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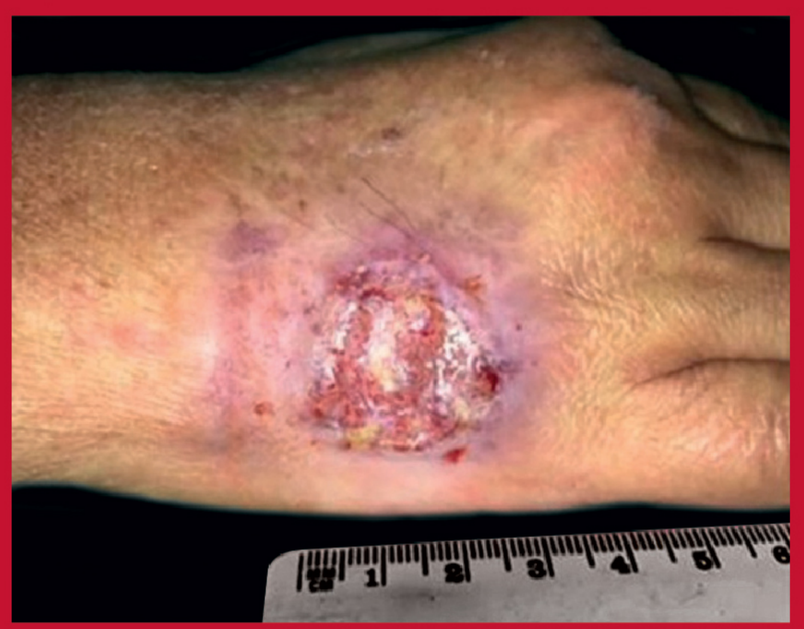

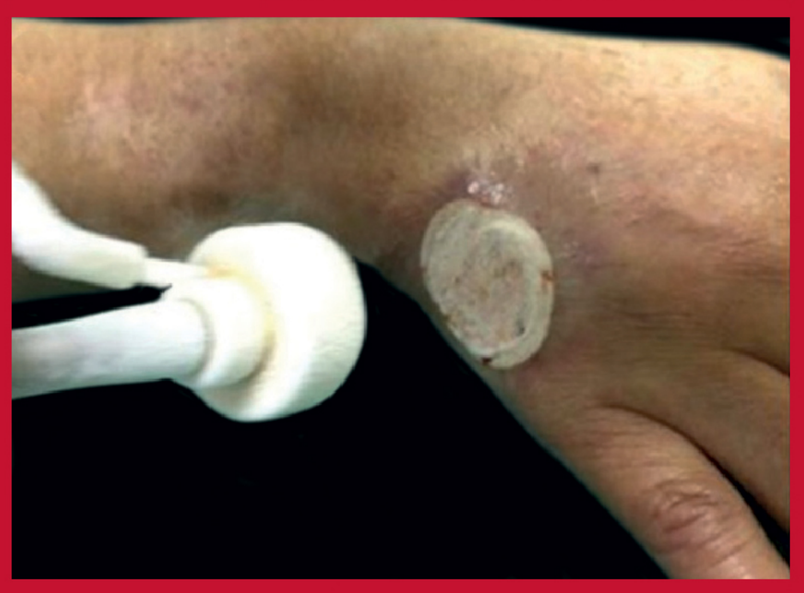

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Resultados: descrever os principais resultados que devem ser acompanhados de estimativas pontuais e medidas de dispersão (p.ex., média e erro padrão) ou de estimativas intervalares (p.ex., intervalos de confiança), bem como os níveis descritivos dos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

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

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

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# Hydroquinone: hero or villain?

## *Hidroquinona: vilã ou heroína?*

DOI: http://dx.doi.org/10.5935/scd1984-8773.20179301

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**ABSTRACT**

Hydroquinone has been used as a whitening agent for more than 50 years, however its safety and toxicity have been questioned in the last two decades. In the present literature review, it is possible to verify that its carcinogenic and mutagenic potential in humans has not been proven to date. In addition, the population is in fact much more exposed to hydroquinone than commonly perceived, via both cosmetic compounds (e.g. hair dyes) and foods (e.g. pear, beverages and coffee). Therefore, prescribing hydroquinone as a depigmenting agent in concentrations of up to 4% is safe and devoid of systemic consequences.

Keywords: hydroquinone; toxicity; melanosis; safety

**RESUMO**

*A hidroquinona é usada como agente clareador há mais de 50 anos, e, nos últimos 20, suas segurança e toxicidade têm sido questionadas. Nesta revisão bibliográfica, pode-se verificar que seu potencial carcinogênico e mutagênico não foi comprovado até hoje em humanos. Além disso, estamos muito mais expostos à hidroquinona do que imaginamos, tanto em compostos cosméticos (por exemplo, tinturas de cabelos) quanto em alimentos, como a pera, bebidas e o café. Portanto, sua prescrição como despigmentante em concentrações de até 4% é segura e sem consequências sistêmicas.*

***Palavras-chave**: hidroquinona; toxicidade; melasma; segurança*

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## INTRODUCTION

Hydroquinone is an aromatic phenolic compound used as a bleaching agent for over 50 years. It is also present in cosmetics, such as hair dyes, with multiple roles when in low concentrations (up to 2%); as an antioxidant, fragrance and inhibitor of polymerization. It is also used as a reducing agent for photography manufacturing. Like this, it is present in the everyday life of a large part of the population, mainly for women. Hydroquinone's toxicology and safety have been investigated since 1986 by the Cosmetic Ingredient Review (CIR). The target for the reviews is its carcinogenic potential. According to the assessment performed by the **International Agency for Research on Cancer (IARC)** in 1999 on its carcinogenic risk in humans, hydroquinone is not classifiable according to its carcinogenicity to humans (Group 3).[1] In a study about its safety in 2006, Nordlund et al demonstrated that there is no malignancy risk and that the risk for ochronosis is low when used with a medical prescription and surveillance.[2]

Study conducted at Instituto Brasil de Tecnologias da Saúde (Ibts) – Rio de Janeiro (RJ), Brasil.

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**Conflict of interests:** None

## HISTORY

Hydroquinone's bleaching effect was first observed in cats by Oettel in 1936. In the 1950s, the substance was used as a sunscreen and its bleaching effect was seen randomly. Not too long after, it was available in some places in the USA as a topical agent, when its bleaching effect in human skin was noted. Spencer, in 1961, performed the first study using hydroquinone in the concentrations of 2.3 and 5% twice a day for 3 months on the dorsum of the hands of Caucasian men with solar lentigos. He noticed that the results were dose-de- pendent, with recurrence upon discontinuation. In 1998, in a non-randomized study of the use of hydroquinone 4% with a broad-spectrum sunscreen, 89.5% of patients improved. In 2000, Ennes et al. conducted a comparative study of hydroquinone 4% with placebo for the treatment of melasma, and found that 38% had a complete preliminary response against 8% of the patients on placebo.[3]

## PHARMACOLOGY

Hydroquinone (1,4 dihydroxybenzene) is a phenolic derivative that acts inhibiting tyrosinase, possibly through the connection with this enzyme or the interaction with copper molecules in its coupling site, leading to a change in the melanosome and an increase of its destruction, besides also a possible inhibition of the DNA and RNA synthesis.[3]

## HYDROQUINONE ABSORPTION

We can assume the exposure to hydroquinone throughout life is not a worrisome issue. Excessive exposure to hydroquinone 4% cream for 6 months (let us say that 6 56.8g tubes have 13.6g of hydroquinone, of which half is absorbed, (a total of 6.8g) is comparable to life-long exposure of hydroquinone in coffee (62g/cup X 1 daily cup X 365 days/year X 40 years = 0.9g) or pears (2500 g/pear X 1 pear/week X 52 weeks/year X 10 years = 1.3g).What can be even more significant is that humans have a baseline excretion of 115.4g/h or 2770g/day of hydroquinone with no exposure to bleaching agents. Over 60 years, this amount reaches 61g of hydroquinone in the urine,that presumably found its way to excretion after systemic exposure, as through food.[4]

## HYDROQUINONE TOXICITY AND SAFETY

In the last decade, there has been a great concern about the use of topical hydroquinone due to the lack of clinical studies that fulfill the new federal rules and because of the therapy risks that have been observed. Ochronosis, a blue-white discoloration, has been noticed in dark-skinned individuals from South Africa. In the United States, ochronosis is much less frequent. An explanation for this phenomenon is the fact that hydroquinone in concentrations higher than 8% can be found in OTC products in other countries. This uncontrolled access to high concentrations for a prolonged period can increase the risk of adverse effects related to this medication. Besides, these formulations can contain other substances, such as resorcinol, lime juice, mercury, potash, crushed camphor spheres, peroxides and chlorides, all of which can contribute to the development of ochronosis.[5-8]

In 1982, the Food and Drug Administration (FDA) determined initially that hydroquinone would be safe and effective enough to be sold in the concentrations of 1.5 to 2%. However, in 2006, the FDA announced that they would change their position, indicating that commercially available OTC and prescription products containing hydroquinone that had not been previously studied as drugs, should be submitted along with clinical studies as "new drugs", otherwise they would be removed from the market. The only preparation not affected by this rule is the triple formulation, because it was marketed after investigation with clinical studies.[9,10] There are many reasons for these concerns by the FDA, such as systemic absorption, ochronosis and drug-induced carcinogenesis. The European Union banished hydroquinone from cosmetic products in 2001, even though is it still sold with a medical prescription.[5] One of the concerns with hydroquinone is its potential risk for the production of a Benzene derivative after processing in the liver. These derivatives could cause bone marrow toxicity and could have an antiapoptotic effect. When applied on the skin, however, hydroquinone deviated from the hepatic route, and its main excretion route is through the kidneys, as hydro soluble molecules. Another concern is regarding the risk of development of renal adenoma because of the potentially toxic metabolites. Besides, there are no reports on skin or internal organ cancers with the topical use of hydroquinone since the mid-XX century.[5]

Hydroquinone is a compound commonly found in food and beverages such as coffee, tea, fruits, red wine, wheat and pear skin. A controlled study with workers that deal directly with hydroquinone, either manufacturing the substance or exposed to a large amount, did not show any evidence of premature death or malignancies. Oral or injectable hydroquinone in animals was not shown to be carcinogenic and did not cause any bone marrow changes. In a study about the safety of hydroquinone in 2006, Nordlund et al. demonstrated that there is no risk for malignancy and the ochronosis risk is low if hydroquinone is used with medical prescription and supervision.[2]

## HYDROQUINONE EFFICACY

In 1998, Amer assessed the efficacy of hydroquinone 4% in combination with a broad-spectrum sunscreen in patients with different pigmentation disorders. Of the 70 patients in the study, 50 had melasma, 10 freckles, and 10 post-inflammatory hyperpigmentation. The study demonstrated a response that was from good to excellent in 89.5% of melasma patients. These results should be interpreted with no parsimony, since it was not a controlled nor a randomized study. Haddad et al. conducted a randomized, double-blind, controlled study with 30 melasma patients, comparing a skin bleaching complex(*skin whitening complex* - SWC), which the study fails in not informing its components, and hydroquinone 4%. There was an improvement in 76.9% of patients treated with hydroquinone. *Hurley et al.*, tested glycolic acid peel in 21 Hispanic patients, and concluded that monotherapy with hydroquinone 4% combined with daily sunscreen not only improves melasma, but also has a similar efficacy to treat-

ment associated with chemical peel. The use of hydroquinone with a medical prescription has been recommended in the United States in concentrations higher than 2%, applied twice daily. If there is no improvement after 2 months, the recommendation is to discontinue treatment, even though some cases only show improvement after 6 months of use. Most of the adverse effects, such as irritation, erythema and peeling can be associated to the excessive use or misuse of the product, or even to the use of an inappropriate soap or too much rubbing of the skin.[11]

## CONCLUSION

American drug regulation laws have gone through changes over the years, imposing safety and efficacy testing to long used drugs, of more than 50 years.

