Chemicals), Phenoxyethanol, Methylparaben, Ethylparaben, Propylparaben, Butylparaben, Isobutylparaben (Mapric), BHT (Mapric), Disodium EDTA (Mapric), aqua.

Was also analyzed a commercial gel-cream based on: aqua, Octocrylene, glycerin, Dodecane, Homosalate, Ethylhexyl salicylate, Butyl methoxydibenzoylmethane, Cyclopentasiloxane, Dimethicone reticulate copolymer, Hydroxyethyl acrylate copolymer / Sodium acryloyldimethyl taurate, Squalene, Polysorbate-60, Dicaprylyl ether, Castanea sativa seed extract, Phenylbenzimidazole sulfonic Acid, C12-15 Alkyl benzoate, Caprylic/Capric triglyceride, Diethylamino hydroxybenzoyl hexyl benzoate, Glyceryl Stearate (and) PEG-100 Stearate, Soybean (Glycine soja) extract, Biosaccharide gum-2, Biosaccharide gum-3, Xanthan gum, Sodium hydroxide, Phenoxyethanol, Acrylates/C10-30 Alkyl acrylate crosspolymer, Tocopheryl acetate, fragance, BHT, Biosaccharide gum-5, Disodium EDTA, Methylchloroisothiazolinone, Coffea robusta seed oil extract, Lycopene.

Spreadability analysis

In order to assess the contribution of the studied sunscreens and active principles (alfalfa oligosaccharides and cassava polysaccharides) on the developed formulation's physical and mechanical properties, a TA.XT plus texturometer device and a TCC spreadability Rig probe were used in the present study. The trials' results were provided by the device's software. The

parameter *work of shear* was evaluated (Area F-T 1:2).[15]

To this end, the developed multifunctional formulation was subdivided into 3 portions. Accordingly, the F1 (vehicle formulation), F2 (F1 plus sunscreens) and F3 (F2 plus active principles) formulations were compared, the latter being the object of analysis. It worth to note that these formulations had their stability proven by a stability test.[16]

METHODS

This stage was previously approved by the Research Involving Human Subjects Ethics Committee of the Faculdade de Ciências Farmacêuticas de Ribeirão Preto – USP (SP, Brazil) (Protocol: 1.0420228 04/2015).

Sensory analysis

The sensory analysis was performed in 2 stages. The first was aimed at evaluating the contribution of sunscreens and active principles in the sensory characteristics of the developed formulation. The second was aimed at evaluating the sensory characteristics of the studied formulation as compared to a commercial formulation.

Both analyzes were performed in the anterior region of the forearm in all 20 volunteers in the first stage, and in 10 volunteers in the second stage.

In the first step, the forearms were divided into 3 quadrants, with each volunteer applying one of the formulations (F1, F2 and F3) in one of the quadrants, performing 10 clockwise rotations. After the application, the volunteers answered a sensory evaluation questionnaire containing the following parameters: *touch sensation*, *spreadability*, *skin smoothness*, *absorption*, *oiliness*, *brightness*, *absorption*, and *white residue*. The parameters were scored according to the following criteria: 1 - Very poor, 2 - Poor; 3 - Fair, 4 - Good, 5 - Excellent.

In the second step, a random application of 20 μL of the formulations FA (commercial formulation) and FC (multifunctional formulation F3) was performed in 3 regions (one of them being the control region) of the forearms of 10 volunteers. Before starting the study, the volunteers were instructed to spread the formulation performing 10 clockwise rotations. The questionnaire "check-all-that-apply" (CATA) was used, with questions on the sensory characteristics related to the parameters perceived immediately after the application (*oily/greasy*, *sticky*, *smooth*, *easily absorbed* and *easy to spread*) and those related to the effects on the skin perceived 5 minutes after the application (*oily residue*, *hydrated skin*, *smooth skin*, *whitish residue* and *intention to buy*).[18]

Clinical effectiveness evaluation

Ethical aspects

The volunteers were informed and advised on the study's goals and methods, having agreed to participate, signing a Term of Free and Informed Consent approved by the Research Ethics Committee (Resolution 466, 12/12/2012, Brazilian National Health Council).

Population and sample / Selection of volunteers

For the assessment of the immediate effects of the studied formulations, 10 female volunteers were selected (Fitzpatrick phototypes II to IV, aged from 20 to 50 years). The following exclusion criteria were used in the selection of volunteers: pregnancy or lactation; previous history of adverse reactions to the use of cosmetic products; use of drugs likely to produce abnormal cutaneous response; localized or generalized dermatological diseases; and excessive hair in the study regions.

Evaluation of immediate effects

This stage of the study comprised the assessment of the immediate effects of the studied formulation (F3, which in this stage was renamed with the acronym FC) as compared to a commercially available formulation (FA) containing polysaccharides and sunscreens for improving hydration, transepidermal water loss and the skin's microrelief. In this way, the formulations were applied on 10 volunteers, in 3 previously randomly defined regions in the forearms, with 1 of these regions being established as the control region. The measurements were taken before the application of the formulations and 2 hours after. The outcomes were compared among them and to their respective baseline values. All measurements were performed after 15 minutes of acclimatization in controlled temperature and air humidity (20-22°C and 45-55%, respectively).[10]

Biophysical techniques and skin imaging analysis: Transepidermal water loss (TEWL)

The Tewameter® TM 300 (Courage-Khazaka, Germany) device was used in this study. It measures the water evaporation on the skin's surface based on the diffusion principle described by Adolf Fick in 1885. The probe remained on the skin for 20 seconds, obtaining an average value for the TEWL.[19,20]

Stratum corneum's water content

The stratum corneum's water content was determined using the Corneometer® CM 825 device (Courage-Khazaka, Germany), coupled to a software that measures the stratum corneum's hydration level. This technique's principle is based on measuring the electrical capacitance of the skin, according to the amount of water present in it. Ten measurements were performed in the studied region, with the results expressed in arbitrary units (A.U.) by the device itself, depending on the stratum corneum's water content.[11]

Cutaneous microrelief

The Visioscan® VC 98 device (Khazaka, Germany) was used to determine the skin's cutaneous microrelief. The device provides qualitative and quantitative information about the skin's surface in physiological conditions using optical profilometry techniques, which are based on the digitalization process of images obtained by a video camera. With this method, the following parameters related to the skin's surface were evaluated (SELS - Surface Evaluation of Living Skin): *roughness* (SEr) -

portion of dark spots representing the skin's roughness; *wrinkles* (SEw) - number and width of wrinkles, the greater the number of wrinkles the greater is Sew; *smoothness* (SEsm) - shape and width of wrinkles, the higher the value of this variable, the better the texture and softness of the skin.[21]

Statistical analysis

The data were tested for normality by the Shapiro-Wilk test for each evaluation performed, using the statistical software Origin 8.

To evaluate the correlation among all studied parameters in each of the regions, the Pearson correlation was used with the assistance of the software GraphPad Prism 5. The ANOVA (Bonferroni test) for comparison of means was performed for all parameters ($p < 0.05$).

RESULTS

Spreadability analysis

According to the spreadability test results (Graph 1), a significantly greater value for *work of shear* was gauged for the formulation F1 than for F2 and F3 ($P < 0.05$), suggesting that the addition of sunscreens and active principles to the formulations have improved their spreadability. Moreover, the comparison of F2 with F3 did not evidence significant differences in spreadability values, indicating that the decrease in the *work of shear* value is exclusively due to the addition of sunscreens to the formulations (F2 and F3).

Sensory analysis

Based on the analysis of these results (Graph 2) it was possible to notice that the formulations in general fared well in the volunteers' percentage of acceptance, while the formulation containing sunscreens and active principles (F3) had the highest percentages of maximum ratings in most of the evaluated parameters, regarding the other formulations.

In the second stage of the sensory analysis, it was possible to observe that the formulations in general have obtained the same percentage of characterization for each of the parameters evaluated.

It is important to note that, immediately after the application (Graph 3) the commercial formulation (FA) received a higher percentage of characterization regarding the parameter *easily absorbed* and a lower percentage regarding the parameter *sticky*. On the other hand, regarding the effects 5 minutes after the application of the formulations (Graph 4) the FC formulation stood out regarding the parameters *smooth skin* and *intention to buy*.

Clinical effectiveness evaluation

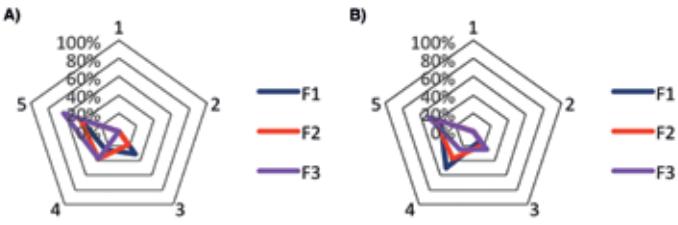
Transepidermal water loss (TEWL)

Based on the analysis of the results (Graph 5) it was observed that 2 hours after the application, a reduction trend could be observed in TEWL for both formulations.

Stratum corneum'a water content

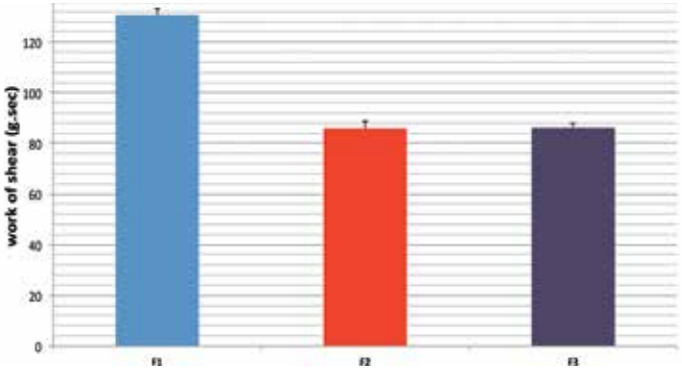
Based on the analysis of the results (Graph 6), it was possible to observe a significant increase ($p < 0.05$) in hydration

Graph 2: Sensory analysis of F1, F2 and F3 formulations



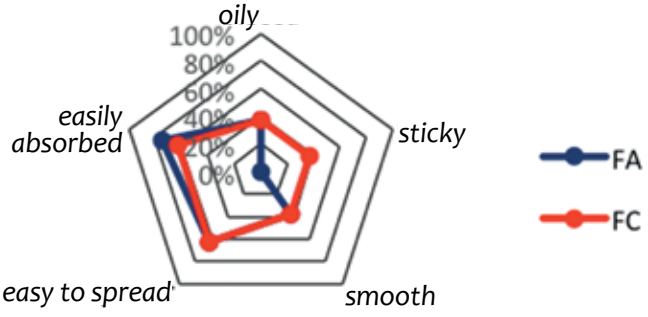
Evaluation of the formulations regarding the parameters spreadability **(A)**, touch sensation **(B)**; ratings: 1 - Very poor, 2 - Poor; 3 - Fair, 4 - Good, 5 - Excellent

Graph 1: Spreadability test



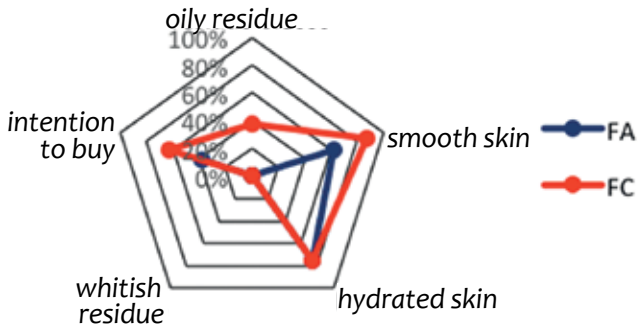
Spreadability test based on the evaluation of the parameter work of shear. Comparison between F1 (vehicle formulation), F2 (vehicle + sunscreen) and F3 (F2 + active principles). *Statistically significant values in the comparison with other formulations' results

Graph 3: Análise sensorial comparativa entre as formulações FA e FC- 2ª etapa



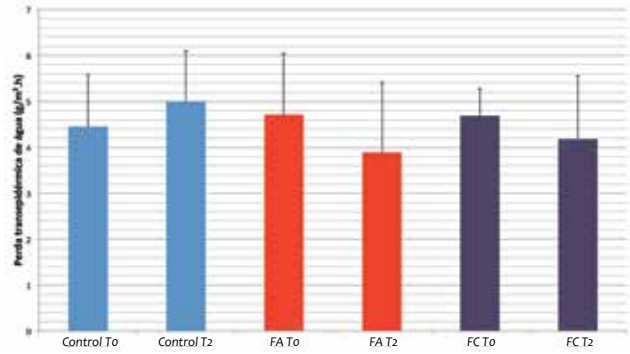
Comparative sensory analysis between FA and FC formulations – 2nd stage. Comparative sensory analysis between FA (commercial formulation) and FC (study formulation). The following parameters were evaluated immediately after the application: *oily/greasy, sticky, smooth, easily absorbed and easy to spread*

Graph 4: Comparative sensory analysis between FA and FC formulations – 2nd stage



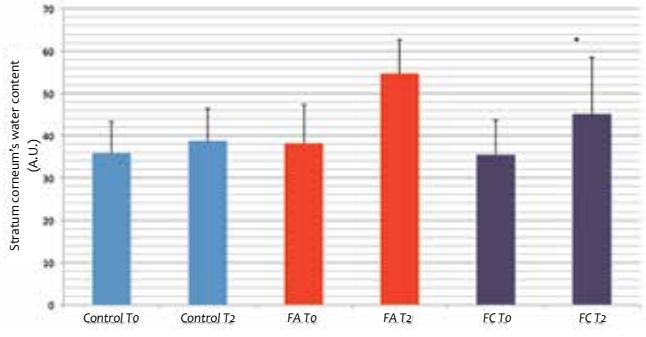
Comparative sensory analysis between FA (commercial formulation) and FC (study formulation). The following parameters were evaluated 5 minutes after the application: *oily residue, hydrated skin, smooth skin, whitish residue and intention to buy*

Graph: Transepidermal Water Loss (TEWL) analysis



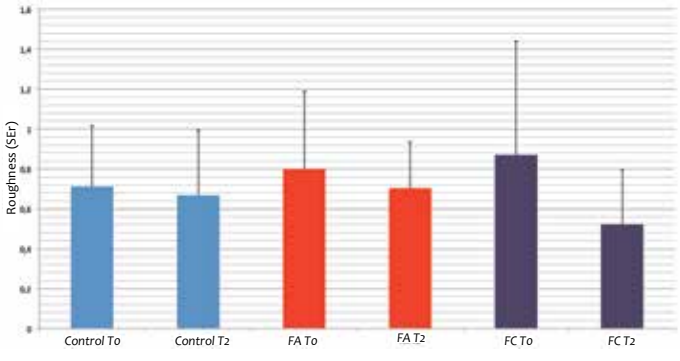
Transepidermal water loss analysis (Tewameter®) before and after the application of FA (commercial formulation) and FC (study formulation), compared to a control area

Graph 6: Stratum corneum's water content analysis



Stratum corneum's water content before and 2 hours after the application of FA (commercial formulation) and FC (study formulation), compared to a control area. * Different statistical means as compared to their baseline values. FA (p = 0.0005), FC (p = 0.0311) and FAt45 compared to FCt45 (p = 0.0232)

Graph 7: Spreadability test



Evaluation of the skin's roughness based on the parameter SEr (portion of black dots representing the degree of skin roughness) before and 2 hours after the application of FA (commercial formulation) and FC (study formulation), as compared to a control area

linked to the application of both formulations, with the comparison results indicating superiority of the FA regarding FC formulation.

Cutaneous microrelief

Based on the analysis of the data related to the parameter SEr – which evaluates the skin's roughness – it was possible to observe that the FC formulation showed a higher tendency of decrease for this parameter 2 hours after the application (Graph 7).

DISCUSSION

Despite being crucial, evidence of clinical effectiveness alone is not sufficient to ensure the success of a new cosmetic product, since these products must have sensory features that meet consumers' expectations, thus assisting in the adherence to the prescribed treatment. As a result, the analysis of texture and sensory characteristics of cosmetic products are instrumental for securing that formulations meet expectations.[12,18]

In this context, the spreadability analysis can be considered a very important pre-requisite in the development of formulations, for it enables developers to understand the influence of certain components in the product's final physical properties in an objective manner.[13]

Based on the results obtained, it was possible to observe that the formulations containing sunscreen had a lower value for *work of shear* than that of the vehicle formulation, which suggests that it will have better spreadability on the skin.This phenomenon may be related to the fact that the emulsifying polymer used in the formulations forms polymeric networks with water, in a way that when there is addition of oily sunscreens, the formulation's viscosity decreases, consequently decreasing the *work of shear*.[22]

The application of sensory analysis in the development of cosmetic formulations is key to developing formulations that are well accepted by consumes. In addition, a formulation's sensory

characteristics is as important as its clinical effectiveness since it is known consumers stop using formulations that have unpleasant sensory characteristics even knowing they can bring benefits for the skin.[18, 23]

In this manner, the first sensory analysis was aimed at characterizing the formulations as well as evaluating its acceptance by consumers, which can be measured based on the rating attributed to each assessed characteristic.[24,25] The results obtained with this analysis showed that the formulations had good acceptance percentages attributed by the study patients. Furthermore, it was demonstrated that the formulation containing sunscreens and active principles (F3) had higher percentages for the maximum rating for most of the parameters evaluated as compared to the other formulations. This outcome suggests that the presence of the active principles, which are the object of analysis of the present paper, when present in the formulations containing sunscreen, improved their sensory characteristics due to the cassava's extract filmogenic properties,[9] for instance.

Moreover, the outcomes demonstrated that adding sunscreens to the cosmetic formulations has contributed to their sensorial improvement, which was also demonstrated in the objective assessment of spreadability. Therefore, these results are satisfactory, for the presence of sunscreens in cosmetic formulations for daily use is very important for the protection of the skin against solar radiation.[26]

In the second analysis of the sensory characteristics, the *benchmark* concept, already used in a number of scientific studies and methodologies for comparing outcomes, was employed.[27,28] In the present study, this concept was used to compare the multifunctional formulation F3 with a commercially established formulation that was chosen based on the expectations regarding clinical effects to be derived from the developed formulation (gel cream formulation with immediate tightening effect and capable of increasing cell regeneration and photoprotection) as well as the intended target consumers.

Based on the analysis of the results, it was possible to observe that the formulations had similar sensory characteristics: the parameter *sticky* was attributed to the FC formulation (but not to the FA formulation), however the parameters *smooth skin* and *intention to buy* were more pronounced in FC. This indicates that, in general, the formulations had similar performances; nevertheless regarding the decisive factor *intention to buy*, the study formulation outstripped the commercial formulation. Conclusively, the developed formulation showed desirable sensory characteristics, comparable to those of a well-established commercial formulation.

Clinical effectiveness analyzes are of great importance for evaluating the effects of formulations under actual conditions of use, so that they meet the expectations regarding the improvement of both the visible general conditions of the skin and the damage caused to it by the aging process.

In line with this, the TEWL analysis plays a key role in the clinical efficacy evaluation, since the skin's hydration is directly related to the integrity of the skin barrier function and a low level of transepidermal water loss. This implies that it is possible to evaluate, for example, whether certain cosmetic formulations contribute to reducing TEWL using the Tewameter® device.[29]

Based on the analysis of the results, it was possible to observe a decrease trend in the TEWL values. A plausible explanation for this reduction is the fact that both formulations have various components, such as silicones, polysaccharides and emollients that aid in the formation of a hydrophobic film on the skin's surface, preventing the transepidermal loss of water. [30]

The evaluation of the stratum corneum's water content is instrumental in the assessment of the cosmetic formulation's ability to moisturize the skin. For that end, the Corneometer® device was used in the present study to analyze whether the formulation in question would be able to significantly increase the skin's hydration 2 hours after application, compare outcomes with those of the commercial formulation and the baseline.[11]

Based on the analysis of the results, it was possible to verify that there was improvement 2 hours after the application of both formulations. It is important to note that the statistical comparison of the results of the two formulations suggested that the commercial formulation FA provided greater hydration. This increase can be attributed to the fact that FA has a greater number of hydrating ingredients than FC.

In addition, the results were consistent with the sensory evaluation's outcomes, for most patients attributed the rating *hydrated skin* to both FA and FC.

Finally, analyzing the cutaneous microrelief also has great importance in the clinical effectiveness evaluation of cosmetics, since it allows obtaining an indirect measure of hydration through the evaluation of images – turgid cells provide a more uniform and less rough skin surface. Furthermore, the film-forming active principles' effectiveness of both formulations could be tested and compared regarding the formation of a film on the skin, thus decreasing its roughness.[21]

Based on the results, it was verified that the FC formulation was more prone to decrease the skin's roughness, thus indicating that the cassava's polysaccharides were effective in forming a film on the skin, which contributed to improve its microrelief.

These results were in line with the stratum corneum's water content analysis, as well as with the sensory analysis, where it was evidenced that the patients perceived increased softness of the skin 5 minutes after applying the FC formulation. Therefore, the improvement in the skin's microrelief resulting from decreased roughness and the formation of film was more pronounced in FC as compared to FA, especially according to the patients' perception of effectiveness.

The immediate tightening effect attributed to the cassava's polysaccharides confirms the outcomes previously observe by the authors' research group, [31] which had already used the same device to verify the cassava extract's immediate tightening effect in a gel formulation.

In summary, according to the analysis of the obtained results, it was possible to demonstrate the importance of the set of techniques employed in the present study for the development of an effective formulation with good sensory acceptance. Thus,

knowledge of the interaction between the formulation and the skin is critical, for the adherence to the treatment and the proven clinical effectiveness of a cosmetic formulation are strongly correlated to the success of a medical prescription.

CONCLUSION

The application and correlation analysis of the techniques employed allowed specifying and obtaining a formulation with proven sensorial acceptance and clinical effectiveness for the improvement of the skin's texture and hydration. In this manner, the present study contributes for the dermatologic field, given that appropriate sensory characteristics helps the patient to adhere to the use of the product, therefore favoring the treatment's success.

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Original Articles

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Monocentric prospective study for assessing the efficacy and tolerability of a cosmeceutical formulation in patients with melasma

Estudo monocêntrico, prospectivo para avaliar a eficácia e a tolerabilidade de formulação cosmecêutica em pacientes com melasma

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ABSTRACT

Introduction: Melasma is a common pigmentary condition that affects exposed body areas, especially in the frontal and malar regions. Hydroquinone is an effective active principle in the treatment of hyperpigmentation, however, due to issues linked to its tolerability, many studies are being conducted aimed at developing alternative therapies with equivalent effectiveness.

Objective: To evaluate the efficacy and tolerability of a cosmeceutical formulation containing ellagic acid, hydroxyphenoxy propionic acid, yeast extract and salicylic acid in Brazilian patients with mild to moderate melasma.

Methods: Forty patients with mild to moderate melasma on the face used the cosmeceutical twice daily, combined with sunscreen for 90 days. Subjective assessments of efficacy and tolerability were carried out. Measurements of the MASI grade and the application of the MELASQoL-BP questionnaire were also performed. The evaluation of the skin's brightness and the colorimetric characteristics were obtained by colorimetry.

Results: After 90 days of treatment, a significant improvement could be observed in the clinical and colorimetric parameters evaluated, and in the quality of life questionnaire. In addition, the MASI score improved by 43%. The treatment was effective without causing adverse events.

Conclusions: The evaluated cosmeceutical formulation was proven as an effective alternative to hydroquinone for the treatment of melasma, with excellent cutaneous tolerability profile.

Keywords: hyperpigmentation; melanosis; bleaching agents

RESUMO

Introdução: *O melasma é doença pigmentar frequente que acomete áreas expostas, principalmente nas regiões frontal e malar. A hidroquinona se mostra ativo eficaz no tratamento da hiperpigmentação; no entanto, devido a problemas com sua tolerabilidade, diversos estudos são conduzidos para desenvolver alternativas terapêuticas com eficácia equivalente.*

Objetivo: *Avaliar a eficácia e tolerabilidade de formulação cosmecêutica contendo ácido elágico, ácido hidroxifenoxi propiônico, extrato de levedura e ácido salicílico em pacientes brasileiros apresentando melasma leve a moderado.*

Métodos: *40 pacientes portadores de melasma leve a moderado na face utilizaram o cosmecêutico duas vezes ao dia, associado a filtro solar durante 90 dias. Foram feitas avaliações subjetivas de eficácia e tolerabilidade, medida do grau Masi e questionário MelasQoL-BP. A avaliação da luminosidade da pele e das características colorimétricas foram obtidas por meio de colorimetria.*

Resultados: *Após 90 dias de tratamento, observou-se melhora significativa nos parâmetros clínicos avaliados, nos parâmetros colorimétricos, no questionário de qualidade de vida e no escore Masi em 43%. O tratamento se mostrou eficaz sem causar eventos adversos.*

Conclusões: *A formulação cosmecêutica avaliada demonstrou ser alternativa eficaz à hidroquinona para o tratamento do melasma com excelente perfil de tolerabilidade cutânea.*

Palavras-chave: *hiperpigmentação; melanose; clareadores*

INTRODUCTION

Melasma is a frequent pigmentary disease that manifests as symmetrical hyperpigmented macules on the skin,[1] and affects exposed body areas, especially the frontal and malar regions.[2,3]

With a 90% prevalence in women, it mainly occurs during their reproductive age.[4,5] It has higher prevalence in individuals of East Asian and Hispanic origins, as well in patients with high Fitzpatrick skin phototypes (IV to VI), and particularly in individuals who live in locations where incidence of UV radiation is intense.[4,6-8]

Melasma can still be classified according with its clinical and histologic characteristics.[9] Regarding the body site, the pigment may be located in the epidermis, dermis or in both (mixed location).[10-12] The relevance of this classification dwells is the fact that it can be instrumental in determining the most adequate treatment and prognosis.[1,13] In fact, the dermal compartment is capable of controlling cutaneous pigmentation, since the latter is regulated by a complex melanogenic network in which both keratinocytes and fibroblasts synthesize growth factors and cytokines, such as the hepatocyte growth factor (HGF), the keratinocyte growth factor (KGF) and the stem cell factor (SCF), which in turn directly influence pigmentation.[14,15]

There are several therapeutic options for the treatment of melasma that act at different stages of melanogenesis. Among the inhibitors of the tyrosinase enzyme is hydroquinone, and azelaic and kojic acids. Topical corticosteroids act as non-selective suppressors of melanogenesis. The action of azelaic acid inhibits the reactive oxygen species, since some studies suggest that free radicals lead to increased production of melanin by melanocytes. There are also options of direct removal of melanin using procedures such as peels.[2]

Hydroquinone is still deemed as the most effective active principle in skin whitening treatments. Nevertheless, several studies are being conducted aimed at developing skin hyperpigmentation treatment alternatives with similar effectiveness, since many patients have poor tolerability and experience adverse events – such as ochronosis – and public health agencies – such as the FDA – has indicated the presence of issues involving hydroquinone's safety. An alternative to increase the whitening effect of these other molecules is to combine them in a single formulation.[16,17]

In a 12-week investigator-blind study, Draelos et al. demonstrated that a cosmeceutical formulation containing ellagic acid, hydroxyphenoxy propionic acid, yeast extract and salicylic acid was as effective as the combination of 4% hydroquinone and 0.025% tretinoin in improving the skin's hue, decreasing the spots' intensity and size and improving pigmentation in general.[17] The tolerability problems experienced with the combination of 4% hydroquinone and 0.025% tretinoin (dry skin, for instance) were not observed with the new cosmeceutical.[17]

Another study by Draelos et al. demonstrated that the same cosmeceutical formulation was also effective in maintaining the results obtained with the combination of 4% hydroquinone and 0.025% tretinoin during the summer. The patients also had significant improvement in the skin's hue ($p < 0.001$), intensity and size of spots ($p < 0.001$ and $p < 0.05$, respectively) and overall hyperpigmentation ($p = 0.002$).[18]

Hydroxyphenoxy propionic acid led to a significant decrease in melanin production by melanocytes in an *in vitro* model, without affecting its viability.[19] A diverse depigmenting mechanism involving this active principle is the transfer of melanin from the melanocyte cell to the keratinocyte.[17] Ellagic acid is also an inhibitor of melanin production, and is found in many fruits, such as strawberries and raspberries. This active principle has a powerful antioxidant in plants and an antioxidant and anti-inflammatory in humans.[17] A randomized study involving 54 patients showed that after 12 weeks, the treatment combining 0.5% ellagic acid with 0.1% salicylic acid is as effective as 4% hydroquinone.[16]

The yeast extract is obtained from cells of *Saccharomyces cerevisiae,* and its action mechanism consists in stimulating lysosomal degradation in the keratinocytes, which can assist in the degradation of melanin.[17] Moreover, the yeast extract stimulates dermal fibroblasts, lending resistance to pigmentation recurrence to he skin.[18]

Salicylic acid acts increasing the skin penetration of the active principles described above, facilitating cutaneous exfoliation and the desquamation of keratinocytes containing melanin pigments.[17]

The present study was aimed at evaluating the effectiveness and tolerability after 90 days of treatment with a cosmeceutical formulation containing ellagic acid, hydroxyphenoxy propionic acid, yeast extract and salicylic acid (Advanced Pigment Corrector, SkinCeuticals, New York, United States) in Brazilian patients with melasma.

METHODS

A monocentric, prospective, open clinical study was carried out with 40 patients (men and women, aged 18 to 55 years) clinically diagnosed with mild to moderate facial melasma for at least 12 months, with absence of uniformity in the skin's hue. The participants were instructed to use the investigated product twice a day (in the morning and in the evening), associated with sunscreen SPF 50 in the morning (Physical Fusion UV Defense SPF 50, SkinCeuticals) and neutral cleansing soap. The study lasted 90 days, with evaluations at 30, 60 and 90 days of treatment.

The study was conducted according to the standards of Good Clinical Practice (GPC), the international research standards for research with humans (Declaration of Helsinki), the resolution No 196 (10/10/1996) of the Brazilian National Health Council and amendments, having been approved by the Research Ethics Committee of the Universidade São Francisco (Bragança Paulista, SP, Brazil).

The selected patients underwent a dermatological clinical evaluation on the first visit for confirmation of the inclusion and exclusion criteria. All patients were instructed to use the investigated product according to the study protocol's recommendations, and answer the effectiveness subjective evaluation

questionnaire and melasma patients quality of life questionnaire (MelasQoL-BP).[20,21]

Participants also underwent a standardized frontal view photograph (Visia® device), for the measurement of the main spot with the colorimeter Konica Minolta model CR400.

MASI – Melasma Area and Severity Index

In order to compute the MASI score, the evaluation of the hyperpigmented areas of the face was firstly carried out. For that end, the face was subdivided into four areas: frontal (F), right malar (RM), malar left (LM) and jaw (M), corresponding to 30%, 30%, 30% and 10% of the total area, respectively. The evaluation was preformed using standardized photographs obtained by the Visia® device.

The melasma in each of the four areas received numerical ratings ranging from 1 to 6: 1 (<10%), 2 (10-29%), 3 (30-49%), 4 (50-69%), 5 (70-89%) and 6 (90-100%). The pigment's intensity as compared to that of the normal skin (D) was evaluated in each area on a scale of 0 (absent) to 4 (severe). Likewise, the pigment's homogeneity (H) was evaluated on a scale from 0 (minimum) to 4 (maximal). The computation of the MASI score corresponded to the sum of the severity ratings for D and H, multiplied by the numerical value of the involved area (A). The maximum score was 48, and the minimum was 0.

Standardized photographs

The Visia® device was used on D0, D30, D60 and D90 to perform photographic records of the participants' face (frontal view) and evaluate the following attributes: *total spots*, *spots visualized under UV radiation* and *brown spots*.

Colorimetry

A Konica Minolta CR400 colorimeter was used on D0, D30 D60 and D90 for gauging the participants' facial skin coloration parameters. The device's light source generates different incidence angles, and the internal sensor receives the light reflected vertically by the surface in the color spectrum (Cielab, 1976). The present study evaluated the following parameters: L* (luminosity, ranging from 0 to 100, with values close to 0 representing darker colors and values close to 100 representing lighter/white colors); and ITA, which is the individual typological angle obtained by the formula ITA° = [Arc Tangent ((L* - 50) / b*)] 180 / π. The angle ITA° is proportionally related to the skin's pigmentation, with narrower angles indicating greater pigmentation and wider angles, lesser pigmentation. The evaluated area was selected and properly recorded by dermatologist physicians in the D0 visit, with three points from this area being evaluated in all visits. The value recorded was the average of the three points.

Melasma Patients Quality of Life questionnaire - MelasQoL-BP

Skin conditions like melasma can lead to a significant impact on the bearer's social, family and professional life, therefore quantifying this influence on the patient's quality of life is highly relevant. The MelasQoL was designed and validated in the English language and assists in the collection of valuable information on the impact of the pigment alterations on the quality of life. It consists of systematic form with 10 questions (Chart 1). The answer to each question ranges from 1 to 7, according to the melasma's impact on the patient's quality of life. In the present study, the participants were instructed to answer the questionnaire's Brazilian Portuguese language version (MelasQoL-BP, validated and published on the British Journal of Dermatology), on D0 and D90.[2]

Subjective assessments

The subjective evaluations were based on the physician's and patient's perceptions, and comprised effectiveness and safety evaluations of the investigated product. The subjective safety evaluations were performed at D0, D30, D60 and D90, when the physician focused on the following attributes of the patients' facial skin: *erythema*, *edema*, *dryness* and *desquamation*. The self-assessment carried out by the participants evaluated the following attributes: *stinging*, *tingling*, *itching* and *burning sensation*.

The subjective clinical assessment consisted in completing a comprehensive evaluation questionnaire on the clinical response after the dermatological analysis of the photographs

Chart 1: MelasQoL-BP model used in the study. The patient must answer each question with ratings ranging from 1 to 7, according to the impact on his or her quality of your life

1 - Not bothered at all
2 - Not bothered most of the time
3 - Not bothered sometimes
4 - Neutral
5 - Bothered a few times
6 - Bothered most of the time
7 - Bothered all of the time

Considering the condition you have, melasma, how do you feel about:

1 – The appearance of your skin ❑
2 – The frustration caused by your skin's conditions ❑
3 – The embarrassment caused by your skin's condition ❑
4 - Feeling depressed due to your skin's condition ❑
5- The effects of your skin's condition on your relationship with people (e.g. interaction with family and friends, intimate relationships..) ❑
6 - The effects of your skin's condition on your desire to be with people ❑
7 - The effects of your skin's condition makes it difficult to show affection? ❑
8 – The spots on your skin make you do not feel attractive to others ❑
9 - The spots on your skin make you feel less important or productive ❑
10 - The spots on your skin affect your sense of freedom ❑

TOTAL

taken at D0, D30, D60 and D90. The investigator dermatologist physician answered to the questionnaire evaluating the following attributes: *hyperpigmentation*, *intensity of spots*, *coloration homogeneity*, *imperfections*, *texture*, *lushness*, *luminosity*, *hydration*, *smoothness*, *general appearance*, *erythema*, *edema*, *dryness* and *desquamation*. The dermatologist physician's subjective evaluations were based on the photographs taken with the Visia® device.

For the assessment of the perceived effectiveness, the participants were asked to answer the questionnaire, which was aimed at capturing their opinion on the initial condition of their skin, as well as their perception regarding the improvement or worsening of the attributes during and after using the product. The questionnaire was applied on D0, D30, D60 and D90, with the following attributes: *imperfections*, *texture*, *hydration*, *smoothness*, *general appearance*, *amount of spots* and *intensity of spots*.

Statistical analysis

The effectiveness evaluations were performed on the 34 participants who completed the treatment, with the results from the subjective questionnaires and objective analyzes being assessed.

Descriptive statistics (i.e. mean, median, standard deviation, minimum and maximum values) were drawn from the participants' data (age, skin phototype, ethnicity). Regarding the categorical variables, the number of and percentage of individuals were provided for each answer category.

The Kruskal-Wallis paired test and the Dunn's multiple comparisons test were used for the analysis of the clinical questionnaire.

The marginal homogeneity test was used for the analysis of the questionnaires answered by the patients.

The Wilcoxon signed rank test for paired data was used for the analysis of the MelasQoL-BP.

For the assessment of the results obtained from the objective analysis and the MASI questionnaire, the ANOVA for repeated measures was used, followed by the contrast profile test, aiming at analyzing the development between visits. The data were converted into ranks due to the absence of normal distribution.

The adopted significance level was 5%.

RESULTS

Study patients' profile

Forty patients were included and evaluated at baseline. After the 90 days, 34 patients completed the study; most of them were skin phototype III and IV women, with an average age of 43 years (min = 26 years, max = 55 years) (Table 1).

Figure 1 shows standardized photographs of patients #007 and #022, obtained with the Visia® device at T0 and T90 experimental timepoints. A significant improvement in the skin coloration's uniformity and a decrease in the spots' intensity can be observed.

MASI – Melasma Area and Severity Index

The analysis of MASI scores showed statistically significant reductions both throughout the study period and between the experimental timepoints. At the end of the 90th day of the study, a statistically significant decrease of 43% in the MASI grade of melasma as compared to the baseline. Graph 1 depicts the values obtained from the Masi measurements.

Colorimetry

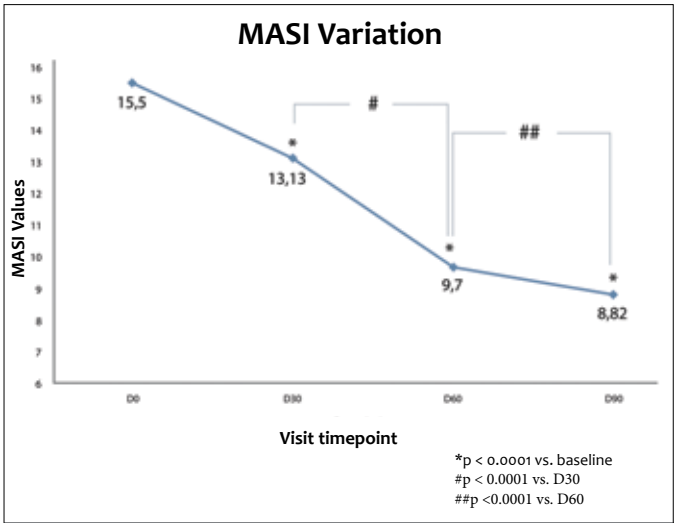
The analysis of colorimetric measurements showed a statistically significant increase in the skin's luminosity immediately after the 60 days of treatment ($p < 0.0001$ vs. baseline) and after 90 days of treatment ($p < 0.0001$ vs. baseline). The same could be observed for the visual typological angle (ITA), where there was a statistically significant increase immediately after 60 days of treatment ($p < 0.0001$ vs. baseline) and after 90 days of treatment ($p < 0.0001$ vs. baseline). Graphs 2 and 3 summarize the luminosity and ITA values for all experimental timepoints.

Table 1: Profile of the volunteers who completed the study (N = 34)

	Frequency		%
Phototype	II	3	8,82
	III	16	47,06
	IV	14	41,18
	V	1	7,94
Gender	Female	34	100
Age	Average	43	na
	Range	26 to 55	na

MASI – Melasma Area end Severity Index

MASI – Melasma Area end Severity Index



GRAPH 1: MASI values in all experimental timepoints

There was a significant and progressive decrease in all measurement timepoints ($p < 0.0001$ in all timepoints). After 90 days of study, there was a 43% decrease in the MASI scale as compared to the baseline ($p < 0.0001$)

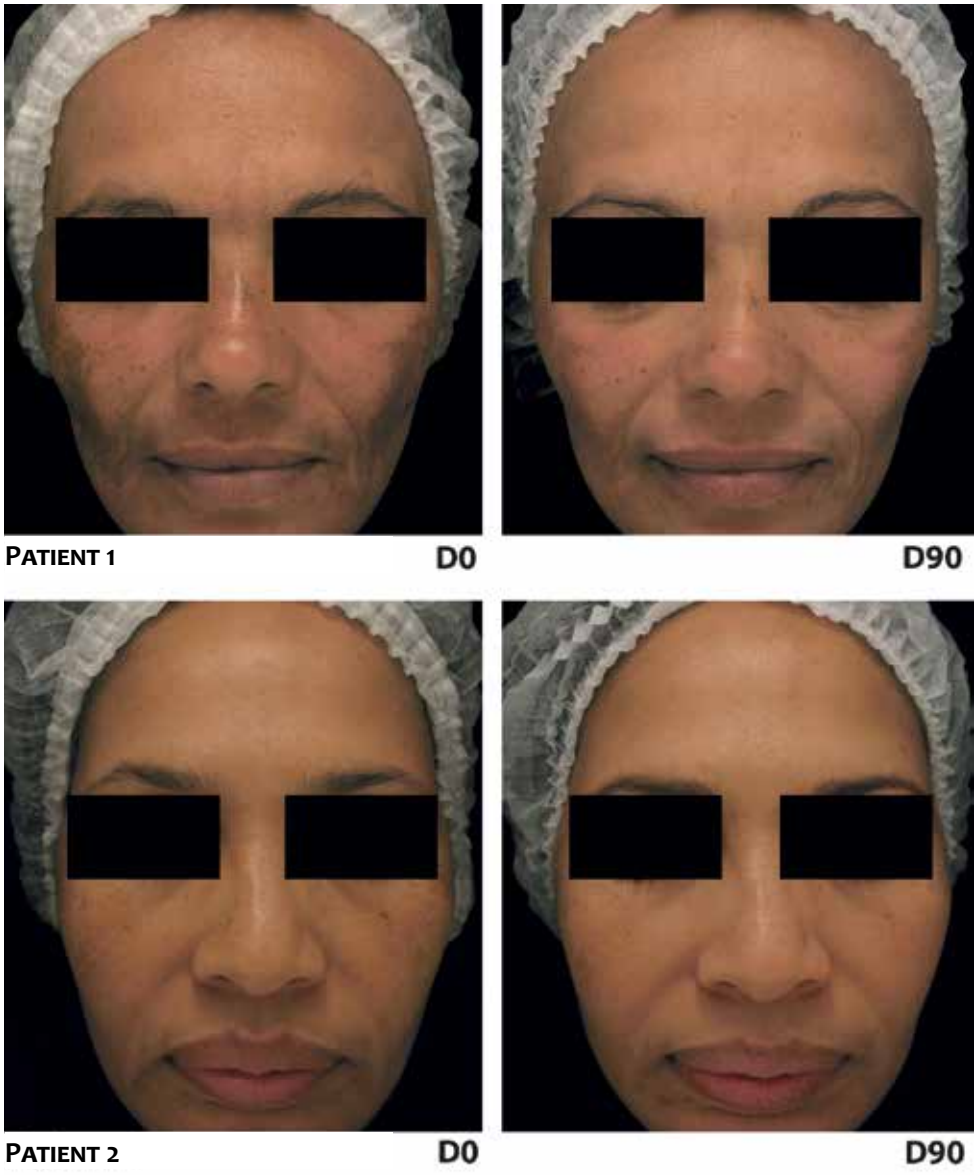


FIGURE 1: Photographs of patients #007 and #022 at baseline and after 90 days of treatment with the cosmeceutical product. It is possible to observe reductions both in the intensity and size of the spots. There is also improvement in the skin's homogeneity of coloration and luminosity

Visia®

The score provided by the Visia® device offers an arbitrary global measure of the impact that the occurrence of a specific characteristic has on the patient's skin, taking into account, for this measurement, the size, total area and intensity of the characteristic in question – which in the present study were brown spots, total spots and spots visualized under UV radiation.