The pharmaceutical industry has no financial interest in funding these studies. The mutagenic and carcinogenic effects of hydroquinone have not been proven till this day. The worse side effect ever published with topical hydroquinone is ochronosis, which is rare in North America, but very common in Africa, where it is marketed in high concentrations, such as 8%, besides being associates to products that also promote this side effect, such as resorcin. The study by Jacob Levitt, published in the Journal of the American Academy of Dermatology in 2007, is largely scientifically based and shows the safety of hydroquinone. Lewitt is a dermatologist and also the vice-president of Taro Pharmaceuticals, which manufactures hydroquinone 4%, and he has openly declared conflict of interests due to the strict regulations in the USA. In face of this review of the publications on hydroquinone safety and toxicity, we can assume that hydroquinone is safe if used in the proper concentration, with medical prescription and supervision. The triple formula with hydroquinone showed proven efficacy and safety in controlled, double-blind, randomized studies. Consider maintenance with low dose hydroquinone and other bleaching agents for the treatment of melasma. ●

**DECLARATION OF PARTICIPATION:**

**Leandra d'Orsi Metsavaht:**
Study conception and planning, Preparation and wording of the manuscript, Data collecting, analysis and interpretation

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Original Articles

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# Diagnosis and treatment of hyaluronic acid adverse events: Latin American expert panel consensus recommendations

## *Diagnóstico e tratamento dos eventos adversos do ácido hialurônico: recomendações de consenso do painel de especialistas da América Latina*

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## ABSTRACT

**Introduction**: In the last decade, the use of hyaluronic acid fillers for facial enhancement has increased in Latin America. Hyaluronic acid fillers are considered relatively safe with a low incidence of adverse events. Because adverse events are not seen frequently in clinical practice or have been potentially underreported, there is a need for more guidance on the diagnosis and treatment of Hyaluronic acid-related adverse events.
**Objective**: To provide an enhanced understanding of hyaluronic acid-related adverse events and to propose recommendations for their diagnosis and treatment.
**Methods**: A 25-member multi-disciplinary expert panel meeting of Latin-American physicians was convened in Sao Paulo, Brazil to discuss what is known about hyaluronic acid-related adverse events and to provide insights based on clinical experience. Recommendations and algorithms were developed through a consensus process.
**Results**: The panel categorized hyaluronic acid-related adverse events based on 3 time frames of onset (immediate, early, and PIDS Persistent Intermitent Delayed Swelling) and proposed a new term for adverse events that display persistent intermittent delayed edema ("PIDE"). Algorithms were created for diagnosis and treatment for each time frame.
**Conclusions**: The new consensus algorithms for time-related diagnosis and treatment of hyaluronic acid-related adverse events will provide guidance for best practices in the clinical use of hyaluronic acid fillers.
**Keywords**: cosmetic techniques; dermal fillers; hyaluronic acid; inflammation; subcutaneous injections

## RESUMO

***Introdução**: Na última década, o uso do preenchimento com ácido hialurônico para aprimoramento facial aumentou na América Latina. O preenchimento com ácido hialurônico é considerado seguro com baixa incidência de eventos adversos. Como eventos adversos são pouco observados na prática clínica ou têm sido possivelmente sub-relatados são necessárias mais orientações para diagnosticar e tratar eventos adversos relacionados ao ácido hialurônico.*
***Objetivo**: Compreender melhor os eventos adversos relacionados ao ácido hialurônico e propor recomendações para o diagnóstico e tratamento.*
***Métodos**: Reunião em painel de 25 especialistas médicos multidisciplinares da América Latina foi realizada em São Paulo, Brasil, para discutir o que se conhece sobre eventos adversos relacionados ao ácido hialurônico e fornecer conhecimentos baseados na experiência clínica. Por meio de consenso, foram desenvolvidos recomendações e algoritmos.*
***Resultados**: O painel categorizou eventos adversos relacionados ao ácido hialurônico baseado em três momentos de início (imediato, precoce e tardio) e propôs um novo termo para eventos adversos que apresentam edema tardio intermitente persistente ("Etip"). Foram criados algoritmos para diagnóstico e tratamento em cada momento.*
***Conclusões**: Novos algoritmos consensuais para diagnósticos e tratamentos associados ao momento de início dos eventos adversos relacionados ao ácido hialurônico orientarão melhores práticas no uso clínico do preenchimento com ácido hialurônico.*
***Palavras-chave:** técnicas cosméticas; agentes de preenchimento dérmico; ácido hialurônico; inflamação; injeções subcutâneas*

## INTRODUCTION

The use of minimally invasive cosmetic procedures is rapidly increasing in Latin America and around the globe. Hyaluronic acid (HA) injections is among the most popular cosmetic procedures for facial rejuvenation, restoration of volume and aesthetic improvement of facial volume.[1] Insofar as the indications for these products increase, the number of procedures increase, and treatment paradigms evolve (for example, new products, stratification techniques and greater injection volumes), there is the need of raising awareness in regards to adverse events (AEs) that can occur as a consequence of their use.[1,2]

The safety profile of injectable HA fillers is usually considered favorable, with a low incidence of AEs.[1] Since those AEs are rare, some clinicians might not encounter them frequently in their practices and, therefore, are not experienced to recognize, diagnose, manage and treat them. Besides, there is relatively little clinical evidence on the appropriate approach for AEs related to HA.[1] Considering the lack of clinical evidence and the need for clear diagnosis and treatment strategies, an expert panel meeting was conducted in order to discuss AEs related to HA and to develop recommendations for the professionals that treat patients with injectable HA fillers.

## OBJECTIVES AND METHODOLOGY OF THE CONSENSUS

In May, 2016, in São Paulo, Brasil, a Latin-American multidisciplinary panel convened in order to discuss and develop guidelines to adequately identify and treat AEs related to HA injection in aesthetic medicine.A total of 25 specialists attended the meeting, including dermatologists, plastic surgeons, radiologists, one pathologist and one immunologist from Brazil, Mexico,Argentina and Colombia.

The objectives of the meeting were:

Analyze the evolution of the understanding, incidence and description of AEs related to HA;

Provide a classification that allows prompt identification of HA-related adverse events;

Provide knowledge on the diagnosis and treatment of HA-related AEs based on clinical experience;

Reach a consensus and recommend algorithms for the diagnosis and treatment of HA-related AEs.

The methodology of the consensus included questionnaires distributed among the experts and, presentations and discussions within the panel afterwards. Recent examples from the literature about injectable HA-related AEs and their treatments were discussed. All the participants were involved in the creation of algorithms and tables.The polling was conducted by the moderator and consensus was reached when at least two-thirds of the participants were in agreement.

Specific recommendations presented in this article represent the expert panel assessment based on their collective experience.

### HA-related AEs overview

The literature available on HA-related AEs consists on retrospective studies, case reports and expert assessment.

## PROGRESS

The understanding of HA-related AEs progressed over the last 15 years. In 2002, HA-related AEs were considered a consequence of the bacterial fermentation impurities.[3] In 2005, it was seen that the same clinical AE could have two different histologic patterns, either with a granulomatous or a non-granulomatous process.[4] This raised the question whether there were different etiologies when the same clinical manifestation was seen. In 2009, the classification of nodules was suggested (painless/painful or inflammatory/non-inflammatory).[5] In 2010, the crucial role of biofilms in the complications from fillers started to gather attention.[6] From 2009 to 2015, some authors published reviews on the treatment of HA-related AEs with hyaluronidase.[7-9] During this period (2014), blindness[10] and vascular complications[11] were reported as HA-related AEs.

## INCIDENCE

In an article from Friedman et al., the incidence of HA-related AEs was estimated in 0.15% in 1999 and 0.06% in 2000.[3] This apparent reduction could have been caused by the availability of more purified raw materials for HA. In 2015, the incidence of AEs was estimated in 0.5% in a retrospective graphical analysis of 4,702 patients.[12] A member of the panel noticed that Friedman's article[3] had post-marketing data, while other reports could come from the experiences of the physicians who performed the injections and represent the most recent increase of the indications for HA.

## DESCRIPTION

HA complications are frequently described with different terminologies that changed over the years. Some of the most common AEs reported in the beginning of the 2000s were hypersensitivity, edema not related to hypersensitivity, , infections, hematomas and ecchymosis, persistent erythema, pigmentary changes, overcorrection, necrosis (ischemia) and papulo-pustular lesions.[13] As more patients were treated with HA fillers, reaction on the area of application, inadequate location, product sensitivity, infections and necrosis were also seen.[14] In the end of the decade (2009), terms such as overcorrection, implant visualization, vascular damage, angioedema, erythema and telangiectasia were used to describe the AEs.[15] Since the perception of the AEs evolved, additional descriptions became of note, including inadequate location, late immunomediated local reactions, hypersensitivity reactions, site infection and systemic AEs.[16] Other terms were used to described AEs, including purple spots, edema, skin hypopigmentation, infection, nodular masses, paresthesia and vascular damage.[2]

According to Alijotas-Reig et al.,[17] AEs usually begin as allergic granulomatous tissue reactions that evolve to abscesses, localized granulomatous reactions, abscess-like nodules, late granulomatous reactions, sterile abscesses, foreign body nodules ou late onset reactions. One of the members highlighted the fact that different descriptions of AEs are probably related to the same medical/clinical condition; therefore, a more consistent terminology is needed.

**Other aspects of HA-related AEs**

Anatomical, pathological, histological, immunological and radiological findings can help the diagnosis and treatment of HA-related AEs. From anatomical and pathological perspectives, absorbable fillers such as HA are associated to AEs with one of three different patterns of inflammation: (1) suppurative, (2) hypersensitivity reaction and (3) foreign body granuloma. The main histological findings that are relevant for the AE are: colloidal iron, that can be used as a specific stain for HA; eosinophilia, which is a typical pattern on the histopathology of HA-related AEs, that usually does not occur with other fillers (observe that HA cannot be seen on this histological finding); and capsulated HA, that can be seen in histopathological findings of foreign body granulomas with multinucleate giant cells.

From the immunological perspective, there is a lack of high level evidences to assess the effects of HA fillers. One exception was a study in 2007 by Hamilton et al.[18] where it was confirmed that stabilized non-animal HA was not immunogenic in 433 participants, considering humoral immune response, because there was no activation of IgG and IgE antibodies after HA injection. Bacterial contamination and immunodeficiency were seen as factors that could contribute to the inflammation with the injection of HA fillers.

From a radiological perspective, ultrasound is a reliable method for dermatological evaluation, including for the investigation of AEs due to fillers.[19] Ultrasound can help identify cosmetic fillers, characterize the AE and act as a guide for the injection of hyaluronidase. Fillers are distinct on ultrasound, and HA appears as a round or oval-shaped anechoic cyst. Wortsman *et al.*[20] described standardized methods for the use of ultrasound in dermatology.

**HA AEs Classification: Retrospect**

There are some classifications of HA-related AEs described in the literature, usually time-related. The definition or time cut-off should be well demarcated for the accurate diagnosis and treatment of the AEs. A member of the panel offered examples of time-related classifications from the available literature. In 2009, Narins et al. described time-related classifications of AEs, into immediate, intermediate (two weeks to one year) and late (after one year) onsets.[5] Also in 2009, Sclafani et al. utilized an alternative regimen of classification: immediate (0-2 days), early (3-14 days) and late (>14 days).[15] In 2010, Rohrich et al.[6] proposed a classification strategy that involved larger time intervals (≥14 days): early (<14 days), late (14 days-1 year) and delayed (>1 year). Cassuto and Sundaram (2013)[21] described one classification of AE subdivided into a time scale similar to Scalfani et al.: acute (48 hours), subacute (≤2 weeks) and late (>2 weeks). Funt and Pavicic proposed a more generalized scheme of classification: early events (up to a few days) and late (from weeks to years).[2] It is clear that there is a need for a classification based in consistent intervals. In 2014, Signorini et al convened a panel that proposed a more generalized scheme of classification: early and late reactions.[1] The time interval of these classifications was not specified.

**Diagnosis and treatment: History**

**Treatment of HA-related AEs**

The panel considered that the treatment for the AEs changed over the years −previously, immunomodulation was considered the primary treatment because HA-related AEs were predominantly hypersensitivity reactions;[3] it was also acknowledged that the biopsy plays an important role in the diagnosis and treatment of HA-related AEs;[4] however, the conclusion was that patients seeking aesthetic treatment would not consent to a biopsy unless absolutely necessary and that a medico-legal process is always justified.

In regards to the use of hyaluronidase for the inflammatory nodules, it was questioned whether hyaluronidase should only be used in dissolving HA (as described below)[22] or if it can be used to break the biofilm's matrix. The first evidence published on biofilms related to fillers was based on the recovery of bacteria form histological slides.[23] The panel considered if bacterial culture would be an effective method to diagnose the presence of bacteria. Even though negative bacterial culture reports are commonly found in clinical practice, new evidence suggests that a more sophisticated method (such as polymerase chain reaction, fluorescence in situ hybridization, for example) can identify bacteria in cases of negative bacterial culture results.[24,25] Historically, there has been inconsistencies in the literature about the antibiotic utilized and the duration of treatment for biofilms related to the use of HA fillers. A member of the panel proposed that antibiotic therapy for biofilms should continue for at least three months. Sixteen pre-clinical studies demonstrate that antibiotic therapy can be used as a preventive measure against the formation of biofilms,[26] and that some studies suggest prophylactic antibiotics to prevent biofilms.[6,25]

**Hyaluronidase**

Hyaluronidase enzymatically degrades HA through specific cleavage between C1 of the glucosamine portion and C4 of glucuronic acid.[27,28] Most Latin American countries do not have approved regulated hyaluronidase available for injectable use. Even in countries where the product is available, it is not specifically approved for HA fillers. Hyaluronidase is quickly inactivated when administered intravenously.[29] When hyaluronidase is administered via the subcutaneous route, the dermal barrier removed by the compound takes 24 to 48 hours to be restored.[28]

Hyaluronidase used in Latin America is more commonly obtained in compounding pharmacies and is not approved by the regulation agencies. For example, in Brazil, the most frequently used is Hyaluronidase 2.000U-Biometil (source:purified bovine testicle). The following hyaluronidases have regulatory approval for ophthalmologic injection in listed countries: Vitrase® (Bausch + Lomb; source: purified sheep testicle; approved in the USA and Canada); Hy-lenex® (Halozyme Therapeutics; source: recombinant human produced in ovary cells of Chinese hamsters; approved in the USA and Canada); Hyalase® (Sanof-Aventis; source: purified bovine testicles; approved in the USA, Canada and Europe); and Re-ductonidasa® (Advanced Cosmeceuticals; source:purified bovine testicles; available for use in Europe).[28,30,31]

One member of the panel alerted the group of known uses of hyaluronidase apart from the approved indication for HA-related AEs according to the time to reaction: 1) for early onset AEs (a cut-off of 15 days was proposed based on clinical experience), hyaluronidase is known to be used for the treatment of overcorrection/dislocation, vascular occlusion, hypersensitivity (hypersensitivity reaction type IV) and angioedema (hypersensitivity reaction type I); 2) for late onset AEs (occurring after 15 days) hyaluronidase is known to be used for the treatment of non-HA related nodules (hyaluronidase is effective even when the filler is not HA, but the mechanism is unknown) or nodules related to HA, migration of the implant (even for non-HA fillers), Tyndall effect, chronic biofilm by (even for non-HA fillers), and granulomatous reaction (even for non-HA fillers). In the published literature, the dose and interval of hyaluronidase injection differ among publications and there is no standardized protocol. One of the most common hyaluronidase uses described in the literature is for the treatment of overcorrection.[9,32]

**Factors that influence the onset of HA-related AEs**

The panel discussed some important factors regarding he onset of the AE. Regarding the injection technique, fanning, rapid injection, fast flow and larger volumes can increase the incidence of HA-related AEs.[33] The use of larger caliber needles can minimize trauma and, therefore, reduce the complication rate. The importance of antiseptic agents to prevent bacterial contamination and to avoid the formation of biofilm was discussed in the literature.[6] There is evidence on the efficacy of antiseptic agents for the prevention of bacterial contamination, even though the antiseptics are still underused. Moreover, there is no agreement between clinicians as to which is the best antiseptic agent (for example, chlorhexidine) to be used before the injection.The anatomical location of the fillers (for example, subcutaneous versus supraperiosteum)[34] was also discussed as a possible factor that could influence the occurrence rate of HA-related AEs.