The results regarding brown spots evidenced a significant reduction in the score after 30 days of treatment ($p < 0.0001$ vs. baseline), 60 days ($p < 0.0001$ vs. D30) and 90 ($p < 0.0001$ vs. D30). Regarding the total spots, there was a significant reduction in the score immediately after 30 days of treatment ($p < 0.012$ vs. baseline) and 90 days of treatment ($p < 0.0252$ vs. baseline). Graph 4 and 5 summarize the values obtained with the Visia® device for brown and total spots.

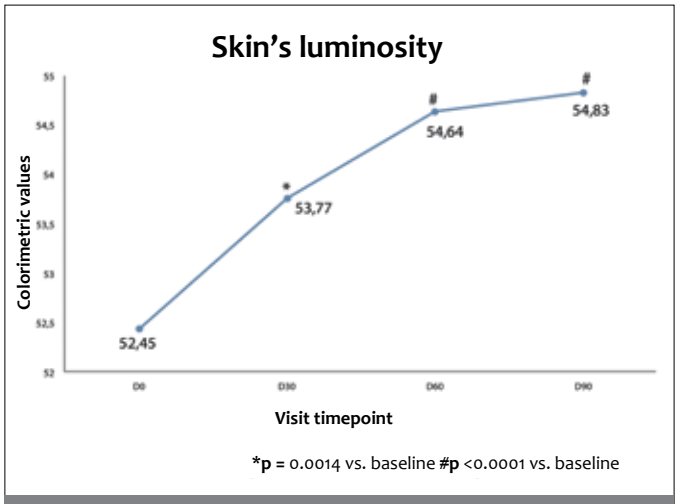
For the spots visualized under UV radiation, there was no significant difference in the results during the study period.

Melasma Patients Quality of Life questionnaire - MelasQoL-BP

After 90 days of study, there was a significant reduction of 23.1% ($p < 0.0001$) in the overall MelasQoL-BP index (Graph 6), indicating that the investigated product provided a reduction of the impact on the patients' quality of life, observed in 79.4% of participants.

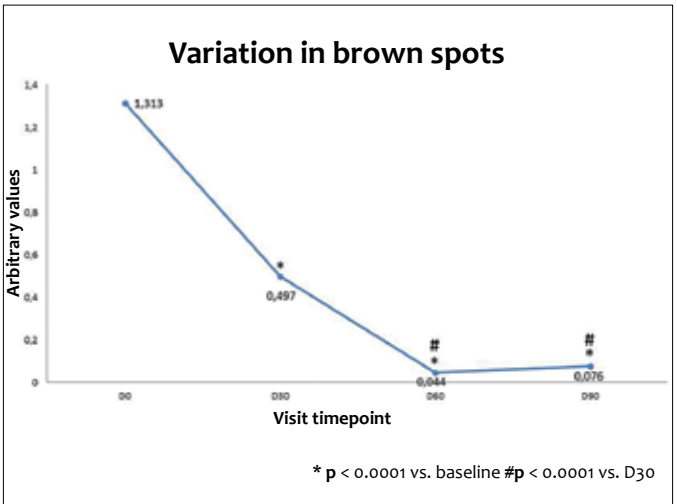
Subjective clinical evaluation

After 90 days using the investigated product, it was possible to observe a statistically significant improvement in hyperpigmentation ($p = 0.0237$), intensity of spots ($p < 0.0003$), col-



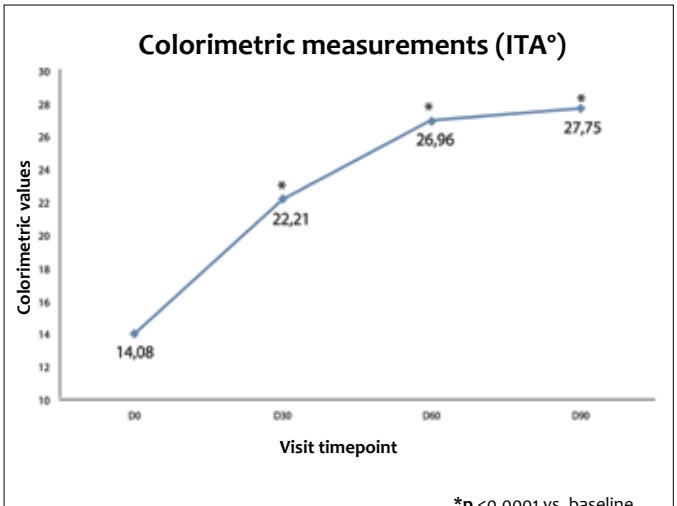
Graph 2: Luminosity values (L) for all experimental timepoints

After the 30th day of the study it was already possible to observe a significant difference in the skin's luminosity. After the 90th day of the study, the outcomes regarding the skin's luminosity improved significantly as compared to D0 ($p < 0.0001$)



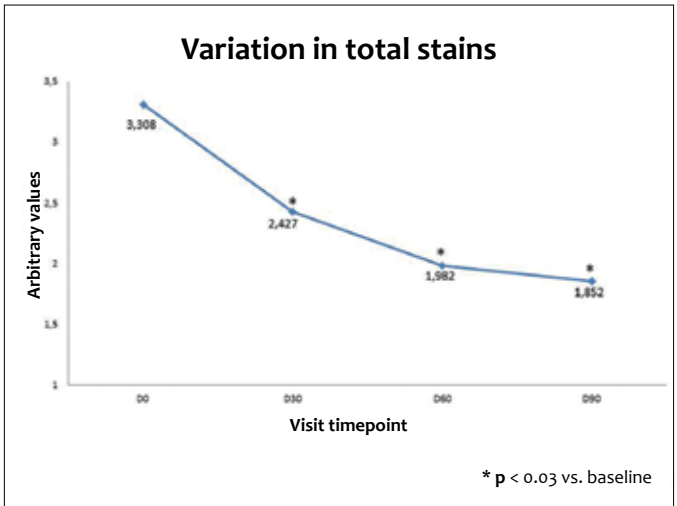
Graph 4: Brown spots values obtained with the Visia® device for all experimental timepoints

After the 30th day of the study it was possible to observe a significant decrease in brown spots. After the 90th day of the study, there was a significant reduction in brown spots as compared to D30 ($p < 0.0001$)



Graph 3: Colorimetry measurements (ITA) for all experimental timepoints

It was possible to observe a significant difference for all colorimetric measurements ITA° in all experimental timepoints. ($p < 0.0001$)



Graph 5: Total spots values obtained with the Visia® device for all experimental timepoints

After the 30th day of the study it was possible to observe a significant decrease in total spots. After the 90th day of the study, there was a significant decrease in brown spots compared to D30 ($p < 0.0001$)

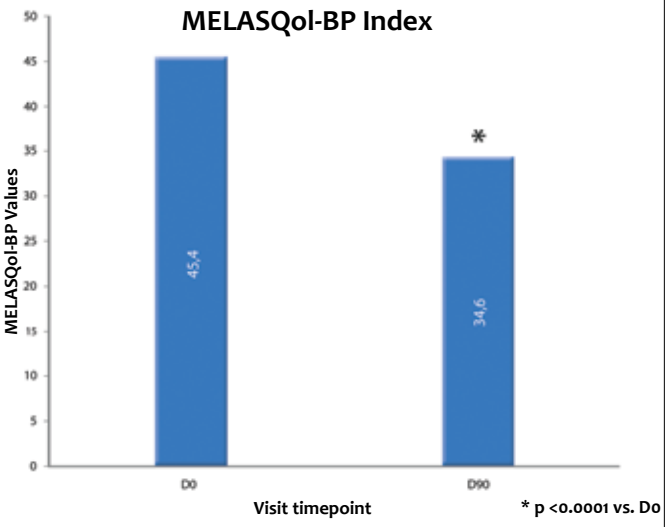
oration homogeneity ($p = 0.0005$), imperfections ($p = 0.0004$), general appearance ($p = 0.0006$), luminosity ($p = 0.0003$), lushness ($p < 0.0001$), texture ($p < 0.0001$), smoothness ($p < 0.0001$) and hydration ($p = 0.0016$). Table 2 shows the results of the Dunn's test for multiple comparisons at intermediate timepoints. There was significant improvement immediately after 30 days in texture, lushness and smoothness, and after 60 days in intensity of spots, coloration homogeneity, imperfections, luminosity and hydration.

Patients' perceived effectiveness

After 90 days of product use, the patients reported statistically significant improvement in the intensity of spots ($p = 0.0001$), imperfections ($p = 0.0016$), general appearance ($p = 0.0025$), and texture ($p < 0.0001$). These results were statistically significant.

Tolerability

The tolerability to the studied cosmeceutical was deemed



Graph 6: Overall values obtained with the MelasQoL-BP questionnaire after 90 days of treatment vs. baseline

After 90 days there was significant decrease ($p < 0.0001$) of 23.1% in MelasQoL-BP, indicating that the investigated product decreased the impact caused by melasma on the patients' quality of life

excellent by all participants in all visits. No erythema, edema, dryness or desquamation was observed during the treatment with the investigated cosmeceutical. Furthermore, during the 90 days of study, there were no reports of stinging, tingling, itching or burning sensation.

DISCUSSION

Of the various options for the treatment of melasma, hydroquinone is still the gold standard therapy. However, there are many adverse events related to its use, such as redness, skin dryness and photosensitivity. Its cytotoxicity is linked to the inhibition of DNA and RNA synthesis, abnormal melanosome formation and metabolic suppression of melanocytes.[22]

The present study was aimed at evaluating the effectiveness and tolerability profile of a cosmeceutical formulation containing ellagic acid, hydroxyphenoxy propionic acid, yeast extract and salicylic acid (Advanced Pigment Corrector, SkinCeuticals, New York, United States of America) in the treatment of mild to moderate melasma.

A treatment's depigmenting effectiveness requires the combination of active principles capable of acting on different stages of melanogenesis – including the dermal compartment – since it interferes in the pigmentation's physiology via growth factors and cytokines, as described by Kovacs et al.[14] The cos-

Table 2: Dunn's multiple comparisons test on intermediate timepoints (D30 and D60). A significant improvement was observed in the skin's texture, lushness and smoothness immediately after 30 days, and in intensity of spots, homogeneity of coloration, imperfections, luminosity and hydration after 60 days of treatment

	Hyperpigmentation			Homogeneity of coloration	
	Significant?	Summary		Significant?	Summary
Do vs D30	no	ns	Do vs D30	no	ns
Do vs D60	no	ns	Do vs D60	yes	***
Do vs D90	yes	*	Do vs D90	yes	**
Intensity of spots	Luminosity				
	Significant?	Summary		Significant?	Summary
Do vs D30	no	ns	Do vs D30	no	ns
Do vs D60	yes	*	Do vs D60	yes	*
Do vs D90	yes	****	Do vs D90	yes	**
Texture	Imperfections				
	Significant?	Summary		Significant?	Summary
Do vs D30	yes	**	Do vs D30	no	ns
Do vs D60	yes	****	Do vs D60	yes	*
Do vs D90	yes	****	Do vs D90	yes	***
Hydration	General aspect				
	Significant?	Summary		Significant?	Summary
Do vs D30	no	ns	Do vs D30	no	ns
Do vs D60	yes	*	Do vs D60	no	ns
Do vs D90	yes	***	Do vs D90	yes	**
Lushness	Smoothness				
	Significant?	Summary		Significant?	Summary
Do vs D30	yes	**	Do vs D30	yes	*
Do vs D60	yes	****	Do vs D60	yes	****
Do vs D90	yes	****	Do vs D90	yes	****

meceutical formulation has a combination of active principles that will act on different stages of the melanogenesis: tyrosinase inhibition and transfer of melanocyte melanin to keratinocytes (ellagic and hydroxyphenoxy propionic acids), cell renewal stimulation and stratum corneum exfoliation (salicylic acid), and fibroblast stimulation in the dermis (yeast extract), lending resistance to pigmentation recurrence to the skin.

The present study evidenced significant outcomes in the clinical and instrumental evaluations, as well as in the effectiveness perceived by the patients. A statistically significant reduction of 43% was obtained in the MASI score after 90 days of treatment, which could also be observed in the standardized photographs.

Colorimetry data also showed interesting outcomes linked to increases in the cutaneous luminosity and the ITA angle, instrumentally confirming the decrease in skin pigmentation. Further studies should evaluate other parameters, such as a^*, which quantifies the reddish hues of the skin linked to the vascular component of melasma, since it was possible to observe a clinical reduction of skin redness in some patients, which is interesting to consider when treating pigmentary conditions such as melasma. A previous study conducted by Kin et al. showed an increase in both the number and the caliber of blood vessels, as well as increased expression of the pro-angiogenic factor VEGF (vascular endothelial growth factor) in the sites affected by melasma, confirming the relevance of future research in this field.[23]

The data obtained from the MelasQoL- BP questionnaire indicate a significant decrease in the impact on the patients' quality of life after 90 days, meaning a better adherence to daily treatment using the studied product. It is also worth noting that the decrease of the impact on the patients' quality of life was observed in almost 80% of the study patients.

Another important factor that should be taken into consideration in the treatment of hypermelanoses is the formulation's tolerability. The cosmeceutical formulation presented a good safety profile throughout the study's duration, with absence of reports of adverse events, therefore arising as an interesting alternative to be used as a monotherapy or maintenance treatment during the summer.

CONCLUSION

The treatment of melasma remains a major challenge in dermatology. At the same time, a great number of new active principles emerge, with possible whitening action. As a result, it is necessary to carry out studies that demonstrate these substances' therapeutic effectiveness and safety profile. According to instrumental and clinical data, as well as the patients' perception, the cosmeceutical formulation evaluated in the present study containing ellagic acid, hydroxyphenoxy propionic acid, yeast extract and salicylic acid was proven an effective alternative to hydroquinone for the treatment of melasma, with an excellent cutaneous tolerability profile.

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Original Articles

Pulsed Radiofrequency with Multineedles (RFPM®) in the treatment of atrophic stretch marks

Radiofrequência pulsada com multiagulhas (RFPM®) no tratamento de estrias atróficas

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ABSTRACT

Introduction: Atrophic stretch marks constitute skin disorders characterized by the loss of collagen and elastin in the dermis, and resemble scars. Fractional lasers, microneedling and chemical peels have led to good outcomes in some cases, however there is no ideal treatment.
Objective: The objective of the present retrospective clinical study was to evaluate the effectiveness of Pulsed Radiofrequency with Multineedles (RFPM®) in late atrophic stretch marks.
Methods: A retrospective study of the safety and effectiveness of the technique was carried out by evaluating outcomes with the application of a patient satisfaction questionnaire and the assessment of clinical results by independent dermatologist physicians.
Results: A total of 8 patients (aged between 22 and 38 years) who underwent the technique were evaluated, of whom 100% reported satisfaction with the outcomes. Additionally, in the comparative evaluation of photographs carried out by two independent dermatologist physicians, the improvement rate was 50% in 2 patients and 75% in 8 patients . Post-inflammatory hyperpigmentation was observed in 10 to 20 days after the treatment in 6 patients, having been reversed after clinical treatment.
Conclusions: The new procedure is an option in the treatment of atrophic stretch marks.
Keywords: striae distensae; pulsed radiofrequency treatment; collagen

RESUMO

***Introdução**: As estrias atróficas representam alterações cutâneas caracterizadas pela perda de colágeno e elastina na derme, assemelhando-se a cicatrizes. Lasers fracionados, microagulhamento e peelings químicos têm apresentado bons resultados em alguns casos, mas não há um tratamento ideal.*
***Objetivo:** Avaliar a eficácia da radiofrequência pulsada com multiagulhas (RFPM®) em estrias tardias atróficas.*
***Métodos:** Estudo retrospectivo da segurança e efetividade da técnica mediante avaliação dos resultados por aplicação de questionário de satisfação aos pacientes e julgamento dos resultados clínicos por dermatologistas independentes.*
***Resultados:** Foram avaliados oito pacientes com idade entre 22 e 38 anos, submetidos à técnica, 100% dos quais relataram satisfação com os resultados, enquanto na avaliação comparativa das fotografias por dois dermatologistas independentes o índice de melhora foi de: 50% em dois pacientes e 75% em seis pacientes. A hiperpigmentação pós-inflamatória foi observada de dez a 20 dias após o tratamento em seis pacientes, tendo sido revertida após tratamento clínico.*
***Conclusão:** Esse novo procedimento se apresenta como alternativa ao tratamento de estrias atróficas.*
***Palavras-chave:** estria por distensão; tratamento por radiofrequência pulsada; colágeno*

INTRODUCTION

The treatment of stretch marks is always a challenge, and good outcomes become even more difficult when treating old and atrophic lesions. Often resulting from skin stretching and rupture of collagen and elastic fibers in the dermis, late stretch marks arise as scars, with substantial compromise of the texture, relief and color of the involved skin.[1,2]

Some regions are more easily prone to stretch marks: lumbosacral and flanks in men, and abdomen, hips and breasts in women. Conditions such as pregnancy, weight gain, muscle hypertrophy and pubertal growth spurt, as well disorderly oral and topical corticosteroids, and diseases such as Cushing syndrome, are favoring factors.[3]

Several treatments have been proposed, offering better results in striae rubra (recent stretch marks) as compared to those obtained in striae alba (late/atrophic stretch marks). Topical tretinoin, peels, microneedling, microdermabrasion, fractional lasers and intense pulsed light are some of the treatment options used in dermatology for approaching these lesions. Nevertheless, there is no treatment that can be considered ideal, and the often poor outcomes indicate the presence of a challenge.[4,5]

Based on the findings obtained with the treatment of eyelids sagging, the author set out on the search for the applicability of pulsed radiofrequency with multineedles (RFPM®) in cases of old stretch marks. The present study is the result of these observations.[6,7]

Pulsed radiofrequency with multineedles (RFPM®)

The use of random high frequency fractional energy shot on the skin results in dermal regeneration in the papillary-reticular interface via the stimulation of fibroblasts with subsequent synthesis of collagen and elastic fibers, as well as epidermal regeneration caused by the migration of keratinocytes.

The author of the present paper proposes an innovative approach to skin rejuvenation, based on sub ablative energy delivered by electrodes with multiple needles, connected to a radioelectrosurgery device.

This technique, performed accurately and in a punctate way, it does not compromise the tissue adjacent to the vaporized microdots and causes significant tissular impact, thus enabling the stimulus for new collagen.

In order to perform the RFPM®, electrodes called Lima 2, Lima 4 and Lima 8 (nomenclature which refers to the author), are necessary. They respectively consist of two, four or eight tungsten needles, with a diameter of 100 thousandths of a millimeter and identical weights and lengths, arranged in parallel, in a way that they reach the same depth when in use. With 2.5mm in length, these needles will slide across the epidermis and act in the dermis, stimulating the collagen's contraction and renewal.

The objective of the present retrospective clinical study was to evaluate the effectiveness of RFPM® in late atrophic stretch marks.

METHODS

Medical records of 8 female patients with atrophic stretch marks who underwent RFPM® were assessed. The procedures were performed by the same physician on an ambulatorial setting, between February and December 2015. The photographic record was carried out with the same digital camera, under the same technical conditions, immediately before and two months after a single intervention. The study was conducted according to the ethical standards of the Helsinki Declaration.

After antisepsis with 1% chlorhexidine, injections were performed in the area of the stretch marks with 2% lidocaine, without vasoconstrictor. The RFPM® application was carried out with the FRAXX® device (Loktal Medical Electronics, São Paulo, Brazil - Anvisa No. 10362610008), operating in the single pulse mode and with parameters set based on the research performed during 12 months. The patients in this group were treated with the device set on CUT mode (power = 30, active = 30ms) and the Lima 8 electrode was used, aligned with the linear path of the stretch marks. Only one pass was carried out and, in order to avoid overlapping, four parallel rows of micropunctures on average were performed with the electrode. The stretch marks must be fully treated in their thickness (Figure 1).

After the procedure the patients received dressings with micropored tape, which was removed on the following day. For the post-operative period, instructions were given for the patients to use skin regenerator (Ciclapast baume®, La Roche-Po-

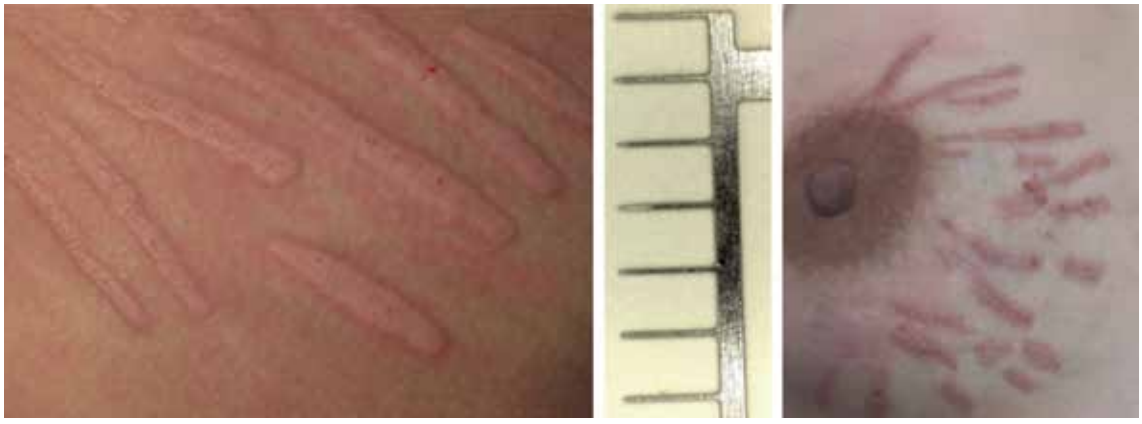

Figure 1: RFPM®'s immediate postoperative period and electrode with 100µ needles in great magnification

say, Rio de Janeiro, Brazil) twice a day, in addition to commercial sunscreen SPF 60, which should be used even in covered areas.

The analysis of the outcomes was performed based on patient satisfaction questionnaires while the rating of the clinical outcomes was carried out by independent dermatologist physicians, two months after the intervention.

The patients' self-assessment questionnaire included questions about the degree of satisfaction with the procedure, measured using the categories *bad*, *reasonable*, *good* and *very good*.

The pictures of before and 60 days after the intervention were assessed by two independent dermatologist physicians, who used the following scale: *regular* (25% improvement), *good* (50% improvement), *very good* (75% improvement) and *excellent* (100% improvement).

RESULTS

Eight female patients between 22 and 38 years of age recruited at the author 's private practice and at the Cosmiatry Ambulatory of the Santa Casa de Misericórdia do Recife (Recife, PE, Brazil) were evaluated. The patients' Fitzpatrick phototypes ranged from II to IV. Fifty percent of the studied lesions were located in the abdomen, 30% in the buttocks and 20% in the breasts.

All patients reported satisfaction with the outcomes, attributing the *good* and *very good* ratings as answers to the proposed questions.

In the comparative evaluation of photographs of the before and after the procedure timepoints – which were performed by two independent dermatologist physicians – the improvement index was: 50% = *good* in 2 patients and 75% = *very good* in 6 patients (Figure 2).

The pain felt during the treatment was tolerable, and tissue regeneration could be observed between 5 and 7 days after the procedure. Return to work was possible 24 hours after. There were no occurrences of infections, dyschromias or unsightly scars in this group.

Mild to moderate post-inflammatory hyperpigmentation was observed after a period of 10 to 20 days of the treatment in 6 (of 8) patients, having been resolved in 30 to 45 days with the use of whitening formulations.

DISCUSSION

The currently large and available therapeutic armamentarium for the treatment of stretch marks provides satisfactory results in recent striae rubra, however when these lesions progress from the inflammatory phase into a late phase, with histology similar to that seen in scars with substantial degradation of collagen and elastic fibers, the treatment becomes problematic.[4,5]

In this way, the author of the present paper proposes the RFPM® for the treatment of late atrophic striae, a methodology thoroughly developed and studied during the last year. The technique employs specific electrodes and is based on results obtained in the treatment of periorbital aging.[6] The data presented in the present article allow the authors to suggest that:

1. RFPM® is a promising therapeutic approach for the treatment of challenging lesions, such as the stretch marks
2. The obtained outcomes are reproducible using the methodology and the electrodes described in the present article
3. The prompt return to normal activities and the few adverse effects observed in the assessed group encouraged the author to recommend the inclusion of this new proposal in the broad and currently available therapeutic armamentarium for the treatment of stretch marks
4. Although reversible, post-inflammatory hyperpigmentation deserves special attention, and the author always recommends the preparation of the skin whiteners before the intervention and soon after the onset of re-epithelialization
5. The procedure requires training and is technic-dependent. The professional applying the technique must be properly qualified and posses all basic knowledge needed to ensure the excellence of the outcomes

The author suggests that the technique be assessed in other groups aiming at confirming the results and conclusions presented in this paper.

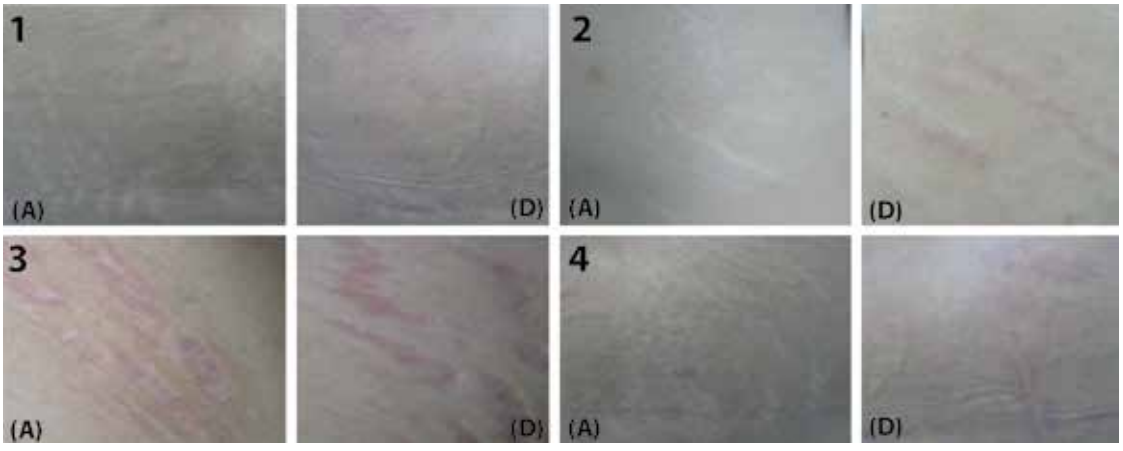

Figure 2: Late atrophic striae before and after 60 days of the treatment with RFPM®. Note the treated striae in cases 2 and 3 (progressed from atrophic to recent)

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Original Articles

Daylight photodynamic therapy: pharmacoeconomics of methyl aminolevulinate cream use for facial actinic keratoses

Terapia fotodinâmica com luz do dia: farmacoeconomia no uso do creme de metilaminolevulinato para ceratoses actínicas faciais

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ABSTRACT

Introduction: Actinic keratoses are the most common premalignant skin lesions, with a chronic and recurrent nature. Daylight photodynamic therapy has been used in the treatment of actinic keratoses of the face and scalp.

Objective: To demonstrate the possibility of implementing daylight photodynamic therapy at a public service, for the treatment of facial actinic keratosis, using one tube of methyl aminolevulinate cream for up to four patients.

Methods: Ten patients were selected to undergo daylight photodynamic therapy at the Centro de Dermatologia Dona Libânia, located in the city of Fortaleza (CE), Brazil. Curettage was performed on the actinic keratosis and a methyl aminolevulinate cream based chemical filter was applied across the face.

Results: One tube of methyl aminolevulinate cream was enough for treating up to four patients with multiple facial actinic keratoses, whereas studies suggest the use of at least one gram to treat one face completely.

Conclusion: It was possible to conclude when administering daylight photodynamic therapy, an amount of less than one gram of methyl aminolevulinate cream in the treatment of facial actinic keratoses is a dosage sufficient to obtain an effective clinical response.

Keywords: keratosis, actinic; photochemotherapy; economics, pharmaceutical

RESUMO

Introdução: *As ceratoses actínicas são as lesões pré-malignas de pele mais comuns, apresentando caráter crônico e recorrente. A terapia fotodinâmica com luz do dia tem sido utilizada no tratamento de ceratoses actínicas de face e couro cabeludo.*

Objetivo: *Demonstrar a possibilidade da realização da terapia fotodinâmica com luz do dia em serviço público para o tratamento de ceratoses actínicas em face, utilizando um tubo de creme de metilaminolevulinato em até quatro pacientes.*

Métodos: *Foram selecionados 10 pacientes para a realização de terapia fotodinâmica com luz do dia, realizando-se curetagem das ceratoses actínicas seguidas da aplicação de filtro químico e creme de metilaminolevulinato em toda a face.*

Resultados: *um tubo de creme de metilaminolevulinato, foi suficiente para tratar até quatro pacientes com múltiplas ceratoses actínicas de face, enquanto os estudos sugerem o uso de pelo menos 1g para tratar uma face completa.*

Conclusões: *O resultado nos leva a afirmar que na terapia fotodinâmica com luz do dia, a utilização de quantidade inferior a 1 grama de creme de metilaminolevulinato no tratamento de ceratoses actínicas de face é posologia factível para obtenção de efetiva resposta clínica.* ***Palavras-chave:*** *ceratose actínica; fotoquimioterapia; farmacoeconomia*

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The present study was performed at Centro de Dermatologia Dona Libânia - Fortaleza (CE), Brazil.

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Conflict of interests: Dr. Luiz Eduardo Garcia Galvão acts as speaker for Galderma

INTRODUCTION

Actinic keratoses (AKs) are the most common premalignant skin lesions, also being chronic and recurrent in character.

They are usually located in sun-exposed areas of the body, such as the scalp, face and forearms, of individuals with fair skin phototypes, who are immunosuppressed, bear some genodermatosis or undergoes chronic exposure to UV radiation.[1] Many studies have tried to estimate its true prevalence in the general population, arriving at varied rates, depending on racial factors, age, assessed anatomical site and selection methods used in the analysis. In Australia, currently the country with the highest known rate of AK in the world, 40-50% of individuals over 40 have at least one lesion due to the large proportion of fair phototypes in its population.[2] Actinic keratosis can be clinically classified in Grade 1 – when the lesions are slightly palpable, erythematous or rough; Grade 2 – when lesions have the appearance of erythematous desquamative plaques; or Grade 3 – when lesions are hypertrophic.[3] Studies describe varying degrees of progression into invasive squamous cell carcinoma (SCC), with about 0.025% to 16% of the AKs undergoing transformation into SCC over the years, with the treatment of all these pre-neoplastic lesions being required.[4]

Photodynamic therapy (PDT) is the first line treatment for multiple AKs of the face and scalp.[5] The concept underpinning PDT in AK is the induction of cytotoxicity in proliferating cells, using a light source with an adequate wavelength. O treatment starts with the application of a solution of 20% 5-aminolevulinic acid (ALA) or 16% methyl aminolevulinate cream (MAL) over an AK area on the face and/or scalp. These are not photosensitizing agents themselves, however they are metabolic precursors of the active compound protoporphyrin IX (PpIX) via the biosynthesis of the intracellular heme.[6] Protoporphyrin IX is deemed as a potent photosensitizing agent and is easily photo inactivated, meaning that it is degraded when exposed to a specific source of light. Protoporphyrin IX has several peaks of light absorption, the main one corresponding to the Soret band at 405nm, equivalent to blue light. Other lower peaks are also important and are called Q bands. Although Q bands' peaks are lower than the 405nm peak, many studies regarding PDT are performed using light sources in the red light spectrum between 620nm and 635nm due to the fact that red light provides greater penetration into the tissue, optimizing PDT for deeper lesions.[7] After a variable period of contact with the skin – in the case of ALA and three hours under occlusion with plastic film and aluminum foil, in the case of MAL cream, synthesis of PpIX occurs, which in the presence of reactive oxygen and light with the appropriate wavelength, causes necrosis and apoptosis in dysplastic keratinocytes, therefore evidencing the presence of selective action on clinical and subclinical AK.

Recent studies have shown that TFD can be performed with the daylight (PDT- DL).[8] In this procedure, PpIX is activated by visible light, which contains the first's two peaks of absorption (blue and red), allowing treatment of AK lesions with less adverse effects of painfulness and erythema. In 2008, Wiegell et al. compared the effects of applying conventional photodynamic therapy (PDT-C) associated with MAL after incubation for 180 minutes with those of PDT-DL during exposure to natural light for 150 minutes, for the treatment of AK in the face and scalp.[9] Continuous production of PpIX in PDT-DL during the outdoor exposure period was demonstrated to be as effective as PDT-C, nevertheless with higher tolerance to pain and a less erythema in the post-procedure period.[10]

The PDT-DL consensus currently indicates that the procedure should be carried out at an outdoor temperature of between 10ºC and 35ºC, avoiding very cloudy or rainy days.[11]

After preparation of the facial or scalp skin with curettage of the AK lesions, the application of chemical sunscreen – without titanium dioxide or zinc oxide – is performed for protection from UV rays, without prejudice of penetration of visible light, which promotes PpIX synthesis. The absence of the solid physical component in the cream enables the activation of PpIX by visible light while maintaining protection against UV radiation. The application of chemical sunscreen can alternatively be carried out before the preparation of the skin, according to the dermatologist's preference. Next, MAL cream is applied throughout the treated area, and the patient is instructed to begin outdoor exposure within 30 minutes. This exposure should take place in the shade for two hours. Once that time is elapsed, the MAL cream should be removed and the photoprotection care intensified.[12]

When compared with PDT-C, PDT-DL's has the advantages of increased patient tolerance, minimum local cutaneous reactions and absence of dependence of an artificial light source at the practice. Yet, it is the high cost of the MAL cream that precludes the indication of any type of PDT treatment in public hospitals and private practices that are subjected to unfavorable socio-economic conditions, as is the case, for instance, in Latin America.

The present study was aimed at demonstrating the viability of performing PDT-DL – which is *per se* more cost effective than PDT-C – in public services to successfully treat facial AK using a single MAL cream tube for 4 patients, depending on the extent of the AK and dimensions of the patient's face.

METHODS

Ten patients were selected in July 2015 to undergo PDT-DL, observing the following inclusion criteria: skin phototypes I-IV, presence of at least four AK lesions on the face, regular use of sunscreen and at least one previous alternative treatment for facial AK (such as cryotherapy and 5-fluorouracil cream) more than six months before taking part in the study. All procedures were performed at Dermatology Center Dona Libânia, in the Brazilian Northeast city of Fortaleza (CE), with outdoor exposure, in the shade, from 7:30AM to 9:30AM, after curettage of the AK and application of chemical filter and MAL cream across the face, including the auricles. Sunscreen was applied in the other sun-exposed body areas, such as neck and arms. All patients were photographed before and three months after the PDT-DL session. The ethical principles emanating from the Helsinki Declaration were followed in the present study.

RESULTS

There was absence of important skin reactions and the patients experienced a reduction in the number of AKs according to clinical and photographic tests performed three months after the PDT-DL procedure (Figure 1 A and B). It was possible to treat 8 female patients and 2 male patients (two albinos) with 3 MAL tubes of 2g each. Of the 3 MAL tubes used, 2 were used to treat 6 patients and 1 was used to treat 4 patients (Figure 1 C, D, E and F).

DISCUSSION

Daylight photodynamic therapy allows the treatment of large areas of the face and scalp in patients with multiple AKs. In contrast with PDT-C, it is possible to treat the cutaneous cancerization field with less discomfort, for there is continuous production of PpIX during the two hours of outdoor exposure.[13] Erythema, edema and desquamation after the session are far less intense when compared to those resulting from the conventional technique and even other treatments conducted at home, such as 5-fluorouracil and imiquimod cream. It is important to observe the weather conditions with a view to a possible rescheduling of the procedure, completely avoiding it if rain or cloudy weather with dark clouds are forecast for the time of the outdoor exposure. The city of Fortaleza is located in the Northeast Brazilian state of Ceara, at a low latitude (03° 43' 02" S), where the average annual temperature is 26.3 °C and the average annual rainfall is 1,448mm (max rainfall in April = 329mm, min rainfall in October = 13mm). These characteristics allow that PDT-DL be performed throughout the year. Other Brazilian cities may have higher rainfall and fewer sunny days, nevertheless as the minimum temperature for the procedure is 10 °C, PDT-DL can be carried out in Brazil almost throughout the year, contrary to what occurs in the European continent.

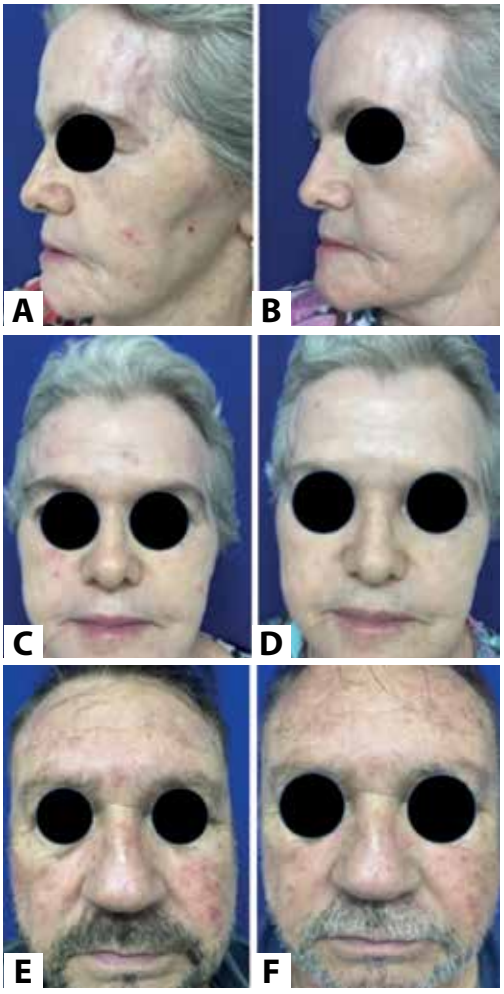

Figure 1: Before and 3 months after PDT-DL treatment

Figure 2: Pharmacoeconomics: Methyl aminolevulinate cream applied with the fingertips to avoid waste

In pharmacoeconomics terms, although the commercial version of the MAL cream is 2g and the fact that major studies suggest the use of at least 1g to treat a full face,[14] the authors of the present paper observed that some simple measures increase the productivity of the MAL cream (e.g. applying the product with the fingertips or a spatula) (Figure 2). The patient's facial size and profile, as well as the number and thicknesses of the AKs also have influence on the amount of cream applied to the face.

CONCLUSION

Daylight photodynamic therapy is effective in reducing the number of AK lesions on the face, with clinical improvement, even when using amounts less than half of one MAL cream tube. Thus, one tube of the product can be used in up to 4 patients, facilitating the treatment of large areas of the face with AKs. As a result, PDT-DL arises as a first line therapeutic option for the treatment of multiple facial AKs due to the feasibility of achieving clinical improvement with absence of significant local skin reactions, without the need for a specialist artificial light source device and the possibility of effectively using a single tube of MAL cream in several patients.

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Review article

Aspiration curettage for the treatment of axillary hyperhidrosis – the technique step-by-step

Curetagem aspirativa para o tratamento da hiperidrose axilar – passo a passo da técnica

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ABSTRACT

Aspiration curettage of sweat glands is a minimally invasive surgical technique for the treatment of axillary hyperhidrosis. It is safe and easy to perform, offers a high success rate and comparatively few side effects. It is generally well tolerated by patients and requires a reduced recovery time when compared to other surgical modalities.

Keywords: hyperhidrosis; surgery; curettage

RESUMO

A curetagem aspirativa das glândulas sudoríparas é uma técnica cirúrgica minimamente invasiva utilizada para o tratamento da hiperidrose axilar. É facilmente executada e segura, possui alta taxa de sucesso e relativamente poucos efeitos colaterais. Em geral é bem tolerada pelos pacientes e requer reduzido tempo de recuperação quando comparada a outras modalidades cirúrgicas.

Palavras-chave: *hiperhidrose; cirurgia; curetagem*

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INTRODUCTION

The majority of patients with severe axillary hyperhidrosis need to consider surgery as a therapeutic option.[1]

Local surgical treatment of axillary hyperhidrosis is aimed at eliminating the greatest possible number of sweat glands from that region, retaining – to the extent possible – the axilla's normal aesthetic appearance and arm's mobility.[2]

Several surgical techniques have been developed and modified over the years. The most important of them can be classified into four types: I) block resection of the subcutaneous tissue and overlying skin (Hurley and Shelley, 1963[3]; Tipton, 1968[4]); II) block excision of a small part of the central axillary region with the removal of subcutaneous tissue in adjacent regions (Bisbal, 1987[5]; Weaver, 1970[6]; Hurley and Shelley, 1966[7]); III) methods which remove only the subcutaneous tissue, without excision of the skin (Skoog, 1962[8]; Jemec, 1975[9]) and IV) methods which remove the subcutaneous tissue and deep dermis, without excision of the skin (Darabaneau, 2008[10], Kim, 2008[11]; Rho, 2008[12]; Boni, 2006[13]; Bechara, 2006[14]; Tronstad, 2014[15]; Feldmeyer, 2015[16]).

Nevertheless, it was only after the development of minimally invasive techniques (e.g. curettage[9,17,18], liposuction[19], laser[20], ultrasonic surgical aspiration,[21,22] and aspiration curettage[10-16]) that its use became more widespread.

Minimally invasive techniques offer many advantages, such as reduced risk of infection, diminished pain in the postoperative period, reduced recovery time and less scarring when compared to traditional surgical methods. However, the small size of the operating field during the implementation of these procedures requires great skillfulness from surgeons.[23]

Aspiration curettage of the sweat glands is a minimally invasive, safe and easy to perform surgical technique, which has high success rates and few side effects. It also offers the possibility of permanent reduction of hyperhidrosis, which corresponds to the most frequent request from patients. [24,25]

For the preparation of the present article, MEDLINE and Cochrane databases were searched using the following terms: hyperhidrosis, axillary hyperhidrosis, surgery, aspiration curettage.