## RESULTS

**Classification of AEs: panel recommendations**

The first objective discussed by the expert panel was to implement a classification to organize the diagnosis and treatment of HA-related AEs. The panel agreed that the classification should be according to time, because the time for the onset of the AE was considered the most important information that a patient can give to the clinician. The panel defined the time for onset of the AE in three intervals: immediate onset (in up to 24 hours), early onset (from 24 hours to 30 days) and late onset (after 30 days). They also defined the most commonly seen signs and symptoms in each interval. Regarding late onset HA-related AEs, the panel also proposed the use of the expression "persistent intermittent delayed swelling" (Pids), defined as edema or swelling that occurs on the site of the filler or vicinity. It was seen that triggers such as vaccination, infection or local trauma are usually present and are frequent causes of edema.

The recommended panel classification and a list of possible signs and symptoms are presented in table 1. Possible diagnoses are presented in table 2.

**Diagnosis and treatment: Recommendations of the panel and algorithms**

Once established the possible diagnoses for each interval, the panel discussed the treatment and the required tests for individualized diagnosis and follow-up based on the published literature and personal experience. This section resumes the group's consensus recommendations, specialist opinions and algorithms considered by the panel to represent best practice of treatment for each diagnosis. These algorithms were built taking into consideration the diagnoses listed in table 2 for each classification related to the timing of the onset of the reaction: immediate onset (up to 24 hours), early onset (from 24 hours to 30 days) and late onset (after 30 days).

**Immediate onset AEs**

The algorithm for the diagnosis and treatment of immediate onset HA-related AEs is sown in figure 1. The panel emphasized the importance of the clinical diagnosis for vascular damage. If vascular damage is identified clinically, the immediate treatment as defined in figure 1 becomes compulsory. Recommendations of tests for follow-up of immediate onset vascular damage include consideration of ultrasound and ophthalmological and/or neurological assessment, if applicable. The panel also observed that severe allergic reactions (such as suspected anaphylaxis) require immediate treatment with adrenaline. They also made recommendations for other less severe immediate onset reactions, but there was no consensus for the treatment of ecchymosis.

**Early onset AEs**

The algorithm for the diagnosis and treatment of early onset HA-related AEs is exposed in figure 2 and for the early onset formation of nodules related to HA, in figure 3. The diagnostic tests include: evaluation of systemic changes, full blood count, reactive C protein and erythrocyte sedimentation rate (ESR); ultrasound, culture (aspirates) and biopsy (the tissue must also be sent for culture) are recommended for nodules. Whenever possible, a biopsy should be performed before commencement of antibiotic therapy. The panel also observed that, in case a biopsy is performed, the tissue should also be sent for culture, because the pathogen sensitivity is higher in tissue than in aspirates. Depending on the type of test needed, a specific stain should be considered for each biopsy. These stain techniques include: hematoxylin and eosin, colloidal iron (to identify HA), Ziehl-Neelsen stain (for mycobacteria), methenamine silver, periodic acid–Schiff (PAS) and Grocott silver methenamine (for fungi). Ultrasound was also recommended as a technique for the differential diagnosis of non-inflammatory foreign body-type reactions, filler build up and for the detection of vascular AEs. Treatment recommendations include the use of antibiotics, non-steroidal anti-inflammatory agents, corticosteroids or hyaluronidase.

**Table 1: Consensus recommendations for the classification of AEs related to HA in regards to onset: possible signs and symptoms**

| Immediate onset (up to 24 hours) | Early onset (24 to 30 days) | Late onset (after 30 days) |
|---|---|---|
| • Color changes: erythema, ecchymosis, hematoma, cyanosis, whitening<br>• Nodule<br>• Pruritusa<br>• Severe pain<br>• Severe edema<br>• Visual disturbances<br>• Irregularities<br>• Neurological disturbances | • Color changes: erythema, ecchymosis, hematoma, cyanosis,Tyndall effect<br>• Nodule<br>• Scar<br>• Severe pain<br>• Severe edema<br>• Lymphadenopathy and fever Irregularities<br>• Ulcer with cutaneous pustule and crust<br>• Telangiectasia<br>• Neurologic disturbances | • Color changes: erythema<br>• Hyperpigmentation<br>• Nodule<br>• Pile<br>• Scar<br>• Severe edema<br>• Telangiectasia<br>• Neovascularization |

Considering a reaction that can cause type I hypersensitivity or allergic reaction.
AEs, adverse events; HA, hyaluronic acid; Pids, persistent, intermittent delayed swelling.

**Table 2: Consensus recommendations for the classification of AEs related to HA in regards to onset: possible diagnoses**

| Immediate onset (up to 24 hours) | Early onset (24 to 30 days) | Late onset (after 30 days) |
|---|---|---|
| • Vascular damage: embolization, arterial occlusion, etc.[a]<br>• Allergic reaction<br>• Hematoma<br>• Overcorrection<br>• Ecchymosis<br>• Paresthesiab | • Vascular damage: ischemia, necrosis, telangiectasia<br>• Color changes: persistent erythema, ecchymosis, Tyndall effect, post-inflammatory hyperpigmentation<br>• Systemic changes: infection, inflammation Paresthesiab<br>• Scars: hypertrophic, atrophic<br>• Irregularities: overcorrection, infiltration (cellulite), nodules | • Vascular damage: telangiectasia<br>• Color changes: post-inflammatory hyperpigmentation, persistent erythema<br>• Scar: atrophic, keloid<br>• Irregularities: Pile, nodules, late edema |

Visual and neurological disturbances are included[b] Paresthesia due to peripheral trauma only; AEs, adverse events; HA, hyaluronic acid; PIDS, persistent intermittent delayed swelling.

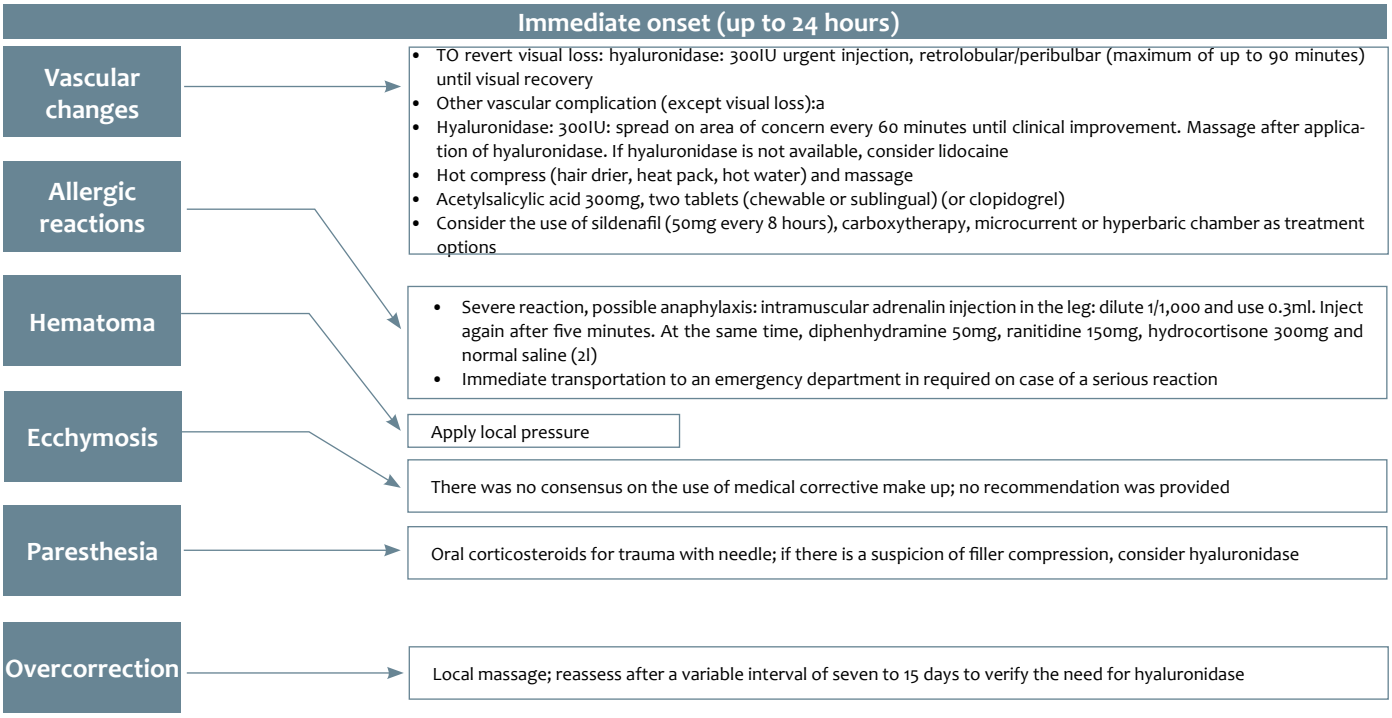


**Figure 1:** Algorithm for the diagnosis and treatment of immediate onset adverse events related to hyaluronic acid.a The following suggestions were mentioned in the meeting to be considered in the treatment of other vascular complications, even though there was no consensus: 1) consider canula instead of needle for the application of hyaluronidase to avoid ecchymosis and reduce tissue trauma; 2) consider intra-arterial injection of hyaluronidase in the closest artery

### Late onset AEs

The algorithm for the diagnosis and treatment of late onset HA-related AEs is in figure 4. It must be noted that the algorithm for the treatment of these AEs was not explicitly discussed during the meeting, but the panel members agreed in utilizing an approach similar the early onset AE.The panel discussed the late onset formation of nodules (Figure 5) and noted that a similar treatment should be conducted for suppurative (abscess) and non-suppurative infection (biofilm) infection, and also for non-infectious foreign body-type reactions in the case of late onset AEs, because the clinical manifestations are similar.

### Considerations for the prevention of AEs

Based on the literature and clinical experience, the panel recommended chlorhexidine over an alcohol background for disinfection, however, it must be used cautiously on the periocular region due to the risk of ocular irritation/damage. Aqueous chlorhexidine can be considered.

Areas of high risk for fillers were considered the areas supplied by the internal branches of the carotid artery (for example, supraorbital and supratrochlear), areas with extensive vascular anastomoses (for example, superficial temporal artery with supraorbital artery and supraocular artery; infraorbital artery with angular artery) and on the areas where the arteries emerge from the cranial foramen (supraorbital, supratrochlear and mental region). The high-risk areas are the nasolabial fold, glabella and dorsum of nose. The recommendations for the injection of HA in high-risk zones are presented in table 3.