Aspiration curettage technique

The treatment of axillary hyperhidrosis based on surgical removal consists of the removal of the eccrine, apocrine and apo-eccrine glands of the region in question. This technique has many variations. The procedure, which is currently carried out ambulatorially with tumescent anesthesia, consists of two main phases: dissection of the dermis from the underlying subcutaneous tissue, and removal of the sweat glands from the dermis and the region comprising the dermo-hypodermic junction.[5]

The region to be treated generally extends for 1cm to 2cm beyond the axilla's hairy area. Nonetheless, the iodine-starch test can be performed before surgery in order to mark the affected area and prevent the occurrence of residual hyperhidrosis areas.

The axillary hair can be shaved from 15 to 30 days before surgery. Once having been shaved, the growing hair should not be shaved again so as to allow easy visualization and delimitation of the area to be treated, therefore serving as a parameter for interrupting the procedure.

Step-by-step of the surgery

STEP 1 – Patient's positioning:

Patients are positioned in the supine position with the arms abducted (90-135° angle) in order to expose the axilla. Excessive abduction should be avoided in order to prevent lesion in the brachial plexus (Figure 1).[26-28]

STEP 2 - Asepsis and antisepsis:

The asepsis and antisepsis are performed using a chlorhexidine or 70% alcohol solution.

STEP 3 - Initial local injection of anesthetic / Incision:

After the initial local anesthetic injection, three small incisions are usually performed outside the area to be curetted, for surgical access. These incisions are made in different points, according to the surgeon's preference: in the superomedial aspect of the axilla, in the anterior and distal borders, in the central portion of the axilla, in the upper inner region[29-31] or infralateral region of the arm (Figures 1 B and C).

STEP 4 - Introduction of the injection cannula / Tumescent anesthesia:

A volume of 100-500 ml of tumescent solution is subsequently injected as superficially as possible in areas previously marked in each axilla, creating the effect of *"peau d'orange"* in the overlaying tissue.[26,30,32,33] The use of small diameter infusion cannulas is important for the patient's comfort. Although the standard formula for tumescent anesthesia is 1,000 ml normal saline, 50-100 ml 1% lidocaine, 1 ml 1:1,000 epinephrine and 12.5 ml sodium bicarbonate, there are many variants of this formula (Figure 1 D).[34]

This solution minimizes bleeding, makes the dissection easier and reduces ecchymosis.[35] The prolonged analgesic effect of lidocaine deposits in the tissue ensures some comfort in the immediate postoperative period.[36] The expansion of the axilla's soft tissue minimizes the risk of lesion in the brachial plexus. [37]

STEP 5 – Back-and-forth movements for the subdermal tunneling:

After the whitening of the region by hemostasis, subcutaneous tunnels are created via precise dissection (a Schroeder curette can be used at this stage), with back-and-forth movements so as to separate the dermis from the subcutaneous tissue. Subcutaneous sweat glands are thus mobilized.

STEP 6 - Removal of the glands through inverted curettage with or without aspiration (dermal and subcutaneous tissue):

Curettage:

Next, a tool with a cutting edge (Fatemi cannula, Cassio cannula or event a dermatological curette) is inserted in order that the dermal curettage is performed. (Figure 1E) Additional care must be taken when these curettes are used in isolation. If used too aggressively, can lead to skin necrosis.

Most of the sweat glands of all kinds (eccrine, apocrine and apo-eccrine) in the axillae of adult Caucasians are located in the subcutaneous tissue, in the interface with the dermis – and not in the dermis.[38]

It would be impossible to eradicate all subcutaneous glands using only superficial liposuction, since some of them are firmly adhered to the dermis, and a considerable force would be required to separate the glands from their ducts.[38-40]

Likewise, curettage cannot be performed in a wrong anatomical tissue layer. [41] Performing the procedure in a deep level makes it virtually impossible to completely remove the sweat glands.[42]

The tension of the overlying skin, as well as the force applied during the scraping movements is of great importance during the inverted curettage. In this way, the surgeon's

non-dominant hand can help in the procedure, compressing the overlaying skin.[26,43]

The curettage must be carefully performed around the incision sites, since the subcutaneous tissue located near the incisions might not be properly removed only by liposuction.[44]

The size cannula's size and orifices, in addition to the vacuum's intensity and the movement's speed, directly affect the amount of tissue removed.[40]

The surgery's success depends on the removal of the sweat glands in the dermis / subcutaneous junction up until the point where the axillary tissue becomes similar to a total skin graft.[24],[38] Thus, a cannula with a cutting edge is more suitable for performing curettage of the deep dermis – a more aggressive procedure – and the more efficient removal of sweat glands, achieving higher cure rates. This area would become irrigated with the blood of the surrounding skin, which did not undergo the procedure.[26]

Aspiration:

The aspiration of the removed tissue can be performed manually or mechanically (Figure 1 F).

In the manual vacuum aspiration variant, a syringe is attached to the cannula, which is inserted into the tissue to be removed before the plunger is retracted. There must be a mechanical lock to keep the plunger retracted. As this system does not provide a deep and continuous vacuum, if the cannula is unintentionally partially removed during aspiration around the incision sites, the vacuum will be lost. If this occurs, the air must be removed from the syringe before reuse.

When a mechanical suction system is used, the cannula is connected to a collection container through a tube. The tissue mobilized by the cannula is conveyed to the container by means of a collection system that uses negative pressure generated by a vacuum pump.[40]

STEP 7 - Sutures:

Profuse irrigation with saline and meticulous hemostasis should be performed at the end of the procedure. Subsequently, the surgical incisions can be closed.

Anchorage sutures can to be used in the areas treated with aggressive liposuction and curettage in order to prevent hematoma formation. [26]

STEP 8 - Compressive dressing:

Large compressive dressings must be used for 2-3 days after the procedure to prevent hematoma and seroma formation (Figures 2A and B).

Prophylactic antibiotic treatment can be performed preoperatively[14], and the dressing can be carried out with antibiotic ointment.[36]

Local measures for the prevention and improvement of the subcutaneous fibrosis (local heat, massage, gels or ointments containing heparin or flavonoids) can be introduced 3 weeks after surgery and should be maintained for three months.[16]

Patients should be instructed to avoid sudden movements with the arms (especially abduction and elevation movements) for 2 weeks. Intense physical exercise should be avoided for 1 month.[24]

INTERRUPTING THE PROCEDURE

Surgeons should perform the procedure with a view to achieve the best results, with the fewest possible side effects.

Clinical evidence indicating curettage sufficiency:

1. Complete elevation of the axillary skin regarding the subcutaneous tissue.[21]

2. Color of the overlaying skin: slight paleness of axillary skin (it becomes slightly bluish or pale, with some petechiae, indicating significant damage to the dermal vascular plexus) (Figure 3).[6,21,24]

3. Skin thickness: the skin becomes very thin and easy to pinch, as it if were a piece of clothing (Figure 3B).[6,24]

4. "Skin with skin" contact: indicates that there is no more fat adhered to the dermis (Figure 3B).[21]

5. Hair follicles are palpable during the "skin with skin" contact.[21]

6. The skin can be seen through the cannula's orifices while being aspirated (Figure 3C).[24]

7. "Suction sounds" caused by the cannula due to the axillary "cavity", indicating complete dissection of the dermis and subcutaneous tissue. [21]

8. Axillary hair easily coming off when pulled by the surgeon. For this reason, the axillary hair should have a length of 2 to 4mm before surgery (Figures 3D and E).[27]

COMPLICATIONS

Despite the fact that minimally invasive techniques have demonstrated a relatively low rate of complications, several light to moderate side effects (most of them transient) have been described. [45] Possible complications include: hematoma, ecchymosis, seroma, superficial cutaneous erosions, loss of local sensitivity, skin necrosis, infection, epidermal inclusion cysts, reduction in the number of hairs, fibrosis, adhesion formation in the subcutaneous, scarring and recurrence of hyperhidrosis.[46,47]

FINAL CONSIDERATIONS

Axillary hyperhidrosis is a disabling and distressing condition. Curettage is effective and can significantly improve the patients' quality of life.[48]

During the first two weeks after surgery, sweating usually stops completely, later rearising at a new individual level.[49]

Given that the removal of all sweat glands is unfeasible, a positive outcome occurs when patients are able to control their transpiration using conventional antiperspirants and deodorants.[32]

Although the technique in question is usually very effective and curative, patients not fully satisfied can be re-operated using the same method. This is almost invariably done with success.

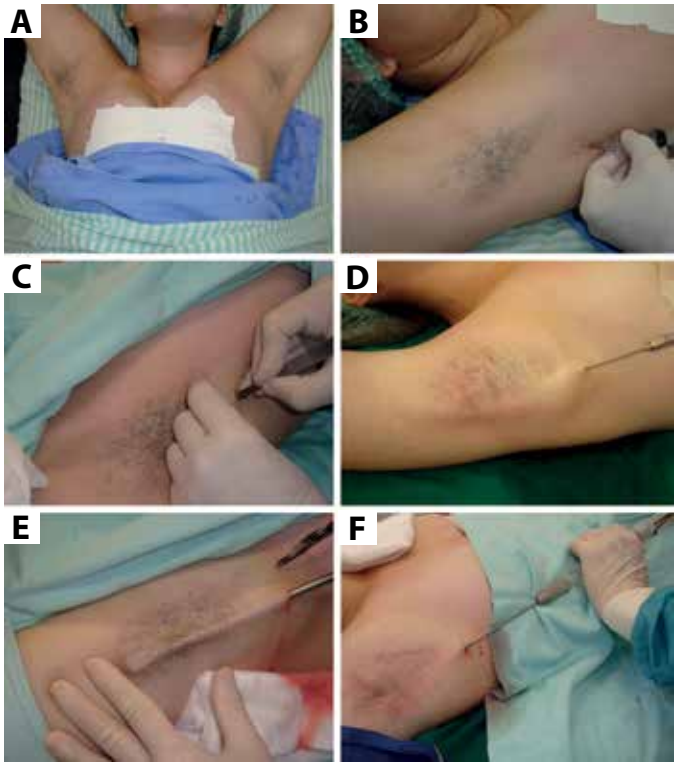

Figure 1: Aspiration curettage technique: **A -** Patient positioning (arms abducted at a 90° - 135° angle); **B -** Initial local anesthetic injection; **C –** Incision; **D -** Tumescent anesthesia; **E -** Removal of sweat glands using reverse curettage; **F -** Aspiration.

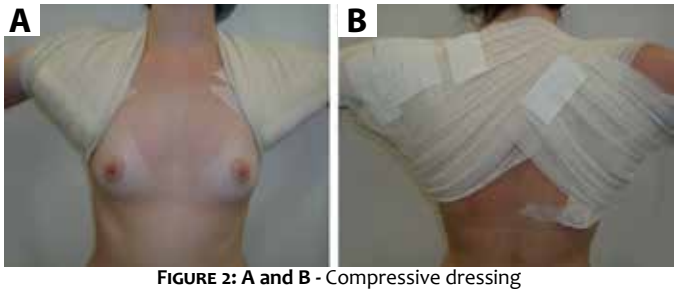

Figure 2: A and B - Compressive dressing

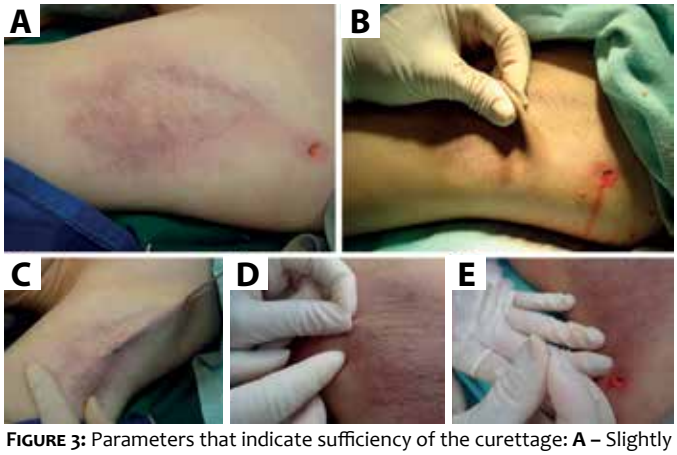

Figure 3: Parameters that indicate sufficiency of the curettage: **A –** Slightly bluish axillary skin; **B -** The skin becomes very thin and easily pinched; C - The skin is aspirated through the cannula's orifices; **D and E** – Axillary hair come easily off when lightly pulled by the surgeon

Likewise, in case of recurrence (insufficient curettage, anatomical variations with great concentrations of sweat glands in the upper reticular dermis, compensatory hyperfunction of the remaining sweat glands, curettage performed in the wrong anatomical layer), curettage can be repeated with effective results, without causing an increase in the occurrence of serious complications.[41]

CONCLUSION

Aspiration curettage or simple curettage of the sweat glands is a minimally invasive surgical technique that is safe and easy to perform, offering high success rates and few side effects.[47]

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Dermoscopic aspects of juvenile xanthogranuloma with multiple lesions

Aspectos dermatoscópicos do xantogranuloma juvenil com múltiplas lesões

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ABSTRACT

Juvenile xanthogranuloma is a form of non Langerhans cell histiocytosis that mainly affects children. It usually emerges as asymptomatic yellow-brownish papules. The diagnosis is clinical and confirmed by histology. Due to its trend to involute, treatment is usually not recommended. Dermoscopy arises as a noninvasive diagnostic tool that reveals a typical pattern for this condition.

Keywords: xanthogranuloma, Juvenile; dermoscopy; histiocytosis, non-Langerhans-cell

RESUMO

O xantogranuloma juvenil é forma de histiocitose não Langerhans que acomete preferencialmente crianças. Em geral, manifesta-se como pápulas amarelo-acastanhadas assintomáticas. O diagnóstico é clínico e confirmado pela histopatologia. Devido à tendência involutiva, o tratamento geralmente não é recomendado. A dermatoscopia emerge como recurso diagnóstico não invasivo, revelando padrão típico para essa afecção.

Palavras-chave: *xantogranuloma juvenil; dermoscopia; histiocitose de células não Langerhans*

INTRODUCTION

Juvenile xanthogranuloma (JXG) is a common form of non-Langerhans histiocytosis. It comprises benign tumors of histiocytes, usually with spontaneous regression and that mainly affects children. It emerges as small-yellowish or brownish, single or multiple papules, most often asymptomatic. Visceral changes are rarely observed. The diagnosis is clinical and in doubtful cases, confirmation is carried out by histology. Treatment is usually not recommended in light of the self-limiting nature of this entity. It is worth to note that regression is capable of generating atrophy and hyperpigmentation.[1] Dermoscopy is useful in assisting the diagnosis, since this condition has a typical pattern, characterized by an orange color background – described as the "setting sun" pattern, the presence of clouds of deposits that are pale yellow in color, and linear or arboriform vessels disposed from the periphery to the lesion's center.[2-4]

CASE REPORT

A one year-old child born and living in the city of Mogi das Cruzes (SP, Brazil), Fitspatrick's skin phototype III, presented at the consultation with a history of emergence of brownish papular lesions with onset at three months of age. The papules were asymptomatic, initially in the upper thoracic region, later on evolving to the abdomen, dorsum and face (mentum, and paranasal and preauricular regions). These lesions did not show signs of inflammation or itchiness, except for when the child accidentally traumatized them. The patient had no comorbidities or was in use of any medication, was up to date with the required vaccination, and there was no reference to similar cases in the family. The dermatological examination evidenced yellow-brownish papules with soft consistency and bosselated surface, measuring roughly 10mm in its longest diameter, located on the face (mentum, and paranasal and right preauricular regions), upper chest, dorsum and scalp's occipital region. The thoracic lesions showed a discrete yellow-orangish halo (Figures 1 and 2). There was no compromise of the patient's general condition. The dermoscopic examination allowed observing a yellow-orangish color background ("setting sun" pattern), presence of delicate brownish interrupted lines (which do not constitute a pigmented network), punctate central vessels and other linear vessels disposed from the periphery to the center of the lesion, yellow-pale clouds and peripheral pigmented ring (Figures 3 and 4). After requesting an ophthalmologic evaluation, a decision was made for maintaining an expectant approach with a series of clinical follow-ups.

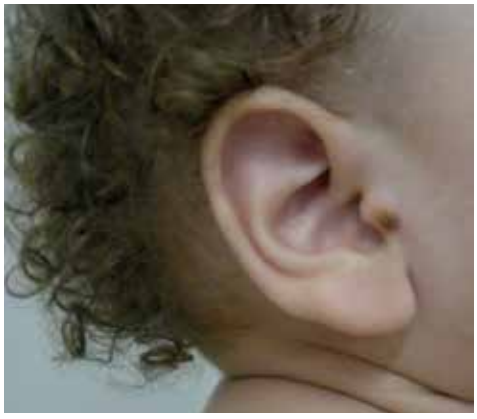

Figure 1: Yellow-brownish bosselated surface papule with soft consistency, located on the right tragus

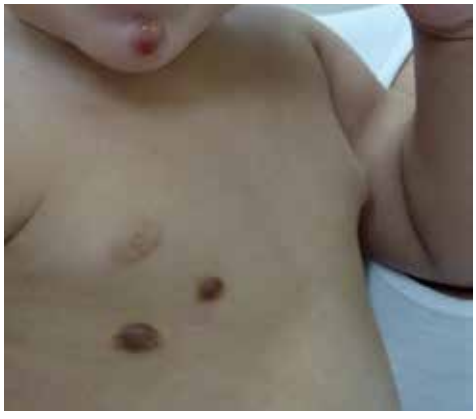

Figure 2: Multiple papular brownish lesions on the chest with a yellowish halo

DISCUSSION

Juvenile xanthogranuloma (JXG) is a common form of non-Langerhans histiocytosis, arising as yellowish, sometimes pinkish asymptomatic papules, measuring between[5] and 20mm in diameter, that may become yellow-brownish in color and display telangiectasias with time.[1,3] About 70% of cases arise in early childhood,[1] but children of all ages can be affected. Single lesions are more common, however children with less than six months often have multiple lesions. There is a predilection for the head and upper trunk segment. They tend to regress spontaneously around a year after the onset. Although uncommon, extra-cutaneous involvement, with lesions in the subcutaneous tissue, eyeball, liver and spleen is possible. The histological examinations of these lesions evidence a diffuse and dense pleomorphic histiocytic infiltrate, with the predominance of vacuolated cells in early stages and xanthomatous cells later on. The Touton cell (xanthomatous multinucleated, with nuclei arranged in the form

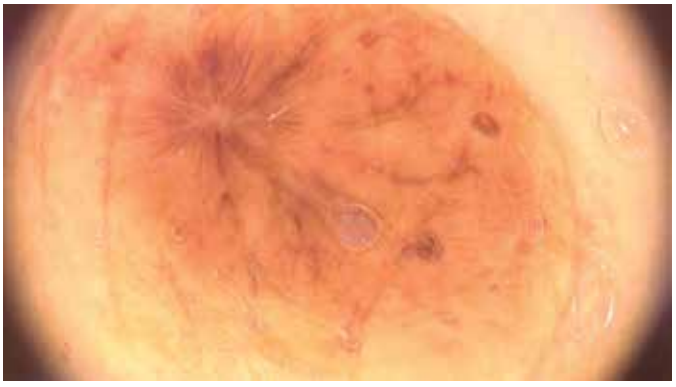

Figure 3: Dermoscopy of one of the lesions on the chest: yellow-orangish color background ("setting sun" pattern), delicate brownish interrupted lines – which do not constitute a pigmented network, central and linear punctate vessels disposed from the periphery to the center of the lesion, yellow clouds and peripheral pigmented ring

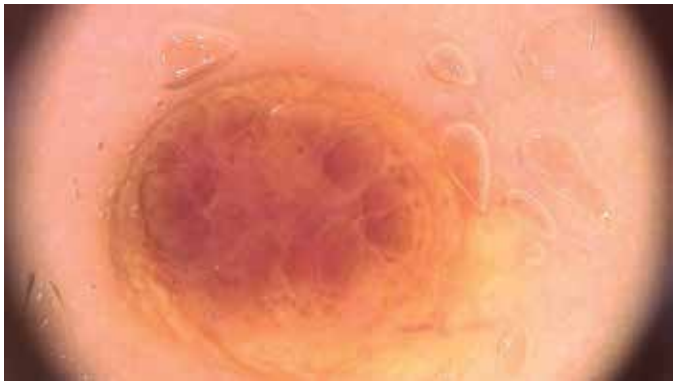

Figure 4: Clearly identifiable "setting sun" pattern in one of the lesions, evidenced in the dermoscopic examination

of a ring is the most typical, nevertheless non-specific element of this condition.[1,2,5] Dermoscopy is a useful tool in the diagnosis, in special when a decision is made for not to perform the lesion biopsy, as is the case in the present paper. Initially described by Palmer and Bowling,[2] the dermoscopic pattern of juvenile xanthogranuloma consists of a yellow-orangish background with an erythematous halo (described as "setting sun" pattern), with pale yellow clouds corresponding to the to dermal xanthogranulomatous infiltrate (similar to the one found in sebaceous hyperplasia) and arboriform vessels disposed from the periphery to the lesion's center.[1-5] In the present case, all these aspects were seen, confirming the clinical and dermoscopic diagnosis of JXG. It is possible to conclude that the dermoscopic examination provides valuable additional information for the diagnosis,[3] thus avoiding invasive procedures, such as skin biopsy, in the pediatric population.

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New Techniques

Compressive dressing for the scalp

Curativo compressivo para couro cabeludo

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ABSTRACT

To make compressive dressings that are capable of preventing hematoma during the recovery period, after surgery on the scalp is a challenge. These dressings can be especially problematic to perform in the vertex region, due to the difficult adhesion of the hypoallergenic tape in that site. The authors introduce a good option for compressive dressings for use after surgeries on the scalp.

Keywords: compression bandages; ambulatory surgical procedures; head; scalp

RESUMO

Criar curativos compressivos que evitem hematomas no pós-operatório de cirurgias no couro cabeludo é um desafio. Tais curativos podem ser especialmente de problemática realização na região do vértex, pela dificuldade de adesão da fita hipoalergênica no local. Os autores apresentam uma boa opção de curativos compressivos para uso após cirurgias no couro cabeludo.

Palavras-chave: *curativos oclusivos; procedimentos cirúrgicos ambulatórios; cabeça; couro cabeludo*

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INTRODUCTION

Approximately 90% of cutaneous neoplasms occur in the head and neck.[1] When the primary closure is not feasible, flaps and grafts are alternate methods.[2] Hematomas should be avoided in the postoperative period of these procedures, however performing compressive dressings after surgeries in the scalp region is often a challenge due to the difficult adhesion of the hypoallergenic bandages to the hair.[3] The purpose of this paper is to introduce a good choice of dressings for surgeries on the scalp, particularly if located in the vertex region.

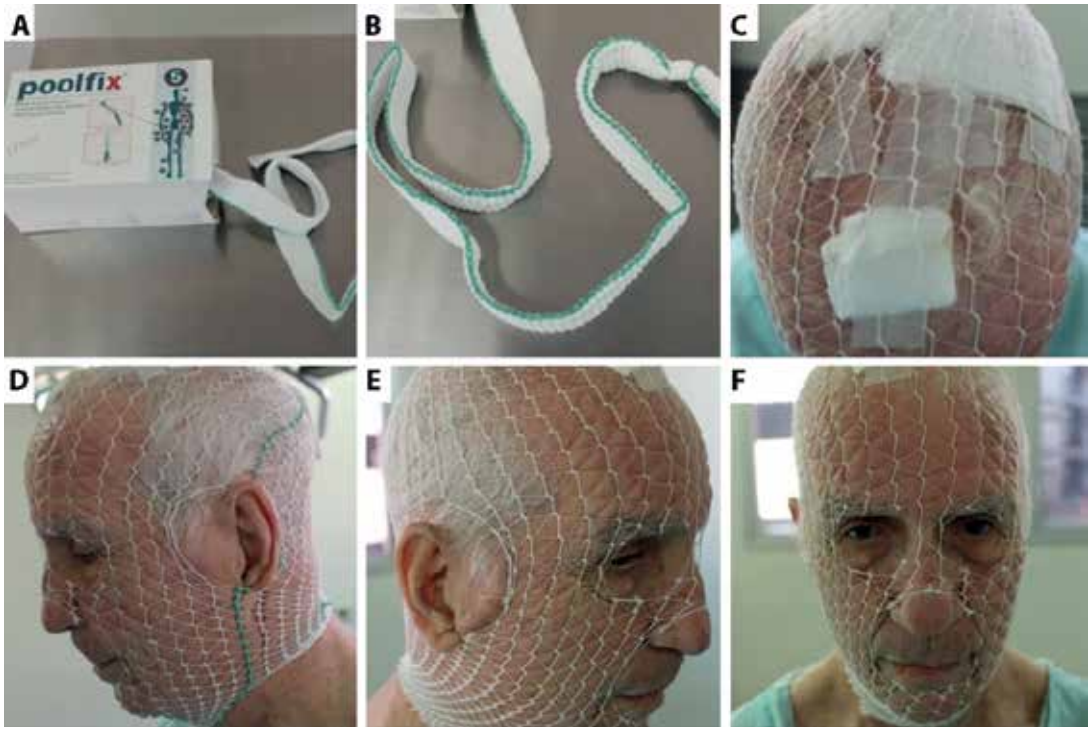

Figure 1: Compressive dressing on the scalp.
Step-by-step preparation: **(A, B)** tubular elastic mesh; **(C)** gauze occluding the surgical wound, with compression exerted by the tubular elastic mesh; **(D, E, F)** cuts are performed on the sites of the mouth, eyes and ears

DISCUSSION

The scalp is intensely vascularized, and the absence of bleeding or hematomas postoperatively from surgeries, which sometimes are extensive in this site – [2] may be instrumental for the success of the procedure.

The anatomy of the face and the presence of hair make it difficult to apply dressings on the scalp. Lebovits et al.[3] proposed a dressing with modified bandages aimed at maintaining local compression, partially attaching it on the neck, a technique still little used among dermatologists.

The technique described in this paper is performed with tubular mesh, and is simple and cost effective. It is indicated as an option after procedures in which there is need for occlusion and compression in the scalp.

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Relato de caso

W-plasty: the role in the camouflage of an unaesthetic postsurgical facial scar

W-plastia: papel na camuflagem de uma cicatriz cirúrgica inestética da face

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RESUMO

A W-plastia é uma técnica frequentemente utilizada na cirurgia cosmética facial para camuflar uma cicatriz linear transformando-a num padrão irregular. Consiste na excisão de uma série de pequenos triângulos consecutivos de pele de cada lado da cicatriz e na interdigitação dos retalhos triangulares resultantes, produzindo um efeito "zigue-zague". Este procedimento é particularmente útil em cicatrizes longas, largas, curvas, contráteis ou perpendiculares às linhas de tensão da pele relaxada, localizadas na fronte, bochechas, queixo e nariz. Relatamos a utilidade desta técnica numa cicatriz facial pós-cirúrgica inestética.
Palavras-chave: cicatriz; procedimentos cirúrgicos menores; retalhos cirúrgicos; procedimentos cirúrgicos reconstrutivos

ABSTRACT

W-plasty is a commonly used technique in facial cosmetic surgery to camouflage the straight line of a scar into a regularly irregular pattern. It consists of excising a series of consecutive small triangles of skin on each side of the scar, and imbricating the resultant triangular flaps, producing a "zig-zag" effect. This procedure is particularly useful on long, wide, curved, contracted, or anti-tension line scars of the forehead, cheeks, chin, and nose. We report the usefulness of this technique in an unaesthetic postsurgical facial scar.
Keywords: *cicatrix; dermatologic surgical procedures; surgical flaps; reconstructive surgical procedures*

INTRODUCTION

Scar formation is an inevitable consequence of the healing process, which can either result from surgical procedures or trauma.[1] In oncologic surgery, the complete removal of the tumor and the aesthetic appearance of the scar are critical criteria in the assessment of the surgical outcome. The surgeon's experience, a careful surgical planning and the implementation of the correct technique, combined with knowledge of anatomy and the healing process, are central to improve surgical outcomes and reduce complications risks.[1–3] The revision of a scar does not eradicate it, nevertheless it helps to make it less obvious and

cosmetically/functionally more acceptable through transforming several variables by: softening irregular scars; improving the color; filling depressions; reorienting, narrowing or flattening the scar; or correcting anatomic units distortions.[2] Aimed at achieving those effects, different surgical techniques (Z-plasty, W-plasty, closure with geometric broken line, V-Y and Y-V advancement flaps, debulking among other) as well as non-surgical techniques can be used (corticosteroids injections, dermabrasion and treatment with ablative and non-ablative lasers), alone or combined, depending on the advantages, limitations and risks of each of them.[1],[3] When planning the revision of a scar, the surgeon must decide on the appropriate timing to intervene and the technique to be used in order to obtain an aesthetically agreeable outcome.[1]

CASE REPORT

A 38 year-old male patient had undergone excision of a basal cell carcinoma located in the mentum three years before, with a nasolabial fold transposition flap being used in the closure (Figure 1A, 1B and 1C). Two hypertrophic, elongated, wide and curved scars, perpendicular to the relaxed skin tension lines (RSTL) resulted from the procedure (Figure 1D). The scars were aesthetically unsightly, and became the cause of significant emotional stress and social impact. The patient accepted the proposal of surgical correction of the scars using the W-plasty technique. After local anesthesia with 2% lidocaine with 1:100,000 epinephrine, small triangular interdigitated skin flaps (in the shape of "Ws") were drawn on each side of the scar, so that the two sides could be interposed after the excision of the scar and de-

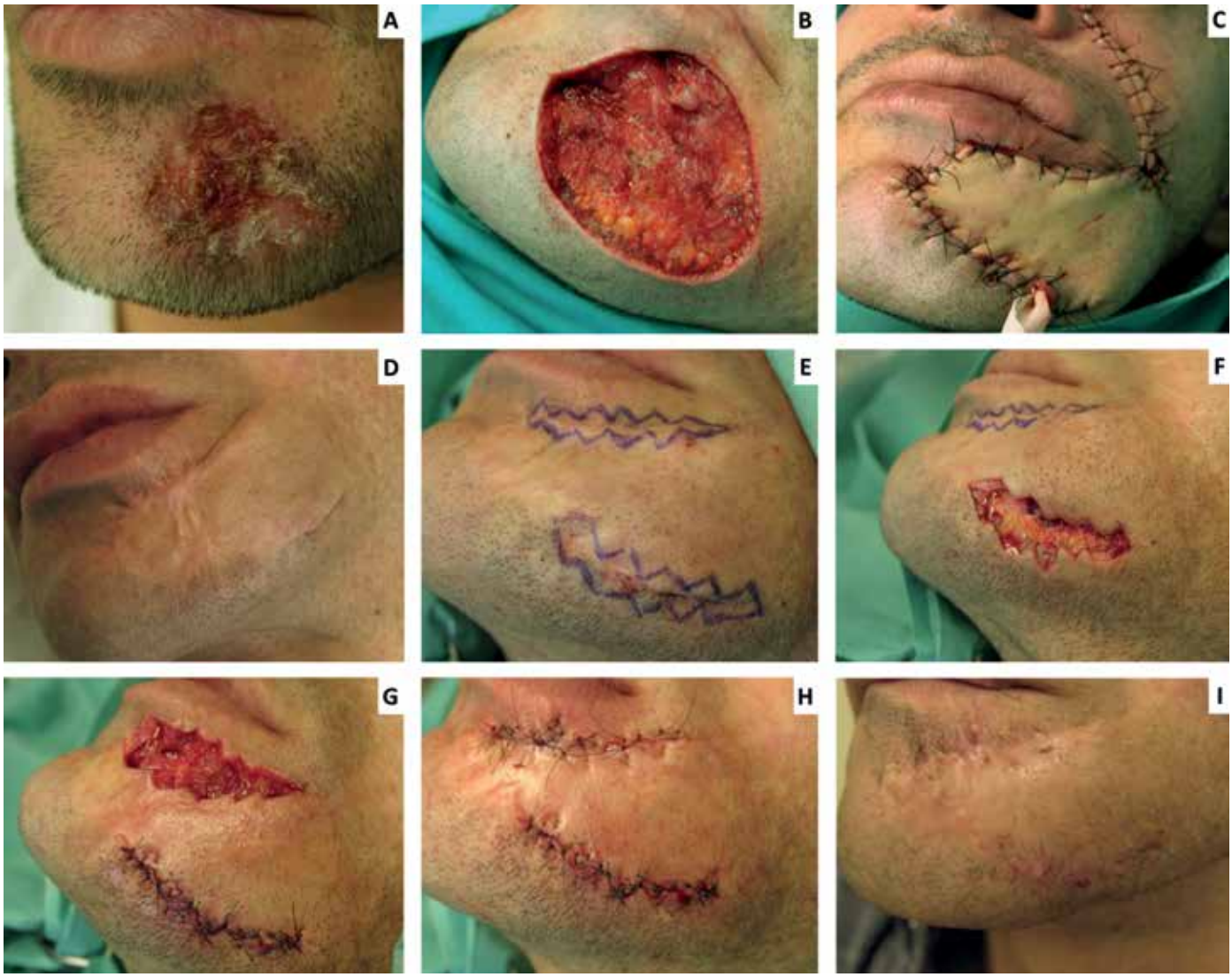

Figure 1: Clinical aspect of the patient's mental basal cell carcinoma **(A),** the surgical defect after excision of the lesion **(B),** and the immediate outcome after reconstruction with pedicled transposition flap **(C);** appearance of the resulting scar three years after surgery **(D);** planning of the surgical correction with multiple drawings of interdigitated "Ws" on each side of the scar **(E);** surgical defect after removal of the inferior **(F)** and superior scars **(G);** appearance in the immediate postoperative **(H)** and two weeks after surgery **(I)**

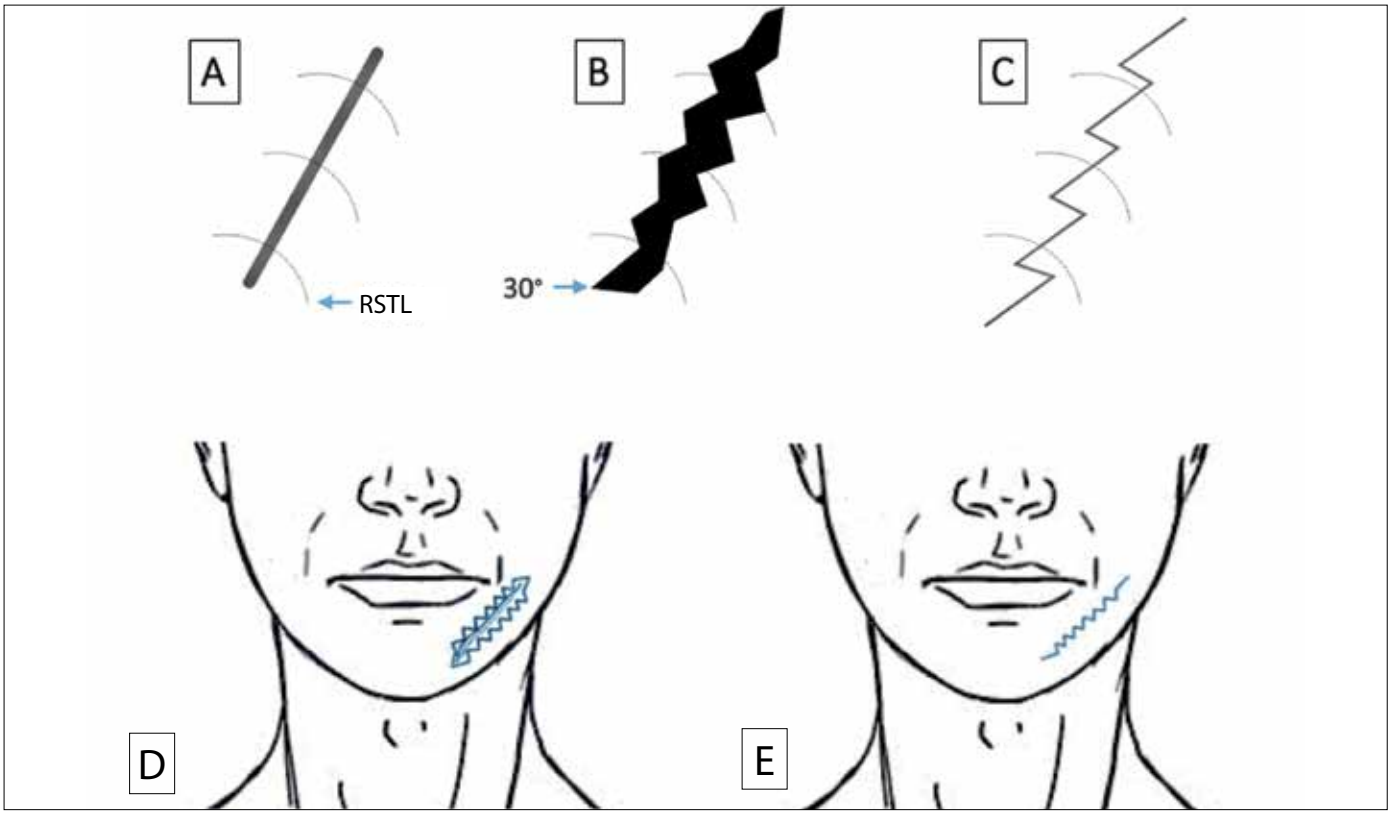

Figure 2: W-plasty technique's descriptive scheme. Linear scar oriented perpendicularly to the relaxed skin tension lines (RSTL) **(A);** excision of the scar following a pattern of interdigitated "Ws" on each side **(B);** line in zigzag resulting from the interposition of the "W's" after the excision of the scar **(C).** Planning scheme of a W-plasty in a mental scar **(D)** and final appearance with zigzag pattern **(E)**

tachment of the flaps (Figures 1E, 1F and 1G). The triangles' borders were approximately 5mm long (with one of them oriented parallel to the RSTL) and the vertices' angles measured less than 30°. The closure was carried out with synthetic non-absorbable synthetic suture thread (Polyamide) 5.0 (Figure 1H). The final outcome achieved was deemed cosmetically good by both the patient and the physician, and there was absence of complications (Figure 1I).

DISCUSSION

The W-plasty is a relatively simple to plan and implement technique, consisting of the excision of the old scar and closure of the surgical wound by re-approximating the small interdigitated borders created, creating a zigzag pattern. Its concept is based on the principle that an irregular line is less visible than a straight line, which is especially advantageous when the scar is not oriented along the RSTL. It is also indicated for scars located on curved surfaces – such as the jaw – or in cavities, wide scars or in scar that have stitch marks similar to a train tracks, as well as to dissipate contracture forces and prevent further cicatricial retractions.[2,4] It should be implemented in body sites where there is adjacent loose tissue – such as in the forehead, temporal regions, cheeks or mentum.[2] There is no elongation of the scar and the tissue is removed, resulting in an increased tension in the area perpendicular to the scar.[4]

In detail, the W-plasty technique consists of (Figure 2):

1. Drawing a zig-zag ("Ws") on one side of the scar and another mirror image on the opposite side. The "Ws" will function as triangular advancement flaps, with their vertices oriented parallel to the RSTL, given that the scar is perpendicular to them.[2,3,5]

2. Drawing the "Ws" so that the angles measure at least 60°, and the tips of the triangles lie between 3 to 7 mm from the periphery of the scar, allowing that an irregular line be abtained.[3] In order to avoid the dog-ear effect, it is essential that the end portion of the plasty be designed in a way to originate a 30° angle at each extremity (Figure 2B).[2,3,5]

3. Excising the scar along the drawn lines and re-approximating the borders in a way that the tips of the triangular flaps interdigitate and generate a single line in zigzag (Figure 2C).

This case highlights the W-plasty's usefulness to correct cosmetically unsatisfactory scars as well as the importance of post-surgical aesthetic outcome for the patient and the physician. The authors' experience with this scar revision technique

shows that if correctly implemented in properly selected cases, it is possible to achieve a marked improvement in the scar's appearance, making it less noticeable. However, the benefit of W-plasty is reduced in long scars since the regular repetitive pattern (zig-zags) can lend enhanced evidence to the scar.[2,5] In these cases it is preferable to use the geometric broken line technique of correction.

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Case Reports

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Merkel cell carcinoma: clinical, dermoscopic and immunohistochemical aspects of a rare tumor

Carcinoma de células de Merkel: apresentação clínica, dermatoscópica e imuno-histoquímica de um tumor raro

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ABSTRACT

The Merkel cell carcinoma is a rare and highly aggressive neuroendocrine skin tumor. The purpose of this paper is to warn of the possibility of this diagnosis, usually not considered as an initial hypothesis in cutaneous neoplasias. The authors describe two cases of elderly female patients with complaints of a single erythematous nodule on the face. The diagnoses of basal cell carcinoma and amelanotic melanoma were considered. The presence of telangiectasias was evident at dermoscopy. The incisional biopsy's histology evidenced Merkel cell carcinomas. This neoplasia typically occurs in Caucasian patients with over 65 years of age, emerging as an erythematous-purplish nodule of rapid growth, with immunohistochemistry being essential for the diagnosis.

Keywords: skin Neoplasms; carcinoma, Merkel cell; neuroendocrine tumors; immunohistochemistry

RESUMO

Carcinoma de células de Merkel é tumor cutâneo neuroendócrino raro e altamente agressivo. Objetiva-se neste artigo alertar para a possibilidade desse diagnóstico, geralmente não considerado hipótese inicial em neoplasias cutâneas. Relatamos dois casos de pacientes do sexo feminino, idosas com queixa de nódulo único eritematoso na face. Aventaram-se hipóteses diagnósticas de carcinoma basocelular e melanoma amelanótico. À dermatoscopia foi evidente a presença de telangiectasias O exame histopatológico da biópsia incisional diagnosticou carcinoma de células de Merkel. Essa neoplasia ocorre tipicamente em pacientes brancos, acima de 65 anos, manifestando-se como nódulo eritêmato-violáceo, de crescimento rápido, sendo a imuno-histoquímica essencial para o diagnóstico.

Palavras-chave: *neoplasias cutâneas; carcinoma de célula de Merkel; tumores neuroendócrinos; imuno-histoquímica*

INTRODUCTION

The Merkel cell carcinoma (MCC) – or primary neuroendocrine carcinoma of the skin – was first described by Cyril Toker in 1972.[1-3] This is a malignant proliferation of highly anaplastic cells that share characteristics with those derived from the neuroectoderm. The estimated incidence in the United States is 0.32 cases/100,000 people.[3] An increase in the number of reported cases has been observed more recently, especially after the emergence of new immunohistochemical markers.[2] When conducting diagnoses, physicians rarely suspect of the presence of this lesion. In a study with 106 patients diagnosed with primary MCC, this clinical hypothesis was suggested in only 1% of cases.[3] The objective of the present paper is to describe two cases diagnosed at a referral center and raise the alert regarding the possibility of MCC, which is often not considered as an initial hypothesis in cutaneous neoplasias, as well as to highlight the importance of early diagnosis and treatment.