## CONCLUSION

This consensus panel meeting of experts from Latin America generated knowledge about the diagnosis and treatment of HA-related AEs.HA is considered an option for aesthetic treatment that is usually safe and has a low incidence of AEs. The panel created recommendations based in algorithms for the

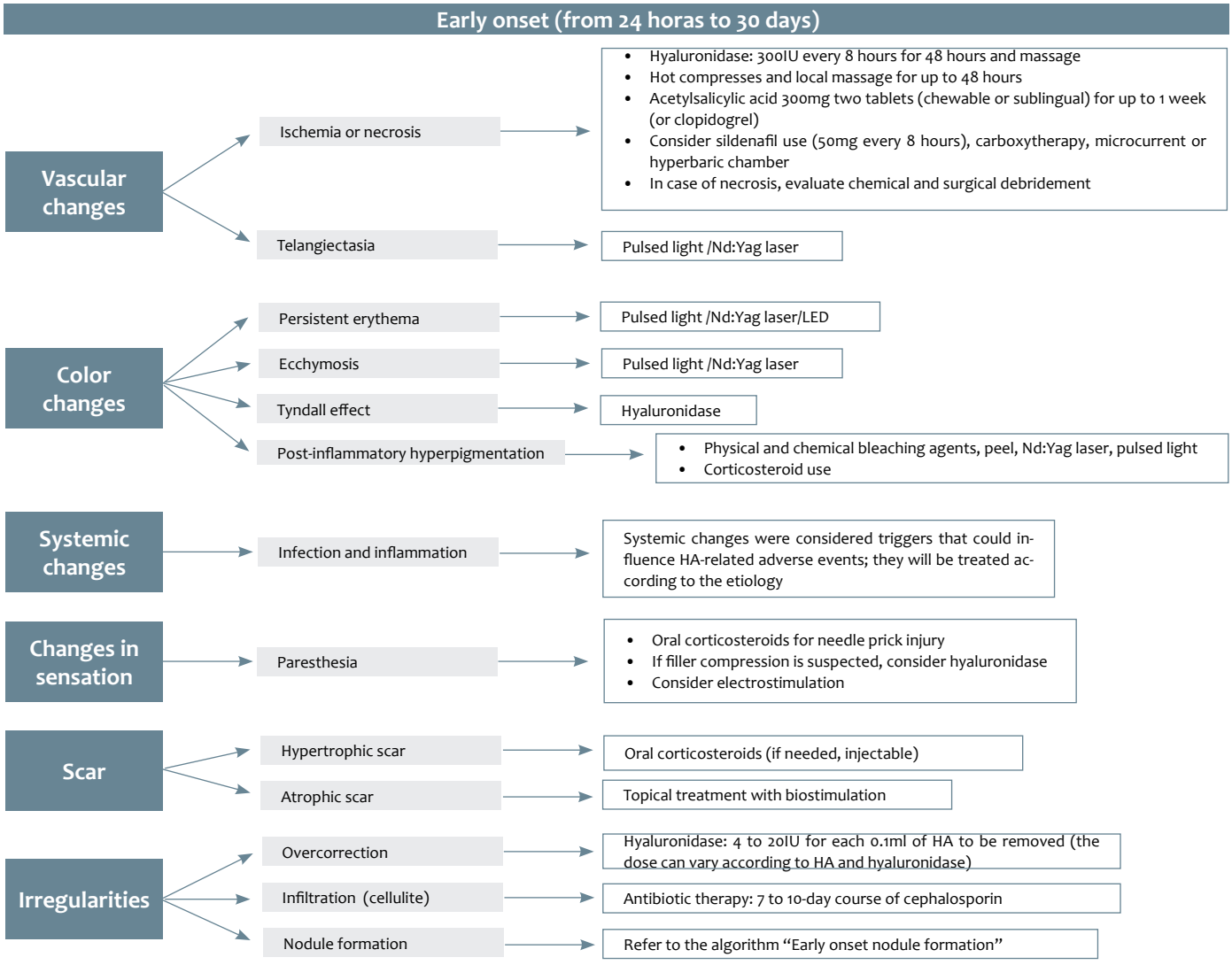


**Figure 2:** Algorithm for the diagnosis and treatment of early onset adverse events related to hyaluronic acid. For the treatment of necrosis, pentoxifylline 400mg every 12 hours for up to 48 hours is suggested

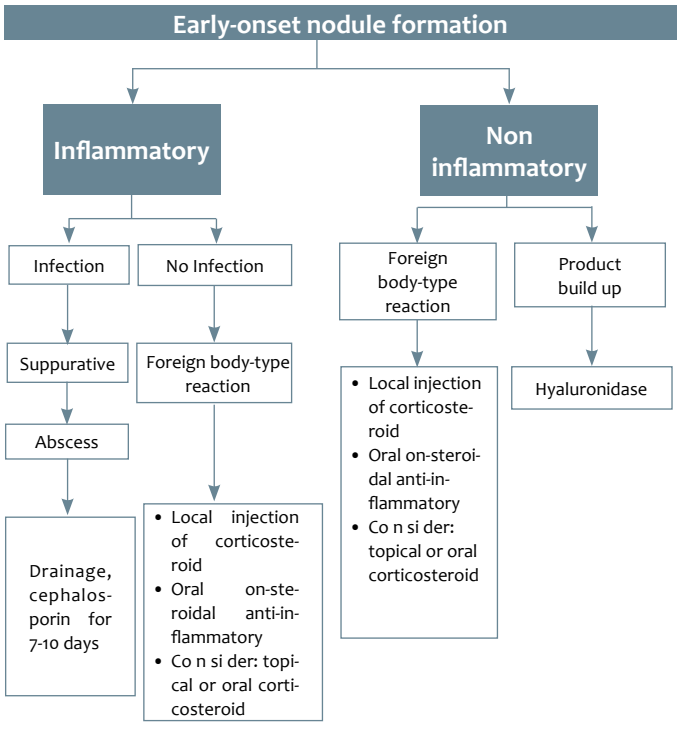


**FIGURE 3:** Algorithm for the diagnosis and treatment of the adverse event of early formation of nodules related to hyaluronic acid

diagnosis and treatment according to the time of reaction onset: immediate onset (in up to 24 hours), early onset (from 24 hours to 30 days) and late onset (after 30 days).The commonest signs and symptoms and the possible diagnoses for each time interval were defined.The panel also proposed Pids as a new term for an AE of "persistent intermittent delayed swelling"occurring on the site of the filler or in its vicinity. Diagnostic and follow-up tests were also defined and recommendations for the steps aiming at preventing most commonly occurring HA-related AEs were made.

The recent increase in the uses and indications for HA highlight the importance of the knowledge shared by the Latin America Expert Panel. Their consensus recommendations provide support for clinicians that use HA fillers and can minimize their occurrence and enable the treatment of AEs. ●

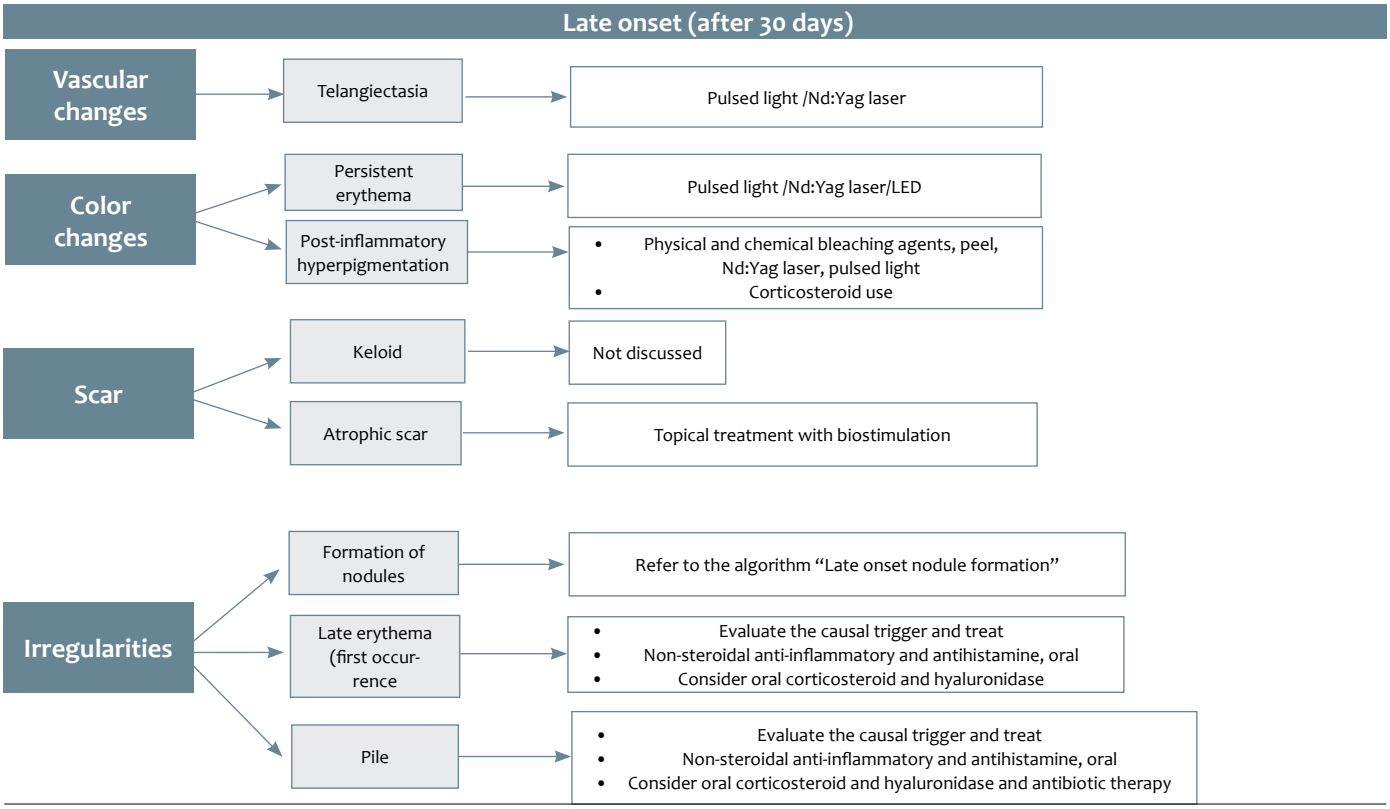


**FIGURE 4:** Algorithm for the diagnosis and treatment of late onset adverse events related to hyaluronic acid.
The algorithm for the treatment of late onset adverse events was not explicitly discussed during the meeting, and the specialist panel agreed to use the information from the early onset treatment algorithm. Abbreviation: Pids, persistent intermittent delayed swelling. Pile is the edema or swelling that occurs in the exact location of the filler or in the vicinity. A trigger such as vaccination, infection, or local trauma is usually seen and responsible for the edema

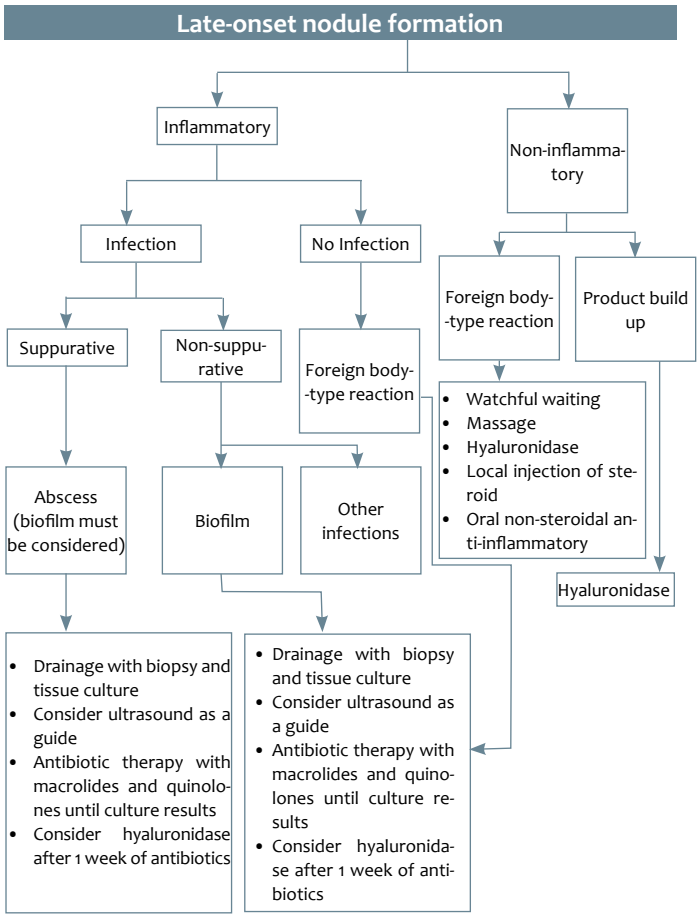


**Figure 5:** Algorithm for the diagnosis and treatment of late onset nodule formation related to hyaluronic acid

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**Table 3: Recommendations of techniques to prevent AEs related to HA injection in high-risk facial regions**

| Region | Recommendation |
|---|---|
| Frontal | • High risk due to the area of anastomosis (superficial temporal artery with supra-orbital artery and supratrochlear artery)<br>• Cannulation (under the muscle)<br>• The injection must be away from the temporal crest (between the frontal and temporal bones) and at least 1.5cm above the supraorbital foramen |
| Glabella | • Supraperiosteal cannulation is recommended<br>• For experimental injectors, the use of injection with an intradermal or supraperiosteal needle could be considered |
| Dorsum of nose | • High risk area for blindness<br>• There was no consensus among the group regarding the safest technique.<br>• In patients with a history of nasal surgery, the panel recommended that HA injection is not done in this area |
| Nasolabial fold | • Injection with intradermal or supraperiosteal needle is recommended<br>• Cannulation is recommended for subcutaneous injections |
| Nasojugal fold and malar | • Needles are not recommended<br>• Cannulation is recommended |
| Temporal | • Injection with supraperiosteal needle is recommended for this region |
| Zygoma | • Injection with supraperiosteal needle or cannulation is recommended |
| Perioral and mental | • High-risk zone for necrosis<br>• Subcutaneous cannulation is recommended<br>• For the mental region, injection with supraperiosteal needle or cannulation are recommended in the upper and lower lips, a superficial needle (intradermal to subcutaneous) or 27-gauge canula is recommended Nos lábios superiores e inferiores, uma agulha superficial (intradérmica a subcutânea) ou uma cânulade calibre 27 é recomendada |

AEs, adverse events; HA, hyaluronic acid

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Original Articles

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**Conflict of interests:** The study was sponsored by Melora, but the methodology, execution and analysis of the results were performed by the institution researchers, with no participation of the company.