CASE REPORTS

Case 1: A 78 year-old female patient sought medical care complaining of nodular lesions in the left pre-auricular region for roughly two months. Her personal history included systemic hypertension and hypothyroidism. The dermatological examination revealed a single erythematous nodule with 3cm in diameter and telangiectasias on its surface, located on the left preauricular region (Figure 1A). The presence of telangiectasias was evident under dermoscopy (Figure 1B). In light of the clinic history and dermatological examination, the diagnoses of basal cell carcinoma and amelanotic melanoma were hypothesized. An incisional biopsy was then carried out and the material sent for histology and immunohistochemistry. The anatomopathological result evidenced infiltration of basaloid cells, with scant cytoplasm in the dermis (Figure 2A) and presence of necrosis foci (Figure 2B). The immunohistochemistry was positive for cytokeratin 20 (CK20), chromogranin, synaptophysin, CD56 and AE1/AE3 (Figures 3A and B), confirming the diagnosis of Merkel cell neuroendocrine carcinoma.

The patient was referred for surgical treatment in the authors' dermatologic service having undergone excision with 3cm margins and continuous suture anchored on the borders with 4.0 nylon for hemostasis (Figures 4A, B and C) and healing by second intention with activated carbon dressing. The patient returned for weekly dressings, with the activated carbon maintained until week 9. Dressings with Kollagenase were applied from week 10 up until the healing was complete (Figure 4D).

Case 2: An 87 year-old female patient (widow, rural worker) sought medical care complaining of a nodular lesion in the left mandibular region that had emerged five months before and had progressive growth. Personal history included lung disease and current use of aminophylline – she had smoked Brazilian tobacco rolled in corn leaves for 50 years in the past. The dermatological examination revealed a nodule with erythematous, smooth glossy surface in the left mandibular region, with 5cm in diameter and many telangiectasias (on the surface) (Figure 5A). In addition, there was presence of a palpable perilesional, hardened and fixed lymph node. Dermoscopic examination showed the presence of telangiectasias (Figure 5B). In light of the clinical history and dermatologic examination, the hypotheses of Merckel cell carcinoma and amelanotic melanoma were considered. After an incisional biopsy with histologic and immunohistochemical studies, the pathological results showed

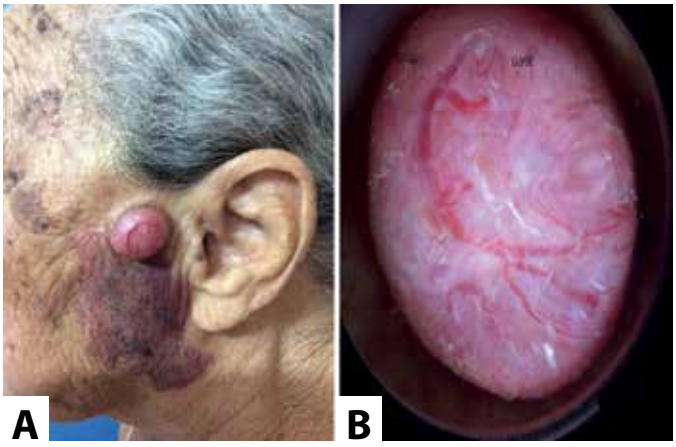

Figure 1: A - Single erythematous nodule with 3cm in diameter, with telangiectasias on the surface, located on the left preauricular region **B -** Dermoscopy of the lesion showing the presence of telangiectasias

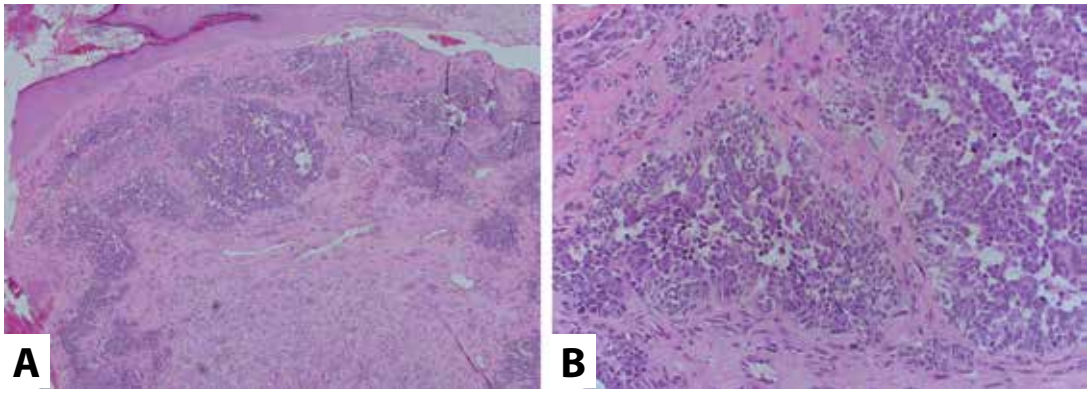

Figure 2: A (HE 10X): Basaloid cells with scant cytoplasm infiltrating the dermis. **B -** (HE 40X) Detail: presence of necrotic foci

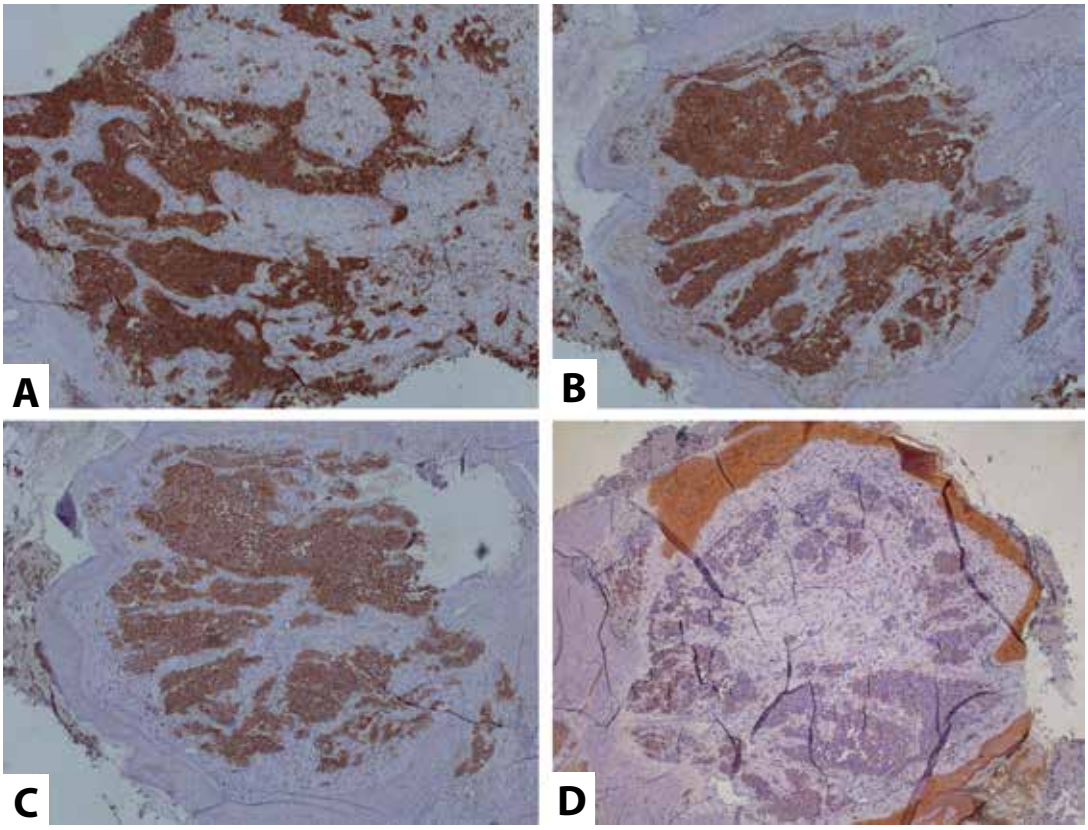

Figure 3: Immunohistochemistry
A - CD56
B - Synaptophysin
C- Chromogranin A
D - AE1/AE3

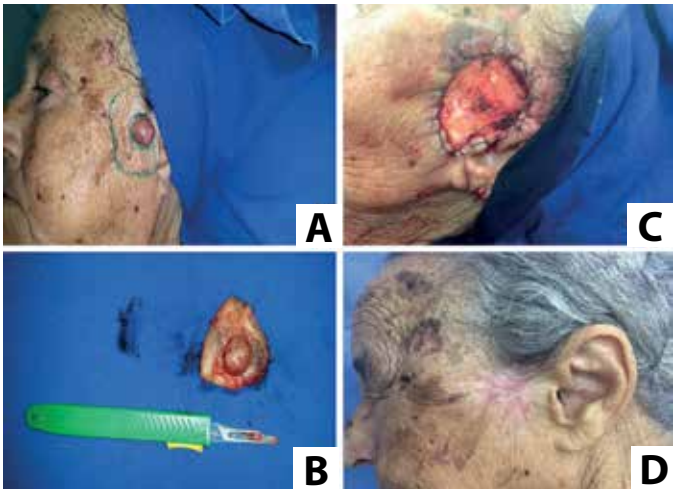

Figure 4: A - Intra-operative **B -** Surgical specimen
C - Immediate post-operative **D –** Late post-operative, 8 months after

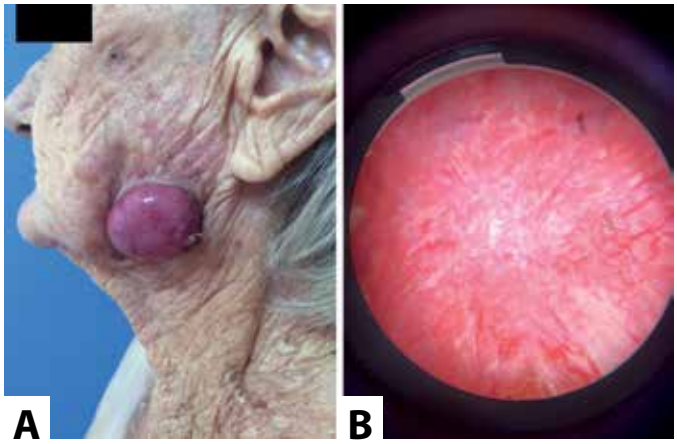

Figure 5: A - Erythematous nodule with 5cm in diameter and telangiectasias on the surface, located on the left mandibular region.
B - Dermoscopy of the lesion showing the presence of telangiectasias

the presence of a undifferentiated small cell neoplasia penetrating the dermis (Figure 6A), and small cells with scant cytoplasm conformed on the dermis (Figure 6B). The immunohistochemistry was positive for enolase and synaptophysin (Figure 7), confirming the diagnosis of neuroendocrine Merkel cell carcinoma. The patient was referred for surgical treatment at the oncology department due to the presence of palpable satellite lymph node and metastasis to the parotid gland.

DISCUSSION

The Merkel cell carcinoma is highly aggressive neuroendocrine skin tumor.[1,4,5] It typically occurs in Caucasian patients with over 65 years of age, with a slight predominance in men,[2,3,5] – which was not observed in the two cases described in the present paper. It manifests clinically as a single painless, erythematous-purplish nodule,[4,3,6,7] of rapid growth and aggressive

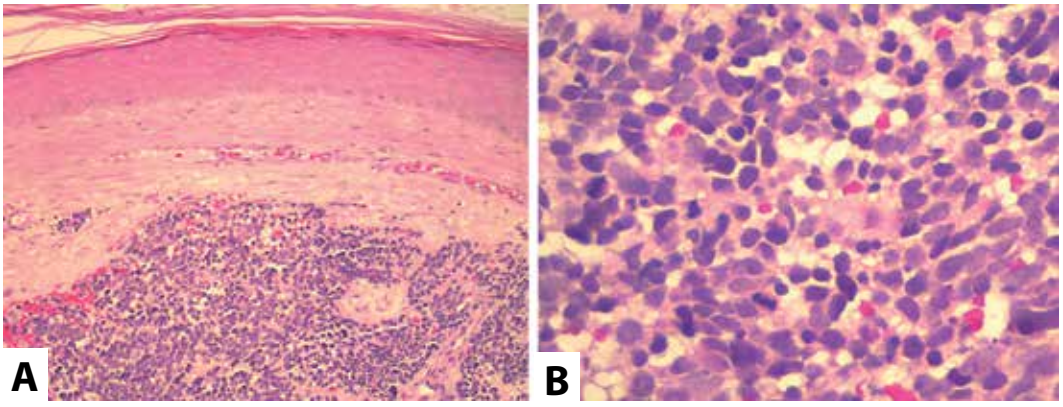

Figure 6: A - (HE 10X): Small cell undifferentiated neoplasm penetrating the dermis.
B - (HE 40X) Detail: small cells with scant cytoplasm conformed on the dermis.

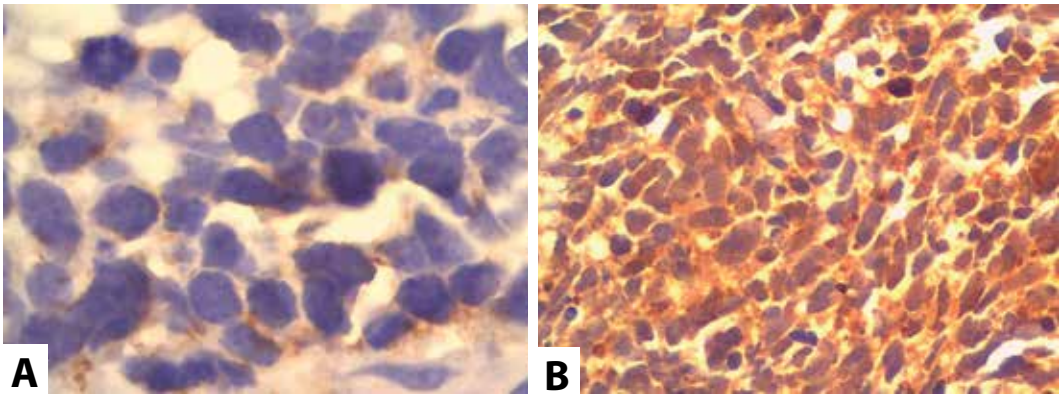

Figure 7: Immunohistochemistry**:**
A - (100X): Synaptophysin
B - (40X): Enolase

nature.[2,5] Telangiectasia are often observed. The most common sites involved are the head and neck (40 - 50%),[2] followed by the trunk and limbs. Its etiology remains unclear, and the hypothesis that describes the tumor as originating from Merkel cells – as a mechanoreceptor of the basal layer of the epidermis – or from pluripotent stem cells which later differentiate into neuroendocrine is controversial.[2,3,5] In a study with 27 MCC cases, 41% were associated with other epithelial lesions, such as carcinoma in situ squamous cell carcinoma , invasive squamous cell carcinoma, basal cell carcinoma and actinic keratosis.[1,3] These findings strengthen the hypothesis of pluripotent stem cell origin in the epidermis, potentiated by the UV radiation's mutagenic effects.[3] Other risk factors include: immunosuppression and polyomavirus infection.[1,3] Immunohistochemistry is crucial for the differential diagnosis with other tumors.[3] There is positivity for epithelial proteins – such as cytokeratins – and neuroendocrine markers – such as neuron-specific enolase, synaptophysin, CD56 and chromogranin A.[2,3,6,8] In particular, CK20 is an important marker of MCC, offering high especificity.[2] About 5% of patients do not express CK20. Differential diagnosis includes: hemangioma, angiosarcoma, small cell cutaneous lymphoma, non-melanoma skin cancer, amelanotic melanoma, Ewing's sarcoma, cutaneous metastases of pulmonary small cell carcinoma, neuroblastoma and rhabdomyosarcoma.[2] Unlike other non-melanoma skin cancers, MCC has a high propensity to metastasize and regionally and distally.[2] Lymph nodal spread occurs early and frequently, with approximately 20% of cases presenting clinically positive lymph nodes.[2] The main sites of metastases are the liver, bones, lung, brain and non-regional lymph nodes.[2,5,6] Due to the rarity of the tumor, there are few treatment protocols based on evidence, nevertheless surgery and radiotherapy are the main therapies.[1] The initial treatment consists of surgical excision with margins in excess of 3cm.[2,5,8] The indication of prophylactic lymphadenectomy due to the high probability of lymph node metastasis is debatable since whilst there is a higher locoregional disease control, it does not improve survival.[5] Adjuvant radiotherapy is often recommended and is associated with decreased local and locoregional recurrence, and increased survival.[2,5] Adjuvant chemotherapy is controversial and its use is limited. [5] Clinical diagnosis of MCC is complex, however suspecting of its presence is important for early diagnosis and treatment,[3,5] factors that can have a positive impact on the patient's survival.

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Complex reconstruction in the right hemiface: the challenge of two synchronous basal cell carcinomas

Reconstrução complexa em hemiface direita: o desafio de dois carcinomas basocelulares sincrônicos

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ABSTRACT

Basal cell carcinoma is the most frequent malignant skin tumor. Its incidence has been increasing, leading to the emergence of a public health problem. The common delay in seeking treatment hampers tumor removal. The objective of this paper was to report a case of two synchronous basal cell carcinomas on the face and the challenge of their surgical resolution. Good aesthetic and functional outcomes were obtained using the rotation flap technique and a complex reconstruction of the hemiface. Surgical reconstruction constitutes a challenge for the surgeon, who should prioritize the oncologic cure while preserving the functionality and aesthetic appearance, when possible.

Keywords: carcinoma, basal cell; surgical flaps; skin neoplasms

RESUMO

O carcinoma basocelular é o tumor maligno de pele mais frequente, e sua incidência está aumentando, emergindo como um problema de saúde pública. O frequente atraso na busca de tratamento dificulta a remoção tumoral. Reportam-se um caso de dois carcinomas basocelulares sincrônicos na face e o desafio de sua resolução cirúrgica. Foi obtido bom resultado estético e funcional por meio da técnica de rotação de retalho e reconstrução complexa da hemiface. A reconstrução cirúrgica constitui um desafio para o cirurgião, que deve priorizar a cura oncológica, preservando a funcionalidade e o aspecto estético quando possível.

Palavras-chave: *carcinoma basocelular; retalhos cirúrgicos; neoplasias cutâneas*

Case Reports

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common malignant skin tumor in the world. Its incidence is increasing and emerging as a public health problem.[1,2] The search for care and treatment is often delayed, making it difficult to remove the tumor.[3]

CASE REPORT

A 70 year-old male patient reported the emergence of two lesions in the right hemiface roughly three years before. The physical examination revealed two erythematous lesions with infiltrated borders, ulcerated center and inaccurate limits in the right temporal and right lateral infraorbital regions (including part of the lower eyelid), both measuring 2cm in their longest diameters. The previous biopsy revealed nodular BCC. Planning was carried out for the exeresis of both lesions in a single surgical time, with preoperative margins being demarcated with naked eye, followed by dermoscopy, which allowed the re-marking of the lateral margins of the two lesions due to the presence of arboriform telangiectasia extending beyond the previously demarcated margins. The two lesions were then excised under local tumescent anesthesia, with minimum margins of 5mm. Flaps were used for the closure using the following technique: the infraorbital defect was closed with a malar flap (Mustardé) by laterally extending the incision along the lower eyelid's line up until the temporal area's defect, uniting them in the same direction, up until the hair line; this incision then run inferiorly, passing in front of the auricular pavilion, to reach the cervical region. The detachment of this flap – as is done in rhytidectomy – and its rotation allowed the closure of the infraorbital defect and the reconstruction of the lower eyelid, in addition to covering part of the temporal area (Figure 1). The closing of the latter, was then completed with the lateral advancement of the eyebrow region's skin, which was incised in the upper line of the eyebrow (Figure 2). The immediate outcome can be seen in Figures 3 and 4. The sutures were performed in a single plane in the skin, with simple stitches and nylon threads, which were removed 10 days after. The histological examination of the parts indicated the presence of ulcerated, nodular subtype BCC, with 5mm free peripheral margins. There was total healing and tissue integration, with good aesthetic and functional results.

DISCUSSION

The body site with greatest incidence of BCCs is the face, and the first choice treatment is exeresis.[1,4] In this location, not only the cure is necessary but also the attempt to preserve the facial aesthetics.[1] In some cases, the tumor's size or the presence of more than one lesion close to one another turns oncologic surgery into a challenging procedure.[1]

The surgical margins were demarcated using dermoscopy – which is a trend in dermatologic surgery – and may have contributed to the excision of both lesions with free margins, since studies suggest that the rate of complete excision of BCCs increases to 98.5% from 95% when dermoscopy is employed.[5,6]

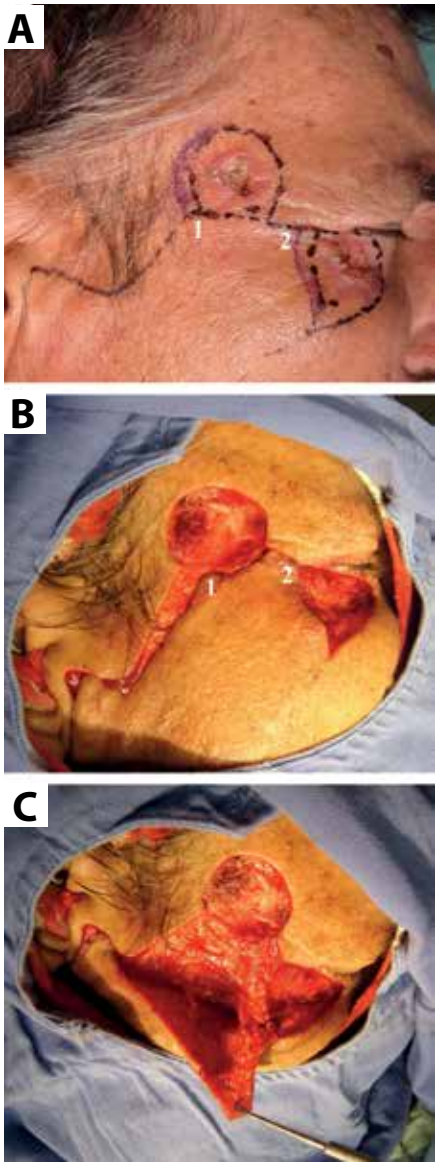

Figure 1: A) Right hemiface demonstrating lateral infraocular and temporal lesion, with preoperative marking assisted by dermoscopy.
B) Surgical incisions in the exeresis locations, and incision reaching the pre-auricular region for flap detachment
C) Flap detachment

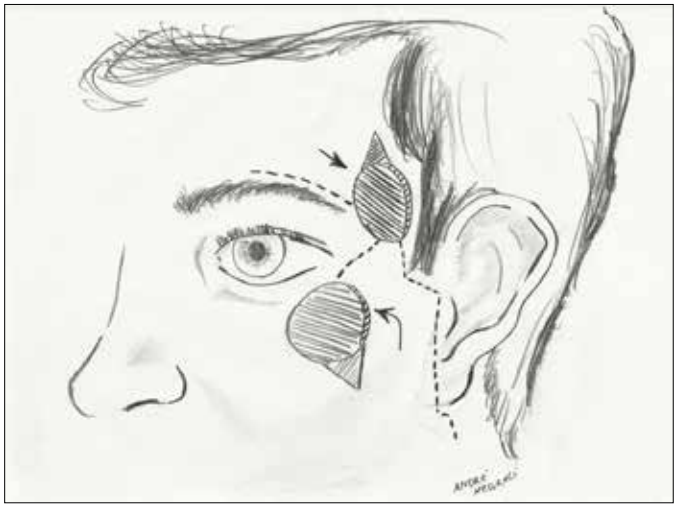

Figure 2: Diagram showing the flaps used for closing both defects

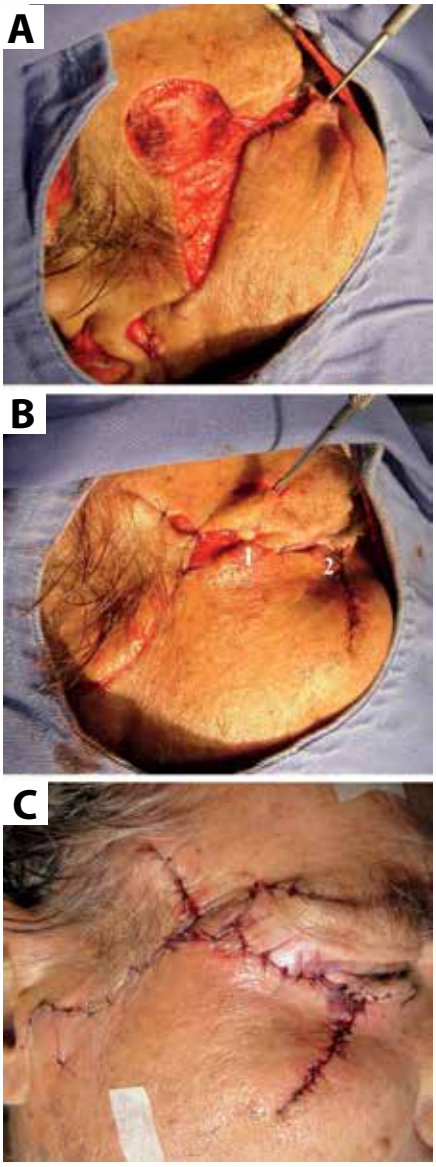

Figure 3:
A) Flap rotation for the fitting in the medial border of the infraocular incision.
B) Cardinal points for positioning the flap.
C) Complete reconstruction in the immediate postoperative

On a smaller scale, the surgery described resembles the east west flap, mainly used in resections of nasal tumors.[5] The temporal region is a risk area, where the resection should be careful and aimed at preventing that the surgical plan be deepened, thus avoiding damage to the temporal nerve.[3] The infraocular area is delicate implying that there should be concern with ectropion formation in the postoperative period, especially in the case of extensive flaps in this region.[3] It is possible to perform advancement flaps or lateral rotations so that this complication be minimized or avoided, as was done in the case described.[3]

Surgical reconstruction is challenging for the surgeon, who should prioritize the oncologic cure while preserving the functionality and aesthetic appearance when possible. The choice of technique should be adequate and individualized for each tumor type, location, skin elasticity and overall condition of the patient. In the authors' experience, the combination of techniques allowed the complex combined excision of two synchronous BCC lesions of large dimensions, in areas next to each other in the face. The excisions were performed in the same surgical time, providing satisfactory functional and aesthetic outcomes, in addition to allowing the prompt return of the patient to his social life.

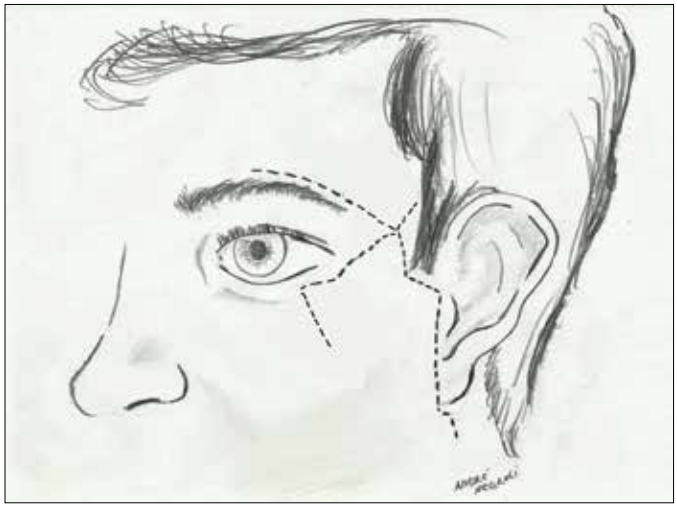

Figure 4: Diagram showing the final outcome

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Case Reports

Triple therapy in the treatment of keloids located in the anterior thoracic region

Terapia tríplice no tratamento do queloide na face anterior do tórax

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ABSTRACT

Keloids have functional, aesthetic and psychological impacts that can influence the patients' quality of life. Moreover, given the high rate of recurrence – particularly in large lesions located in the anterior thoracic region – they are more difficult to treat. This paper reports a successful treatment for keloids in this area using a new technique that combines intense pulsed light, botulinum toxin type A and the conventional treatment with injection of corticosteroids.

Keywords: keloid; intense pulsed light therapy; Botulinum toxins, type A; adrenal cortex hormone

RESUMO

Queloides apresentam impacto funcional, estético e psicológico podendo influenciar a qualidade de vida desses pacientes. Além disso, diante da alta taxa de recorrência, particularmente em lesões de grandes dimensões e localizadas na face anterior do tórax, são mais difíceis de tratar. Este artigo relata tratamento de sucesso para queloide na face anterior do tórax utilizando nova técnica que combina luz intensa pulsada, toxina botulínica tipo A e tratamento convencional com infiltração de corticosteroide.

Palavras-chave: *queloide; terapia de luz pulsada intensa; toxinas botulínicas tipo A; corticosteroides*

INTRODUCTION

Keloids are benign lesions consisting of the exuberant hyperplasia of the dermis' differentiated connective tissue. It can arise from changes in the skin healing process or be induced by trauma caused by lacerations, tattoos, burns, injections, bites and vaccines, as well as dermatoses, such as acne.[1]

This type of scarring can occur in various body regions, preferably in sites above the abdomen, such as the thorax, shoulders and neck. Some related symptoms, such as pruritus, pain and restricted mobility, collaborate to the worsening of the affected patients' quality of life.[1]

This type of scar formation's exact pathophysiology is unknown,[2] although several studies have demonstrated high levels of transforming growth factor beta (TGFb1) in the keloids' fibroblasts, including increased collagen production and integrin expression, decreased expression of metalloproteinases and of inhibitors of metalloproteinases.[3]

Many treatments are available, however most of them have constraints and limited resolution.[4] Some of the established

treatments, such as intralesional corticosteroids and silicone plates, are used to treat unsightly scars due to their ease of use. In patients with wide scars, where the difficulty of treatment is even greater, surgical removal is usually employed.[3] Other types of treatment combining techniques have been described, and among them are adjuvant radiotherapy, intralesional injections of 5-fluourouracil or bleomycin, interferon or imiquimod applications and betatherapy.[1]

Nevertheless, the improvement of the appearance of the lesion by more than 80% is rare in light of the need for maintaining the treatment and the difficulties arising from the dimensions and location of the lesions.[4] Aiming at decreasing such limitations and achieving better outcomes, the authors propose a new treatment modality based on the triple therapy using intralesional corticosteroids, intense pulsed light (IPL) and botulinum toxin type A (BTXA).

CASE REPORT

A 25 year-old female patient, Fitzpatrick phototype II, born and raised in the city of Canoas, in the Southern Brazilian State of Rio Grande do Sul, with a family history of keloids sought treatment for a single cicatricial keloid lesion with irregular borders, erythematous in color, painful to palpation, located in the central region of the anterior chest wall, measuring 8 x 1.7cm, with progressive growth for the previous 15 years. She reported the onset of the lesion following a viral disease, describing various unsuccessful treatments with cryotherapy and corticosteroids (Figure 1).

METHOD

The patient underwent the application of occlusive topical anesthetic with 10% lidocaine and 7% tetracaine for 40 minutes in the keloid area, followed by local antisepsis with 2% aqueous chlorhexidine. The triple therapy combined treatment was carried out with four monthly sessions, according to the following sequence:

1) 540nm IPL, 12mm tip, 15ms pulse duration, 15-17 J/cm2 fluence range, 1-2 passes, cooling 5, across the lesion. The device used was the IPL ETHEREA® (INDUSTRA® Technologies, São Paulo, Brazil).

2) 28UI Onabotulinumtoxin A (Botox®) 100 IU vial, 2.5ml dilution in 0.9% saline solution, applied uniformly in the subdermal plane.

3) 1ml intralesional corticosteroid, 40mg/ml. The application was performed in an evenly fractionated way: the drug was applied across the keloid. The area with greater hypertrophy received a greater amount of the substance.

After the procedure, the treated area was occluded with micropore. The patient was instructed to remove it after 24 hours, maintaining the occlusion of the area treated with a silicone plate at night and using sunscreens during the day.

RESULTS

There was improvement in the lesion's thickness in all treated areas – more markedly in the more elevated portions, improvement of the erythema and decreased local vascularization. The patient had clinical improvement of the pain and discomfort, as well as a reduction in the growth of the lesion since the beginning of treatment, showing satisfaction with the outcomes (Figures 2 and 3).

DISCUSSION

Keloids are pathological scars known as fibroproliferative, thick and elevated alterations that extend laterally to the initial margins of the skin's lesion, being primarily characterized by the overproduction of collagen fibers and secondarily by the hyperplasia of fibroblasts.[5] They do not regress spontaneously and have a tendency to recur after resection. Additionally, keloids are not aesthetically acceptable, especially if associated to symptoms. Currently, there is no universally accepted isolated therapy or combination of techniques that allow an effective treatment and prevent recurrence.

The present case report describes a keloid lesion in active and symptomatic phase, located in an anatomical region of difficult control, therefore offering greater difficulty for achieving satisfactory outcomes using conventional treatments. As a result,

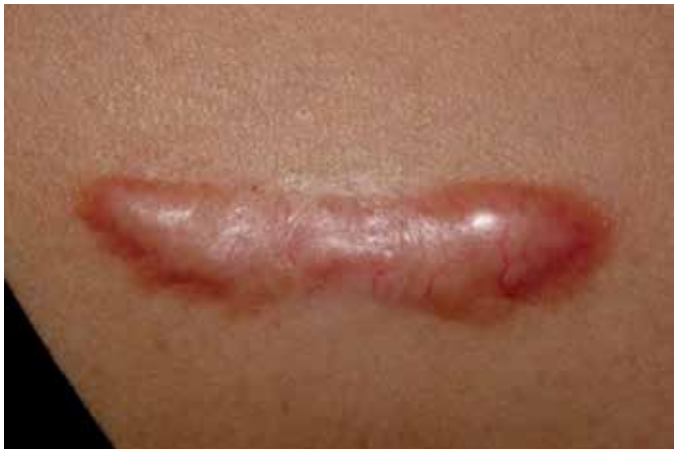

Figure 1: Keloid before the treatment. Enlarged view

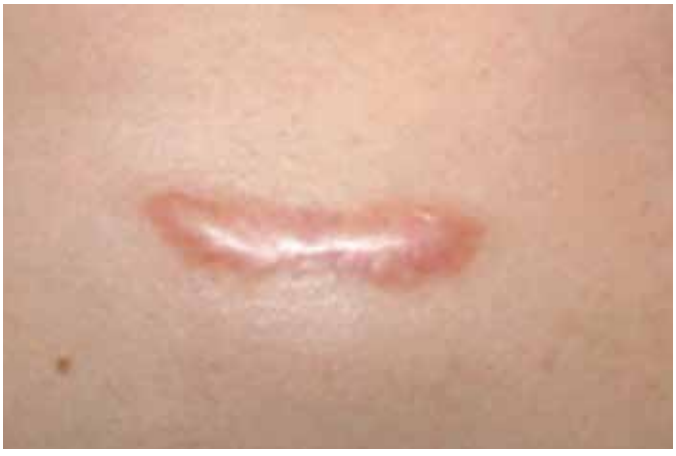

Figure 2: Keloid before the treatment

the authors chose the combined treatment with IPL, BTXA and injection with corticoid, already described by Wu.[6]

Studies have recently shown the importance of the combination of techniques – such as surgery, laser and drugs – for achieving better outcomes in the treatment of unsightly scars,[7] introducing algorithms for the treatment of scars based on the type of cicatricial lesion.

Few studies have reported the IPL effectiveness in the treatment of hypertrophic scars or keloids, quoting limitations in the use of this type of treatment for high phototypes, due to the risk of pigmentary complications.[1] Some have shown improvement in reducing the texture, size and color of the treated keloid, while another suggests the need for at least six sessions at intervals of two to four weeks so that there is improvement regarding the reduction of size in the hypertrophic scar being treated. Using IPL, the authors of the present study obtained improvement in the keloid's vascular appearance, erythema and pain, in addition to a reduction in the size by decreasing the local inflammatory component with only four sessions.

Another technique used in combination included BTXA. Recent studies describe that the use of BTXA as monotherapy assists in inhibiting the growth of hypertrophic scars and improves their appearance by inactivating fibroblasts, and can inhibit the expression and proportion of collagen type I and III.[8] Other studies observed improvements in the lesion's volume, and tension, and in the recurrence in two or three-month treatments. Nonetheless, they concluded that the clinical efficacy of BTXA remains unclear.[9] Additionally, keloids have a greater density of nerve fibers in the dermis than the normal skin. In addition, these nerve fibers are located in deeper planes. In this manner, it was possible to observe that there was a decrease in the keloid's size and proliferative activity after the inhibition of the nerve impulse transmission via subdermal injections of BTXA, due to the reduced tension of muscle activity between the cicatricial fibers.[10]

The injection of corticoid was used in combination with IPL and BTXA, determining the inhibition of protein synthesis and fibroblasts migration. In the study carried out by the authors of the present paper, it was possible to observe a significant regression of the patient's symptoms due to the decrease in the lesion's volume component.

After treatment, the authors chose to use a silicone plate for local compression, maintaining the mechanical pressure and leading to the reorganization of collagen fibers during the treatment. Although this mechanism is not completely understood, it is hypothesized that due to the impermeability on the stratum corneum, there is a continuous hydration of the skin, with a reduction in the incipient hyperemia and fibrosis.[5]

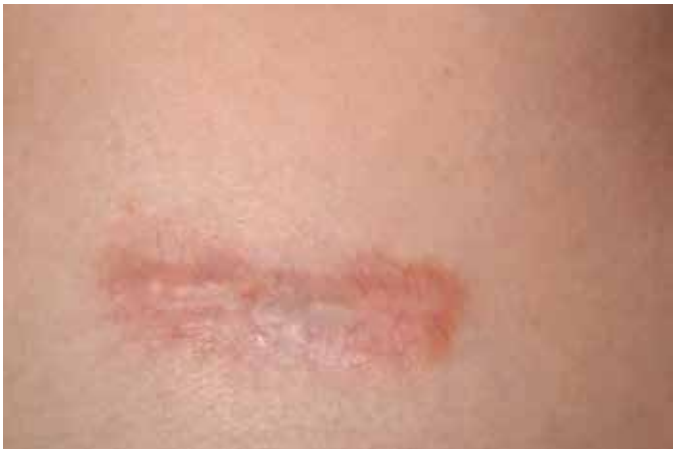

Figure 3: Queloide após quatro sessões de tratamento

CONCLUSION

The outcome obtained demonstrates the efficacy of the triple therapy in the treatment of keloids, despite the recurrence rates of active, symptomatic lesions with unfavorable prognostic factors, such as difficult locations. Moreover, it showed that there is an association of the vascular inflammatory activity, neurological stimulation and collagen hyperproliferation in fibroproliferative scarring. The treatment proposed for this keloid – with the combination of techniques – was safe and well tolerated, and should be considered in the management of this type of lesions.

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Letter to the editor - Grafting by epidermal scraping: a therapeutic option

Carta ao editor - Enxerto por raspagem epidérmica no vitiligo estável: uma opção terapêutica

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Dear Sirs,

In recent years, surgical treatment of vitiligo has been an area of great academic interest for us. We were enthused with the recent paper entitled *Grafting by epidermal scraping in stable vitiligo: a therapeutic option* (DOI: http://dx.doi.org/10.5935/scd1984-8773.201682760),[1] for it addresses a therapeutic modality – melanocyte transplantation – which is still little used in Brazil. However, we have noticed that readers could misinterpret some of the remarks made in literature review carried out by the authors. In this manner, we would like to address those remarks in a critical and constructive way.

In the article's abstract and introduction, the authors state that surgical treatment of vitiligo is preferred over clinical treatment in case of disease stability. However, the idea that surgical treatment should be applied only in cases that are refractory to clinical treatment (besides being stable and devoid of the Köebner's phenomenon) still predominates in practice and literature, as can be verified in seminal articles on the subject.[2-4] Based on this fact, we deem that in light of the risks inherent in any surgical procedure (albeit minimal in this context), clinical treatment should still be tried in the first instance, even in cases of stable vitiligo and devoid of Koebner's phenomenon.

In the *Discussion* section, first paragraph, where it reads "*The main advantage of this method as compared to the original punch micrografting technique is that it does not lead to the "cobblestone" aspect in the treated area, dyschromias in the donor and recipient areas, (…)*", we find it difficult to state so categorically that the technique does not lead to dyschromia in the recipient and donor areas. In principle, any surgical technique for transplantation of melanocytes can lead to that condition. The presence of dyschromia (hyperchromia in both the donor and the recipient areas) is seen in the surgical outcome of the paper in question. Although they are

often temporary, dyschromias can remain indefinitely, regardless of the technique used. I would like to point out that even more "conservative" techniques for obtaining the tissue, such as Suction Blister Epidermal Grafts (SBEG) method, can leave residual hyperchromia in around 40% of cases, as reported in a recent study.[5]

Regarding the statement "*The acral regions and the areas over the joints should be avoided – especially in very young patients – for it is considerably difficult to implement the techniques in these locations and there is risk of treatment failure",* it is important to note that assuming that the primary indications for the surgical treatment of vitiligo (stable disease, absence of Köebner phenomenon and refractoriness to clinical treatment) are fulfilled, these areas can be treated with surgical technique. Although repigmentation rates are lower than those provided by surgical treatment in other areas – such as the face, for example – the technique still achieves good results in more than 50% of cases, as has already been demonstrated in the literature.[6] A recent example is the case of a young patient with vitiligo circumferentially affecting the ankle region, which was successfully treated by us using the uncultured epidermal cell suspension technique (Figure 1).

Moreover, the technique is also not contraindicated for lips and eyelids, as set out in Table 1 of the article in question.[1] On the contrary, it is often used for this purpose.[4]

Furthermore, we consider that the contraindication for young patients is only subjective. In fact, it depends on the patient's understanding and collaboration during the operative and postoperative periods (period during which the dressing must be in place). Studies have already shown the method's safety in this age group, with good therapeutic outcomes.[7]

Finally, contrary to what was reported in Table 1 of the article in question, surgical results with cultured melanocytes suspension are already well reported in the literature, with more than 400 cases treated only in the study conducted by Zhang et al.[8]

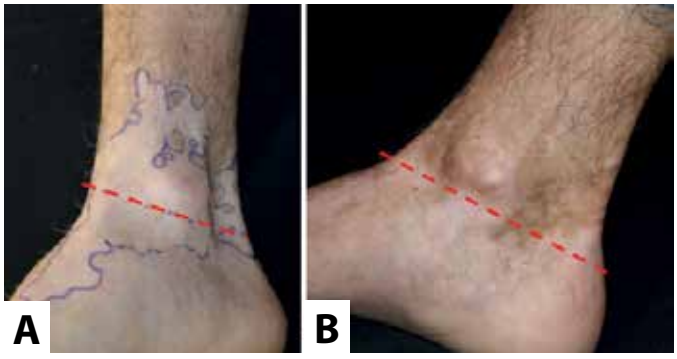

Figure 1 A - Acromic lesions circumferentially affecting the ankle region **B -** Five months after surgical treatment, with uncultured epidermal cell suspension associated with phototherapy NB UVB: repigmentation > 90% in the treated area (supramalleolar region, above the dashed line)

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