# Analysis of melasma quality of life scales (MELASQoL and DLQI) and MASI in Polypodium leucotomos treated patients

## *Avaliação dos índices de qualidade de vida (MELASQoL e DLQI) e do MASI em pacientes com melasma tratadas com Polypodium leucotomos*

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## ABSTRACT

**Introduction**: Melasma is a pigmentation disorder that mainly affects women of childbearing age with high phototypes. Polypodium leucotomos has antioxidant, photoprotective and immuno-modulatory activity, and can be considered as an adjunctive treatment for melasma.

**Objective**: To evaluate the efficacy, in relation to quality of life and objective improvement, of the use of Polypodium leucotomos in the treatment of melasma.

**Methods**: Prospective and individualized study. Nine volunteers with melasma were submitted to treatment with Polypodium leucotomos for 45 days. MELASQoL, DLQI and MASI scores were calculated at the beginning (D0) and 45 days after (D45). Analysis of variance ANOVA with Tukey post-test for comparison be-tween D0 and D45 ($p < 0.05$).

**Results**: All patients were females, mean age of 37.18 ± 6.78 years. Family history of melasma in 55.6%; 88.9% with unprotected photoexposure and use of estrogen. After 45 days of treatment with Polypodium leucotomos there was a significant reduction of MELASQoL and DLQI ($p < 0.05$) and improvement of MASI in 55.6% of the patients.

**Conclusions**:There was improvement of MASI in 55.6% of patients after 45 days of treatment. In spite of the slight improvement in MASI, there was a reflex in the improvement of quality of life scores (DLQI and MELASQoL).

**Keywords**: melanosis; Polypodium; quality of life; indicators of quality of life

## RESUMO

***Introdução:*** *Melasma é distúrbio de pigmentação que acomete principalmente mulheres em idade fértil com fototipos elevados. Polypodium leucotomos tem atividade antioxidante, fotoprotetora e imunomodulatória, sendo tratamento adjuvante do melasma.*

***Objetivo:*** *Avaliar a eficácia, em relação à qualidade de vida e à melhora objetiva, do uso de Polypodium leucotomos no tratamento do melasma.*

***Métodos:*** *Estudo prospectivo e individualizado. Nove voluntárias portadoras de melasma foram submetidas ao tratamento com Polypodium leucotomos durante 45 dias. Escores MELASQoL, DLQI e MASI foram calculados no D0 e no D45. Realizou-se a análise de variância Anova com pós-teste de Tukey para comparação entre D0 e D45 ($p < 0,05$).*

***Resultados:*** *Todas as pacientes eram do sexo feminino, com média de idade de 37,18 ± 6,78 anos, história familiar de melasma em 55,6%, e fotoexposição desprotegida e uso de estrogênio em 88,9%. Após 45 dias de tratamento com Polypodium leucotomos houve redução significativa do MELASQoL e DLQI ($p < 0,05$) e melhora do MASI em 55,6% das pacientes.*

***Conclusões:*** *Houve melhora do MASI em 55,6% das pacientes após 45 dias de tratamento. A despeito da discreta melhora no MASI, houve reflexo na melhora dos escores de qualidade de vida (DLQI e MELASQoL).*

***Palavras-chave:*** *melanose; Polypodium; indicadores de qualidade de vida; qualidade de vida*

## INTRODUCTION

Melasma is a pigmentation disorder that affects mainly women of childbearing age with higher phototypes, due to the induced hyperactivation dermal melanocytes, especially by the ultraviolet radiation. It is a frequent condition in the general population, with a high impact in the quality of life.[1-3]

*Polypodium leucotomos* (PL), a *Polypodiaceae* plant extract has antioxidant, photoprotective and immunomodulatory activity, being adjuvant in photoinduced dermatoses, including melasma.[1,3]

The objective of the study was to evaluate the efficacy in regards to the quality of life, and the objective improvement with the use of PL for the treatment of melasma.

## MATERIALS AND METHODS

A comparative, prospective and individualized analysis of melasma patients, submitted to a 45-day treatment with PL, conducted according to the ethical procedures advised by the Declaration of Helsinki.Eleven volunteers took one 250mg tablet of PL every 12 hours and continued using sunscreen with an SPF equal to or higher than 50, three times a day.The volunteers did not use any topical products containing acids or bleaching agents in the previous three months. Medical (MELAS- QoL and DLQi and MASI) and photographic assessments (Visia®, Canfeld Imaging System- Fairfeld, EUA) of the volunteers were performed in D0 and D45. The use of the device Visia® enabled a most accurate photographic record of melasma changes through ultraviolet lamps (UV spots), and the device's digital analysis system enabled the photographic comparison in the different times of the study. The patients signed an informed consent. Two patients were excluded from the study because they were not present in the final assessment.

The photographs were taken in a frontal view, 45° to the right and 45° to the left on days D0 and D45.MELASQoL and DLQI were filled out by the volunteers. MASI was calculated by three collaborating physicians not involved in the study, previously trained, after seeing the photos of the patients, with no knowledge of the time of picture taking (before and after).

For the comparison of the DLQI, MASI and MELASQoL scores, the variance analysis Anova was performed with Tukey post-test with a program, GraphPad Prism 7.0.

## RESULTS

All volunteers were female, with a mean age of 37.18 ± 6.78 years and a mean course of the disease of 6.36 ± 5.26 years. The majority (55.6%) had family history of melasma. In regard to the phototypes, (Fitzpatrick): 33.3% phototypes I-II; 55.6%, III-IV; 11.1%,V-VI (Table 1).

The most prevalent worsening factors for melasma were: unprotected sun exposure (88.9%) and the use of estrogen (88.9%). Worsening of melasma after pregnancy was observed in two of the nine patients (Table 1).

There was a significant reduction in the MELASQoL before and after 45 days using PL (p = 0.0164), as well as a significant decrease in the DLQI score (p = 0.0483). Despite MASI improvement in 55.6% of patients after 45 days of treatment, overall, there was slight reduction of the mean on D45 (11.01± 6.22) compared to D0 (11.82 ± 7.4). However, there was no statistically significant difference (p = 0.799) (Table 2).

There was a reduction of DLQI and MELASQoL values in seven (77.78%) and eight (88.8%) volunteers, respectively. In regards to MASI values, five (55.55%) patients had a reduction, two (22.2%) had an increase and two (22.2%) kept the same values (Figure 1).

## DISCUSSION

Melasma is more common in females (9:1) and affects 8.8% of Latin women of childbearing age.[1] The mean age seen (37.18 years) was similar to other melasma studies.[4-6]

**Table 1: Social, demographic and clinical data of melasma patients**

| Data | N (%) |
|---|---|
| Current age (Mean ± SDM) Course of the condition (Mean ± SDM) Family | 37.18 ± 6.78<br>6.36 ± 5.26 |
| History of Melasma | |
| Yes | 5 (55.6) |
| No | 4 (44.4) |
| Fitzpatrick Phototype | |
| I - II | 3 (33.3) |
| III - IV - V | 5 (55.6) |
| VI | 1 (11.1) |
| Worsening factors | |
| Pregnancy | 2 (22.2) |
| Estrogen use | 8 (88.9) |
| Unprotected sun exposure | 8 (88.9) |

**Table 2: Comparison of the scores MELASQoL, DLQI and MASI before and after 45 days of treatment with Polypodium leucotomos, represented as Mean±SDM**

| Parameters | Mean | SDM | Minimum | Maximum | p |
|---|---|---|---|---|---|
| MELASQoL Do | 53.44 | 8.46 | 34 | 63 | 0.0164 |
| MELASQoL D45 | 38.89 | 14.08 | 19 | 63 | |
| DLQI Do | 10.22 | 3.42 | 7 | 17 | 0.0483 |
| DLQI D45 | 6.11 | 4.73 | 1 | 16 | |
| MASI Do | 11.82 | 7.40 | 4.2 | 28.7 | 0.799 |
| MASI D45 | 11.01 | 6.22 | 4.2 | 24.4 | |

SDM = standard deviation of the mean. p>0.05.

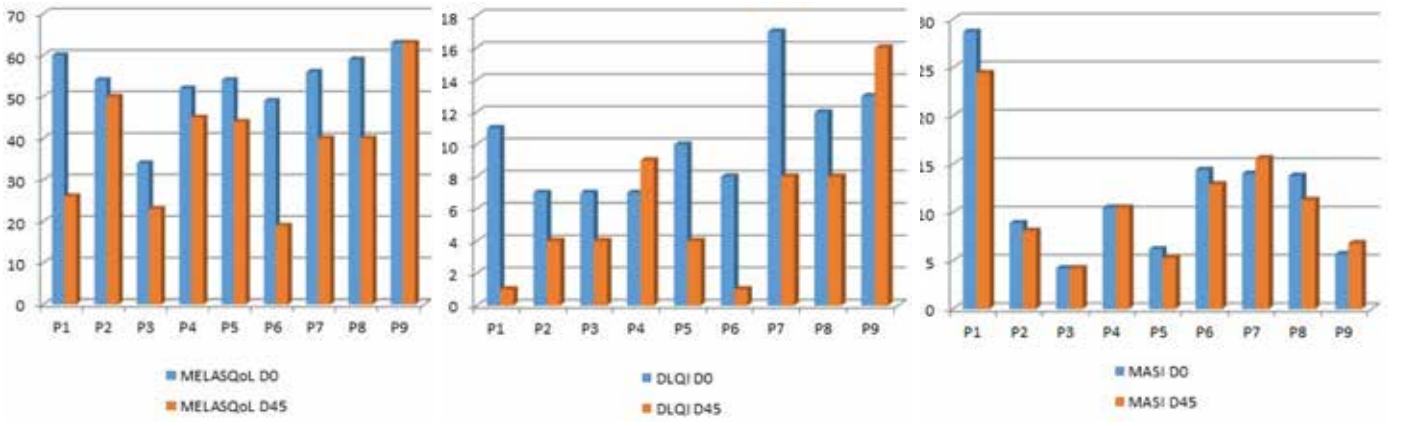


**Figure 1:** Representation of the graph MELASQoL, DLQI and Masi on Do and D45 for each of the nine patients in the study

**Figure 2:** Representation of the evolution of a volunteer before (upper row) and after 45 days (lower row) the use of Polypodium leucotomos

**Figure 3:** Representation of the evolution of a before (upper row) and after 45 days (lower row) the use of Polypodium leucotomos

This condition is particularly prevalent in darker phototypes, especially in Fitzpatrick III to VI.[7] In the present study, 66.7% had phototype III-VI and 55.6%, III-IV.

The exact pathogenesis of melasma is not completely clear, being genetics, sun exposure and hormonal therapy possible causal factors.[5] The majority (55.6%) had first degree relatives affected;in 88.9% there was unprotected sun exposure and the use of estrogen at some point in life, with worsening of melasma. In 22.2%,pregnancy was a worsening factor.

PL use was associated to improvement of the quality of life, DLQi and MELASQoL scores ($p < 0.05$). There was improvement in MASI in five (55.6%)of the patients in the study after 45 days of treatment, however, with an overall $p > 0.05$, with two (22.2%) with higher values and two (22.2%) with the same values upon completion of the study.

Standardized photographic records, such as Visia®, enable better patient follow-up. The comparative analysis of the device's parameters referring to UV spots and polarized light, was consistent with the evolution of the MASI scores obtained, in the majority of cases. Difficulties such as lack of uniformity of the automatic masking and other concomitant dyschromias can, however, contribute to conflicting scores.

The slight MASI improvement reflected in a significant improvement of the quality of life scores (DLQI and MELASQoL). The subjective evaluation of improvement by the patient and by the examiner's perception reflected independent results, consistent with the low correlation coefficients found between MELASQoL and MASI (0.17 to 0.36) in the literature.[4] Similarly, there was a strong correlation of psychometric measures of the perception of the severity of the condition, such as MELASQoL and DLQi.

## CONCLUSION

A slight improvement in MASI improved the quality of life scores significantly (DLQi and MELASQoL) for the patients in the study. The positive results of the adjunctive treatment with PL for melasma favor its use, being a very promising therapeutic alternative. However, new studies with a higher number of patients are needed to best evaluate the efficacy of this drug quantitatively. ●

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# Persistent, Intermitent Delayed Swelling PIDS: late adverse reaction to Hyaluronic Acid fillers

## *Edema tardio intermitente e persistente ETIP: reação adversa tardia ao preenchedor de ácido hialurônico*

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## ABSTRACT

**Introduction**: The use of hyaluronic acid fillers (HA) for esthetic corrections has exponentially grown in recent years. Skin ultrasound (US) is an effective method to identify the filler and its complications. A particular type of adverse effect, characterized by late, persistent edema of an intermittent nature, has been lately observed.

**Objective**: To describe a delayed complication due to easy HA fillers, named by the authors as Persistent, Intermitent Delayed Swelling (PIDS).

**Methods**: From October 2016 to July 2017, US examinations performed at Cavallieri Clinic were selected and referred for evaluation of post-filler complications. Questionnaires were sent to requesting physicians for clinical data collection.

**Results**: Of 108 exams, 33 cases of local subcutaneous edema associated with the presence of HA fillers were identified. Episodes of edema were referred to as recurrent, in the previously affected area, or at another injection site.

**Conclusion**: The authors propose a specific nomenclature: PIDS to refer to this late adverse reaction to HA fillers, which includes delayed and intermittent local swelling, triggered by specific conditions, that persists for as long the HA remains in the subcutaneous tissue.

**Keywords**: dermal fillers; hyaluronic acid; adverse effects; skin ultrasound

## RESUMO

***Introdução:*** *O uso do ácido hialurônico para correções estéticas cresceu exponencialmente nos últimos anos. O ultrassom de pele mostra-se método eficaz para identificação do preenchedor e suas complicações. Um tipo particular de efeito adverso, caracterizado por edema tardio e persistente, de caráter intermitente, vem sendo observado ultimamente.*

***Objetivo:*** *Caracterizar uma complicação tardia após preenchimento facial com ácido hialurônico.*

***Métodos:*** *Selecionaram-se exames de ultrassom da pele realizados em clínica privada de outubro de 2016 a julho de 2017, encaminhados para avaliação de complicação após preenchedores. Questionários foram enviados aos médicos solicitantes para coleta de dados clínicos.*

***Resultados:*** *Em 108 exames foram identificados 33 casos de edema local associado à presença de ácido hialurônico. Episódios de edema foram referidos como recorrentes, na área previamente afetada ou em outro sítio de injeção.*

***Conclusão:*** *Os Authors propõem nomenclatura específica: edema tardio intermitente e persistente para agrupar as reações adversas tardias ao ácido hialurônico, que se traduzem por edema local tardio, de caráter intermitente, deflagrado por gatilhos específicos e que persiste enquanto houver a presença do ácido hialurônico no tecido.*

***Palavras-chave:*** *preenchedores dérmicos; ácido hialurônico; efeitos adversos; ultrassom de pele*

## INTRODUCTION

The use of fillers, particularly of hyaluronic acid (HA), for facial aesthetic corrections increased exponentially over the last few years. Skin ultrasound (US) has been shown to be an effective method for the evaluation of the substance injected, as well as its complications. The technique is useful because it is not invasive, provides a good balance between penetration and image resolution, enables distinction of the different skin layers and presents no risk or discomfort for the patient, nor radiologic exposure, use of contrasts ou confinement in small spaces.

According to Ximena et al[1], the sonographic appearance of injected HA has a round or oval-shape, well-defined, anechoic (black) structure, known as "pseudocyst" because of its resemblance with true cysts (Figure 1). HA formulations that are mixed with lidocaine present with interspersed echoes (debris inside the pseudocysts). Polymethylmethacrylate (PMMA) has the sonographic aspect of multiple hyperechoic deposits (white), that cause a mini-artefact shaped like a comet tail, corresponding to the posterior reverberation. Because calcium hydroxyapatite is a compound of microspheres suspended in a lipopolysaccharide carrier, it is identified by hyperechoic deposits with variable degrees of acoustic shadow. Silicone oil appears as a strongly echogenic image in the subcutaneous tissue, determining a strong posterior acoustic shadow in a snowstorm pattern. The sonographic aspect of polyacrylamide gel is of an anechoic, oval-shaped pseudocyst with hyperechoic lines (white), that does not change in volume over time and that determines an enhancement of the echogenicity of the surrounding tissue. Autologous fat filler is visualized as an oval shaped, well-defined, isoechoic (similar to the fat in the adjacent subcutaneous tissue) nodularity, sometimes with minute interspersed anechoic areas. Polylactic acid usually has no sonographic expression, except in cases where the product acquires a nodular aspect and becomes clinically palpable, when it is visualized on ultrasound as a well-defined isoechoic image.

Regarding the complications caused by fillers, US can identify the filler substance, determine its dimensions and location, and evaluate local vasculature with color Doppler. Ultrasound images differ from inflammatory and/or infectious processes, overcorrections and changes consistent with necrosis of the subcutaneous tissue. The test can also help in guiding aspiration biopsies and hyaluronidase and/or corticosteroid injections.[1-3]

Recently, a particular type of complication that evolves with delayed, recurrent and persistent facial edema, corresponding to the injection site, drew the authors' attention for being the reason for frequent requests for facial soft tissue ultrasound examination. The intention to better clarify the clinical features of this type of complication lead the authors to conduct this study.

## METHODS

In the period from October 2016 to July 2017, all US performed at Clínica Cavallieri de Diagnóstico por Imagem, Rio de Janeiro (RJ), Brazil, referred for the evaluation of complications of facial fillers were selected. All patients underwent facial US, performed by a radiologist with a large experience in skin and soft tissue ultrasound. The device used was EPIQ7 (Philips Medical Systems, Bothell, WA, USA), with two high frequency transducers (7 to 15MHz and 5 to 18 Mhz). The exam included the study of the whole face in all patients, in B mode and with the association of Color Doppler for the assessment of local vasculature. After recording demographic and image data, the authors created a questionnaire that included questions about: commercial name of the HA used, application sites, time for the onset of symptoms, related events, treatment used, recurrence and duration of edema. The questionnaires were sent by e-mail to the referring doctors for clinical data collection.

## RESULTS

In 108 ultrasound exams, performed for the evaluation of complications with fillers, 33 cases of subcutaneous edema associated to HA were seen, all of them in women between 29 and 71 years of age, (mean of 50 years). In 27 exams, HA was identified as the only filler; in six patients, besides HA, another substance was visualized, namely: polymethylmethacrylate (PMMA) in three exams, Poly-L-Lactic acid (PLLA) in one exam, autologous fat in one exam and polyacrylamide gel in one exam. Regarding the presence of the filler, the most affected site by edema was the malar region (15 cases), followed by the lower eyelid region (11), nasolabial fold (eight) and lip (two). Zygoma, chin, pre-jowl region, forehead and nose had one case each. Of the 33 affected patients, five presented with edema in different areas at the same time. Of the 33 patients, the exam was repeated in 12, due to recurrences either in the same site of injection or in other sites.

Among the sonographic findings, the common feature in all 33 cases was the presence of HA associated to a diffuse increase in the thickness and echogenicity of the surrounding subcutaneous tissue, sonographically similar to a diffuse, ill-defined panniculitis, corresponding to the area with clinical edema (Figure 2). No solid nodules or collections of liquid were seen in these patients, therefore ruling out other possible adverse reactions that are characterized by nodules, abscesses or collections. These edema episodes were referred as recurrent by the patients, occurring in the area previously affected or in another injection site. By the features of delayed edema after use of HA filler, intermittent and persistent in nature, all 33 patients were diagnosed as PIDS (persistent intermittent delayed swelling).

Of these 33 cases of PIDS, data of 20 patients were collected through questionnaires. PIDS was characterized clinically

by non-pitting, erythematous or not, diffuse or not, ill or well-defined edemas along the area of HA injection. In all cases, accentuation of the edema was reported upon waking up, with slight improvement throughout the day.

The mean duration for each event was difficult to evaluate and varied considerably between patients; most of them were primarily treated with oral corticosteroids and/or antibiotics before being referred for ultrasound examination. The earliest case appeared 25 days after the injection, whereas the latest occurred three years after the procedure. Twelve patients had the onset of

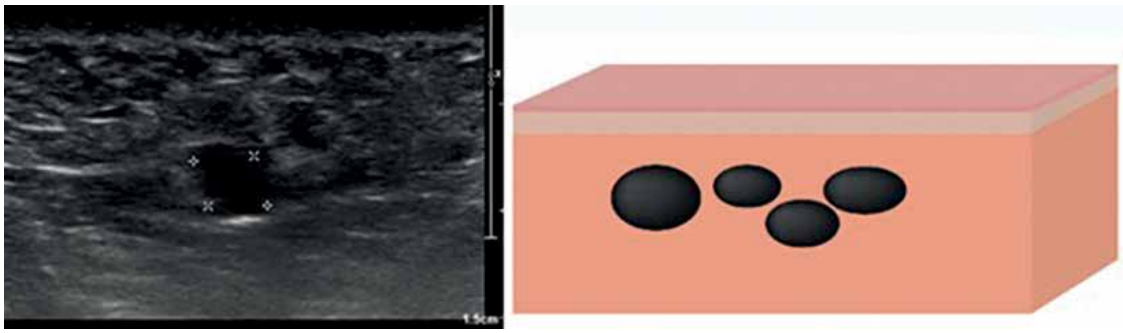

**Figure 1:** To the left, sonographic image of the HA (hyaluronic acid) deposit, interspersed with the subcutaneous tissue in the malar region (between x and + markings); to the right: illustration of the sonographic aspect of HA deposits restricted to the subcutaneous tissue

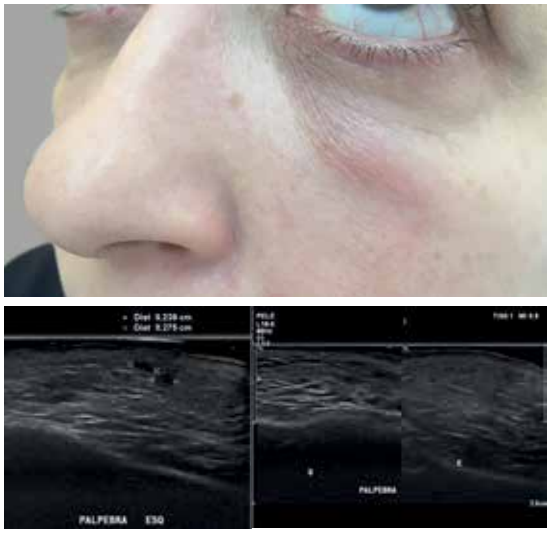

**Figure 2:** Upper: clinical image of left lower eyelid edema in a site of previous injection of HA (Juvederm Volbela®). To the left: sonographic image of the presence of HA deposits (between x and +) associated to the increase in thickness and echogenicity of the subcutaneous tissue surrounding the left lower eyelid. To the right: sonographic comparison of the right lower eyelid (not affected) with the left lower eyelid of the patient, demonstrating the increase in thickness and echogenicity of the subcutaneous tissue

PIDS at the same time as an infectious process (sinusitis, urinary tract infection, respiratory tract infection, dental infection), trauma on the face or vaccination. In one case, the patient noted recurrences of the facial edema during menses. Of the products utilized, eight were identified: Juvederm Voluma® (seven cases), Juvederm Volbella® (seven cases), Juvederm Volift® (two cases), Juvederm Ultra (one case) Anteis Modelis® (one case), Restylane Perlane® (one case) and Emervel Classic® (one case). Medical management consisted in systemic antibiotic therapy (ATB) + hyaluronidase (two cases), ATB + systemic and/or intralesional corticosteroid (five cases), ATB + hyaluronidase + oral corticosteroid (five cases), hyaluronidase alone (two cases), oral ATB alone (two cases), oral corticosteroid alone (three cases). One patient did not receive any treatment and had spontaneous resolution.

## DISCUSSION

Clinically recognized, the persistent intermittent delayed edema consists in recurrent episodes of local edema in the HA injection site, with short of long remission, with no evidence of defined palpable nodules. On the ultrasound, the presence of HA corresponding to the edematous area is seen, associated to a diffuse increase in the thickening and echogenicity of the subcutaneous tissue (panniculitis).

Ultrasound is a non-invasive imaging study, of easy access, that is being frequently used in dermatological practice. Ultrasound offers relevant information on adverse reactions of cosmetic fillers, being an important tool in cosmiatry for the better understanding of complications post-fillers.

Many HA complications have been described in the literature, however, each author classifies them according to their clinical experience because there is no consensus on the classification of these adverse reactions. Nonetheless, many articles describe a late adverse reaction similar to PIDS.

Callan et al[4] reported a single case (1%) of "edema and hardening of the product" in the injected area in a 24-month study with 103 patients treated with Juvederm Voluma®.

Goodman[5] also described a "firm and hardened, non-pitting edema, with no signs of infection or inflammation" in a patient treated with Juvederm Voluma®, 4 months after the procedure.

In a retrospective review of 4,702 treatments with Juvederm Voluma® in 2,342 patients, Beleznay et al[6] described 23 cases (1%) of "firm nodules and local edema of late onset". The time for the development of these nodules was of 4 months, with mean resolution after 6 weeks.

Artzi et al[7] reported a series of 400 patients injected with Juvederm Volbella® in the lips and lower eyelids. Of those, 17 (4.25%) developed "change in color and edema in the treated area", with 8 of these 17 patients having an association with other types of HA besides the Juvederm line. The mean time for onset was of 8 weeks.

In the above-mentioned articles, ultrasound was not used to characterize complications. Perez et al reported the use of US to evaluate one case of complication with HA filler. The patient had "indurated, palpable and asymptomatic lesions" in the marionette lines that appeared 4 months after the injection with Juvederm Voluma® and Juvederm Volift®. US demonstrated a focal subcutaneous area with enhanced echogenicity, suggestive of edema, and an increase vascularization of the area (panniculitis). The patient progressed with improvement of the lesion, but had recurrences in other areas of the face for up to 4 months after the first episode. All 33 cases evaluated in the present study resemble the case in Perez et al article, where HA was identified in areas that corresponded to the edema and associated to the subcutaneous tissue, with increased thickness and hyperechogenicity (signs of panniculitis).[8]

Of the five articles mentioned above, we highlight 43 cases of an edematous reaction after injection of HA fillers. Two of them were single cases (Goodman – Juvederm Voluma® and Perez – Juvederm Voluma® and Volift®). Two clinical studies were conducted with a single product and comprise 24 cases (Beleznay – Juvederm Voluma®; Callan – Juvederm Voluma®). Lastly, 17 cases came from private practices (Artzi). Contrary to what we found in the literature, with cases from controlled groups or private practices, the cases analyzed by the authors come from different sites, referred by dermatologists from their private practices to a radiology clinic, focused on ultrasound. Therefore, the statistics were collected at Clínica Cavallieri with varied patients from Rio de Janeiro metropolitan area, from a total of 30 referring dermatologists.

In the 20 cases where the performing physician reported the brand of HA, Vycross® line of fillers appeared in a higher number of cases (16) compared to other lines of HA fillers (four). The small number of cases where the filler was identified does not allow us to conclude a cause/effect relationship with a specific product line, since this could be the most used brand of filler. A higher number of cases would be required to reach a more accurate conclusion.

Vycross® technology is based in the incorporation of short and long strands of HA to provide a more effective reticulation. Published data suggest that high molecular weight HA strands are mainly anti-inflammatory, while the low molecular weight strands are pro-inflammatory, activating the immune system.[9] It is possible that between three to five months after the injection, when the activation of late inflammatory nodules is more frequently observed, there is a more pronounced breakage of the HA, exposing low molecular weight fragments, that are pro-inflammatory. Even though products from the Juvederm Vycross® line have a higher proportion of low molecular weight particles, is not known if this proportion alone is more inflammatory in comparison to other products.

Regarding triggering factors, 12 patients (36%) associated the event to an infectious condition, and this data was close to what Beleznay described in his article, where 39% of patients reported a respiratory tract infection or a dental procedure before the appearance of the reactions.[6]

Given the spontaneous resolution of the nodules, their early onset, short duration and treatment response, including steroids and hyaluronidase, Beleznay et al defend the idea that these types of reactions seen with HA are more consistent with an immune-mediated etiology as opposed to biofilm, a commonly implicated mechanism in the literature. The opinion of those authors is that, when HA is injected into a predisposed individual, triggers such as respiratory tract infections, dental procedures, systemic bacterial or viral infections, vaccination and facial trauma could trigger an inflammatory process corresponding to the injected area, given the immunogenic nature of the filler, as well as its capacity of retaining water, configuring the local edema.[10]

In 2013, Alijotas et al selected 235 articles published on PubMed from 2000 to 2012 reporting fillers adverse reactions with the aim to report the various types of related adverse events. The results obtained from this review showed that most of the

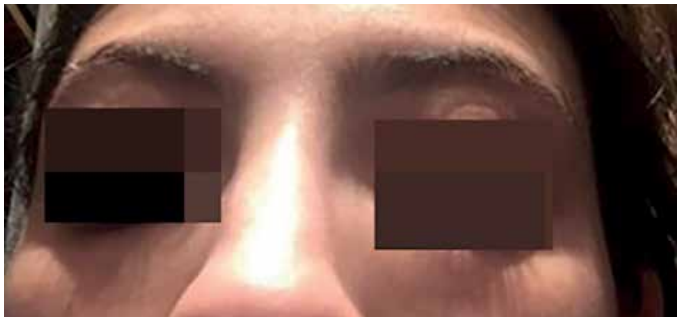

**Figure 3:** Left lower eyelid edema after flu vaccination in an area of previously injected HA (Juvederm Voluma®)

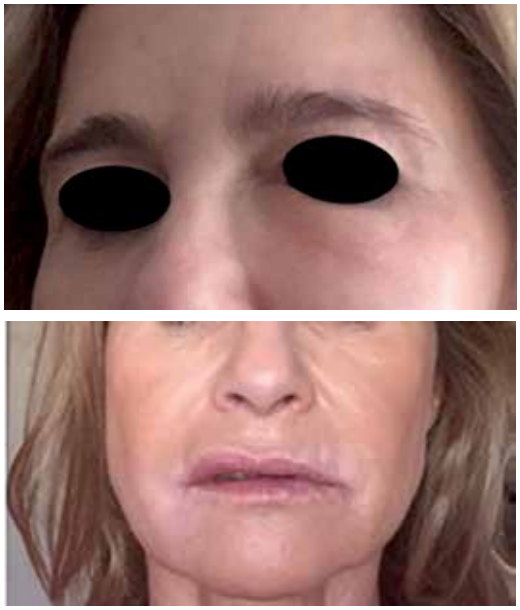

**Figure 4:** Patient with two episodes of facial edema in different times after use of HA filler (Juvederm Volift). Upper: unilateral lower eyelid edema along with sinusitis. Lower: right upper lip edema along with urinary tract infection

late effects are inflammatory or immunomediated in nature, and that factors such as systemic infections could act as a trigger for these complications.[11]

The data obtained suggest that PIDS is a manifestation that can occur after the use of HA facial fillers, clinically characterized as: late onset diffuse, non-pitting edema along the area of HA injection, (it can appear between week and years after HA injection), transient and intermittent and, mainly, persisting while there is HA in the tissue. It is frequently related to some trigger such as local trauma, vaccination (Figure 3) or more commonly after a local or systemic infectious process such as, for example, respiratory infection (Figure 4) or dental procedures, what could explain its intermittent nature.

## CONCLUSION

The authors propose a specific nomenclature: persistent intermittent delayed edema (PIDS) to group late HA adverse reactions, characterized by late local intermittent edema, triggered by specific factors, that persists while there is HA in the tissue.

On US, the common finding is the presence of HA with signs of surrounding panniculitis (increased thickness and echogenicity of the subcutaneous tissue, correlating to the clinical aspect), and the absence of solid nodules or liquids. Since nodules cannot be identified on US, we suggest that PIDS have a specific classification in the group of HA late adverse reactions, commonly described as a group in the literature.

**DECLARATION OF PARTICIPATION:**

**Fernanda Aquino Cavallieri:**
Preparation and wording of the manuscript

**Laila Klotz de Almeida Balassiano:**
Preparation and wording of the manuscript

**Julien Totti de Bastos:**
Preparation and wording of the manuscript

**Gabriela Helena Munhoz de Fontoura:**
Preparation and wording of the manuscript

**Ada Trindade de Almeida:**
Supervision and final review of the manuscript

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Referencias: **1 -** MULINARI-BRENNER, F.; SOARES, I.F. Alopecia androgenética masculina: uma atualização. Rev Ciênc Méd, v. 18, n. 3, p. 153-161, 2009. **2 -** COLSEN, E.A.; et al. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment od androgenetic alopecia in men. J Am Acad Dermatol, v. 47, p. 377-85, 2002. **3 -** Micromedex® Healthcare Series: DrugPoint Minoxidil. Disponível em: <http://www.micromedexsolutions.com>. Acesso em: Jul 2017. **4 -** Internal Report **5 -** Kairos Web Brasil. Disponível em: <http://brasil.kairosweb.com>. Acesso em: Jul. 2017.

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Guarde-o em sua embalagem original. Todo medicamento deve ser mantido fora do alcance das crianças. Gravidez e lactação: Minoxidil 5% não deve ser usado em pacientes do sexo feminino. O produto pode ser prejudicial durante a gravidez e lactação. **Interações medicamentosas: Não são conhecidas interações medicamentosas associadas ao uso concomitante de medicamentos sistêmicos e Minoxidil 5%. Medicamentos de uso local, como por exemplo a tretinoína e o ditranol, capazes de atravessar a barreira córnea, podem levar a um aumento da absorção de minoxidil tópico.** Reações adversas: Reações dermatológicas, devido à intolerância cutânea à formulação tópica (irritação, coceira, dermatite leve do couro cabeludo) foram observadas em estudos clínicos. Eventos comuns (entre > 1/100 e < 1/10): hipertricose, eritema local, coceira, pele seca, descamação do couro cabeludo e exacerbação da perda de cabelos. Alguns pacientes relataram aumento do desprendimento capilar após o início do tratamento, que geralmente ocorre de duas a seis semanas após o início do tratamento e diminui dentro de algumas semanas. Caso persista por mais de duas semanas, o paciente deve descontinuar o uso de minoxidil 5%. Eventos raros (< 1/10.000): dermatite alérgica de contato, foliculite e seborreia. O uso extensivo não mostrou absorção de quantidade suficiente para causar efeitos sistêmicos. Pode haver maior absorção devido ao uso abusivo do produto, ou à variação individual e sensibilidade exagerada levando a um efeito sistêmico e possibilidade da ocorrência de efeitos adversos, como: taquicardia, angina, debilidade ou vertigem, ganho de peso repentino, suor das mãos e pés e edema. Embora não tenham sido associados ao uso tópico de minoxidil 5%, o tratamento deve ser interrompido e, se necessário, tratamento adequado deve ser instituído. Posologia: EXCLUSIVAMENTE PARA USO EXTERNO. Direcionar o frasco para o centro da área calva, pressionar a válvula uma vez e espalhar o produto com a ponta dos dedos em toda a área calva e áreas circunvizinhas. Repetir até o total de seis vezes para completar a dose de 1 ml da solução. Após a aplicação, lavar bem as mãos. A dose total diária não deve exceder 2 ml ou duas aplicações diárias. Após a utilização, limpar a parte externa do aplicador antes de armazenar o produto. Não é necessário lavar os cabelos antes da utilização, e se os cabelos forem lavados, não se deve utilizar xampu com silicone; utilizar um xampu suave. Esperar pelo menos quatro horas após a aplicação para lavar os cabelos novamente. O uso de secador de cabelos, géis, cremes, sprays, tinturas ou permanentes para os cabelos não diminui o efeito de minoxidil 5%. Assegurar-se que não haja minoxidil 5% no couro cabeludo antes de aplicar qualquer produto químico para evitar irritação. Não aplicar no mesmo dia da aplicação de produtos químicos. Aplicar apenas quando o cabelo e o couro cabeludo estiverem secos. Com a suspensão do tratamento, o nascimento de cabelos novos será interrompido. Ocorrerá um efeito reversível e, dentro de três a quatro meses sem tratamento, pode-se voltar ao aspecto anterior ao início do tratamento. Em caso de esquecimento da administração no horário estabelecido, fazê-lo assim que lembrar. Caso estiver perto do horário de administrar a próxima dose, desconsiderar a dose esquecida e utilizar a próxima. "SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO." VENDA SOB PRESCRIÇÃO MÉDICA MS - 1.10573.0487 - "Material técnico científico de distribuição exclusiva a profissionais de saúde habilitados à prescrição e/ou dispensação de medicamentos" (MB 01 - SAP 4528000)

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# Analysis of diagnostic and therapy accuracy index based on non-melanona's skin cancer dermoscopy

## *Análise do índice de acurácia diagnóstica e terapêutica baseado na dermatoscopia do câncer da pele não melanoma*

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## ABSTRACT

**Introduction**: Non-melanoma skin cancer is among the most frequent neoplasms in Brazil and is deemed a public health problem. Initial diagnosis is based on clinical suspicion and includes dermoscopy. Confirmation is carried out via histological analysis. Dermoscopy also contributes to the demarcation of tumor safety margins.

**Objective**: To analyze the accuracy of dermoscopy in the diagnosis of non-melanoma skin cancer and its effectiveness in defining the lateral margins of these tumors in excisional biopsies.

**Methods**: Comparison of the dermoscopy-based diagnostic hypothesis with the final histological outcome and involvement of lateral margins.

**Results**: The data relating to a total of 70 lesions suspicious of non-melanoma skin cancer arising from a group of 50 patients were evaluated from 2015 to 2017. The comparison of the diagnostic hypothesis with the final histological outcome after excisional biopsy, indicated success rates of 79.6% for suspected cases of basal cell carcinoma and 23.8% for squamous cell carcinoma. Safety margins were observed in 74% of basal cell carcinomas and in 60% of squamous cell carcinomas.

**Conclusions**: The diagnosis of non-melanoma skin cancers depends on experienced dermatologists and pathologists, with the interaction between these professionals being crucial. Dermoscopy has contributed in a more significant way to the diagnosis of basal cell carcinoma when compared to that of squamous cell carcinoma.

**Keywords**: skin neoplasms; diagnosis, differential; margin

## *RESUMO*

***Introdução:*** *O câncer da pele não melanoma está entre as neoplasias de maior incidência no Brasil, sendo considerado um problema de saúde pública. O diagnóstico se inicia pela suspeita clínica, incluindo a dermatoscopia, e, de forma definitiva, a análise histopatológica. A dermatoscopia contribui também para a demarcação de margens de segurança do tumor.*

***Objetivo:*** *Analisar a acurácia da dermatoscopia quanto ao diagnóstico do câncer da pele não melanoma e sua eficácia na definição das margens laterais desses tumores em biópsias excisionais.*

***Métodos:*** *Comparação da hipótese diagnóstica levantada mediante a dermatoscopia com o resultado histológico final e comprometimento de margens laterais.*

***Resultados:*** *Foram avaliados de 2015 a 2017, dados de 70 lesões suspeitas de câncer da pele não melanoma em um grupo de 50 pacientes. A comparação da hipótese diagnóstica com o resultado histológico final após biópsia excisional mostrou índice de acerto de 79,6% para os casos suspeitos de carcinoma basocelular e de 23,8% para os de carcinoma espinocelular. As margens de segurança foram respeitadas em 74% dos carcinoma basocelular e 60% dos carcinoma espinocelular.*

***Conclusões:*** *O diagnóstico de câncer da pele não melanoma depende de dermatologistas e patologistas experientes, sendo fundamental a interação entre ambos. A dermatoscopia contribuiu para o diagnóstico do carcinoma basocelular de forma mais importante do que para o do carcinoma espinocelular.*

***Palavras-chave:*** *neoplasias; diagnóstico diferencial; margem*

## INTRODUCTION

Non-melanoma skin cancer (NMSC) is among the most common malignancies, occurring more than the other types of cancers combined,[1,2] therefore being a public health issue due to its increasing incidence and to the consequent costs associated with treatment.[3]

Tumors that are representative for NMSC are basal cell carcinomas (BCC) and squamous cell carcinomas (SCC),[4-6] the latter representing about 20% of skin cancer cases and the former approximately 70%.[6] In general, they cause more morbidity than mortality, but both have the potential to metastasize (0.5% for BCC and 20% for SCC).[7] Diagnostic suspicion of these tumors starts with the clinical aspect and is aided by dermoscopic features.[8] BCC's dermoscopy can present with the following signs, with high specificity: "spoke wheel" areas, large blue-grey ovoid nests, multiple blue-grey globules, "leaf-like" areas (or in "gloved finger"), arborizing telangiectasias and ulcerations (less specific).[9] SCC's is usually not that specific as to differentiate it from the early variants (actinic keratosis and Bowen disease) and, in some cases, even other entities such as seborrheic keratoses, verruca vulgaris, and keratoacanthomas. Glomerular vessels and yellow-white areas are dermoscopic findings in SCC.[10,11]

The gold-standard for the diagnosis of NMSC, either BCC or SCC, is histopathology.[5] There are, however, non-invasive methods to examine the lesions in an initial phase and stratify their risk, dermoscopy being one of them.[12,13] Its importance consists in the necessity to minimize costs with unnecessary biopsies, define the physician's attitude towards the patient and, in some cases, reduce surgical morbidity. On the other hand, dermoscopy contributes for the early diagnosis (early or small lesions) and appropriate treatment (determination of surgical margins). These are key-factors for a more favorable prognosis for NMSC.[14]

The objective of the study is to perform a self-assessment of an academic service of the Brazilian Society of Dermatology (SBD) regarding the clinical-dermoscopic accuracy rates for NMSC and analyze the degree of efficacy of the excisional biopsy in avoiding an incisional step considering the cases accurate for NMSC.

## METHOD

Study conducted at the service of dermatology, Universidade de Mogi das Cruzes, São Paulo, Brazil, from 2015 to 2017, where 70 suspicious lesions for NMSC were evaluated in a group with 50 patients.

Inclusion criteria for the lesions were low-risk NMSC (up to 1cm and well-defined) and prediction of non-complex reconstruction, i.e., edge-edge closure to enable wider excision in case of affected margins. The lateral margin used was 3mm and the deep margin was down to the subcutaneous tissue, with the scalpel at a 90º angle in relation to the skin.

Exclusion criteria were tumors larger than 1cm, ill-defined, recurrences and periorificial.

The lesions were registered in a database with the following information: diagnostic hypothesis, age, gender, and area of the lesion. After this step, the dermoscopic diagnostic hypothesis was compared to the final histologic diagnosis and involvement of surgical margins.

The dermoscopic diagnostic accuracy rate was defined by the degree of agreement of the diagnostic hypothesis with the final histologic report. The therapeutic accuracy rate aided by dermoscopy was defined as the percentage of NMSC cases that had surgical margins clear of malignancy.

The development of the database, as well as the analysis of the data, was done with Microsoft Excel. The statistical analysis was quanti-qualitative and descriptive.

The research was performed within the parameters of the Resolution 466/12 and their complements of the Conselho Nacional de Saúde/Ministério da Saúde, that states that collected data must be anonymous and reliable. The Committee of Ethics in Research – CEP/UMC approved the protocol of research number 50776615.8.0000.5497 and report 1.463.323.

## RESULTS

Seventy skin lesions were analyzed with diagnostic hypothesis (DH) of NMSC in a group of 50 patients, 27 being male (54%) and 23 female (46%) with a mean age of 70 years (Table 1). Of these data, the DH of BCC represented 70% and of SCC, 30%.

The diagnostic accuracy rate for BCC was of 79.6%, and for SCC, 23.8% (Table 2).

Table 3 shows the other histologic diagnoses found, that do not correspond to the clinical hypothesis of BCC.

Table 4 shows other histologic diagnoses found that do not correlate with the clinical hypothesis of SCC.

Regarding the body location, the most affected areas were head and neck, followed by upper limbs and hands (Table 5). The area more prevalent for BCC was the head and neck (63%), and for SCC, upper limbs (48%).

Of the accurate BCC diagnoses, 74% had surgical margins clear of malignancy, compared to 60% of SCC. There was no description of the surgical margins in seven BCC lesions and one SCC lesion (Graph 1).

(70% to 20%, 3,5 relationship).[6] Regarding the results found, the proportion of BCC to SCC was of 39:8 or 4.875. Therefore, in this study, there was a higher relative prevalence of BCC compared to SCC in the histologic results.

In this study, we observed that the accuracy rate for BCC was higher than for SCC. This finding can be explained based on the more specific dermoscopic features for the former, com-

**Table 1: Sample distribution and mean age according to gender, Mogi das Cruzes, 2017**

| Gender | Results | Age (mean) |
|---|---|---|
| Male | 26 (53%) | 69 years |
| Female | 23 (47%) | 71 years |

**Table 2: Clinical accuracy of the diagnosis of BCC and SCC, Mogi das Cruzes, 2017**

| | Historical diagnosis | | | | |
|---|---|---|---|---|---|
| Diagnostic hypothesis of BCC | SCC present (n) | SCC absent (n) | Diagnostic hypothesis of SCC | SCC present (n) | BCC absent (n) |
| BCC present (n) | 39 | 10 | SCC present (n) | 5 | 16 |
| Predictive value (clinical accuracy) = (39 / 49) x 100 = 79.6% | | | Predictive value (clinical accuracy) = (5 / 21) x 100 = 23.8% | | |
| Predictive value considered BCC and SCC (clinical accuracy) = (44 / 70) x 100 = 62.8% | | | | | |

**Table 3: Histopathology results conflicting with the clinical diagnosis of BCC, Mogi das Cruzes, 2017**

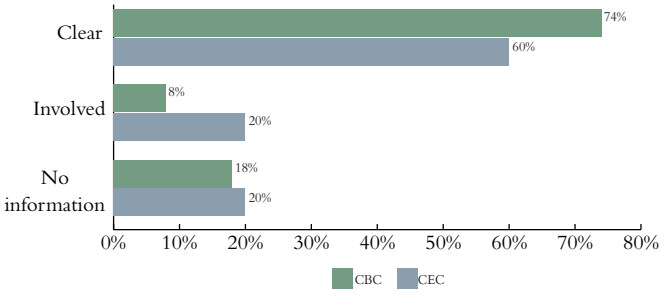
| Histology | Results |
|---|---|
| Actinic keratosis | 3 (30%) |
| SCC | 3 (30%) |
| Seborrheic keratosis | 2 (20%) |
| Chronic dermatitis linfobiatioclinica | 1 (10%) |
| Dermal fibrosis | 1 (10%) |

**Table 4: Histopathology results conflicting with the clinical diagnosis of SCC, Mogi das Cruzes, 2017**

| Histology | Results |
|---|---|
| Actinic keratosis | 9 (56%) |
| Keratoacanthoma | 3 (19%) |
| BCC | 3 (19%) |
| Viral wart | 1 (6%) |

**Table 5: Body distribution of NMSC (BCC and SCC) Mogi das Cruzes, 2017**

| Area | Result |
|---|---|
| Head and Neck | (52%) |
| Upper limbs | (23%) |
| Chest, back and neck | (21%) |
| Lower limbs and feet | (4%) |




**Gráfic 1:** Surgical margin involvement Mogi das Cruzes, 2017

pared to the latter.[17] Dermatoses with clinical and dermoscopic features similar to SCC such as actinic keratosis (AK),[15] keratoacanthoma (KAC)[15,18] and verruca vulgaris (VV)[19] made up an expressive percentage of the diagnoses found among suspicious SCCs. Thus, only 23.8% accuracy rate for SCC is relative. It is considered that SCC, added to this group of dermatoses clinically and dermoscopically similar corresponds to 85% of the results found with the clinical suspicion in some cases. However, we recognize that the clinical criteria to differentiate SCC of these other dermatoses failed frequently in this study.

Misdiagnosis is suspected BCCs can be explained by some factors: non-specific clinical features and dermoscopic vascular features similar in some cases of BCC, KA and SCC; even though possible, the dermoscopic differentiation[17] demands a higher experience of the assistant physicians in the dermoscopy learning curve. Operator-dependent (pathologist) or even laboratory logistic (wrong slides or reports) errors must be considered.

Regarding the surgical margins, we observed that they were insufficient in some cases of NMSC, taking into consideration a 3mm excision from the outer limits of the tumor, dermoscopically marked, with a higher relevance for SCC, justifying larger safety margins than the medical literature recommends for this tumor, compared to BCC.

One possible explanation is the commonly ill-defined limits of SCCs, besides accompanying inflammation.

We should include possible operator-dependent-type biases of the histopathology. Many reports were inconclusive regarding the margins.

## CONCLUSION

NMSC diagnosis depends on consistent and well sound information, using clinical, dermoscopic and, specially, histopathologic criteria. The accuracy of the first two depends largely on the experience of the dermatologist, and the third of a pathologist experienced in skin and, if possible, skin tumors. More than that, the interaction between the two professionals is extremely important.

In tertiary cutaneous oncology services, the assistant dermatologist should specify the type of biopsy (incisional x excisional) and the characteristics that lead to the clinical suspicion, so that the pathologist can fulfill their role with equal accuracy.

Dermoscopy learning curve leads to a higher accuracy rate in clinical suspicion. This resource, however, failed in differentiating SCC from other verrucous conditions. The higher surgical margin involvement in SCC cases reinforces the use of larger margins than the recommended when facing this tumor, when compared to BCCs. For BCCs, dermoscopy contributed to the diagnosis in a greater way, however, was not typical nor unanimous in the resolution of excisional biopsy. ●

**PARTICIPATION IN THE ARTICLE:**

**André Cesar Pessanha:**
Research project, data recording and final review

**Isadora Zambuzi:**
Introduction and organisation of the results

**Carlos Vidal:**
Preparation of the tables, discussion and submission of the study

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Original Articles

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# Comparative study of 1,340nm non-ablative fractional laser for facial rejuvenation: single pass at high energy versus three passes at medium energy

## *Estudo comparativo do laser fracionado não ablativo 1340nm para rejuvenescimento facial: alta energia com passagem única versus energia média e passagem tripla*

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## ABSTRACT

**Introduction**: Currently there is a growing demand for non-invasive therapies aimed at treating facial aging. Non-ablative fractional lasers lead to excellent outcomes, with reduced side effects.

**Objective**: To evaluate the facial rejuvenation achieved by 1,340nm non-ablative fractional laser using a single pass at high energy versus three passes at medium energy, through a prospective comparative study.

**Methods**: Twenty patients with facial aging were treated with 2 or 3 laser sessions with 4-week intervals. The right hemiface was treated with three passes of 1,340nm non-ablative fractional laser at a fluence of 90 mJ, pulse duration of 5ms and 100 mtz/cm2. The left hemiface was treated with a single pass of the same laser at a fluence of 120 mJ, pulse duration of 5ms and 100 mtz/cm2. The evaluated variables were spots, wrinkles, porphyrins and overall appearance.

**Results**: The patients (n = 20) were evaluated during 6 to 24 months. The photographic evaluations demonstrated a significant improvement of the spots on the right hand side and wrinkles on the right and left hand sides. Eighteen of the 20 patients reported satisfaction with the treatment.

**Conclusion**: 1,340nm non-ablative fractional laser was proven as a modern, safe and effective alternative for facial rejuvenation. For spots, the triple passes at medium energy protocol led to a superior response. However, regarding wrinkles there was no difference between the single pass at high energy and triple pass at medium energy protocols.

**Keywords**: laser; rejuvenation; facial aging; face

## RESUMO

***Introdução:*** *Atualmente há crescente procura de tratamentos não invasivos para o envelhecimento facial. Os lasers fracionados não ablativos promovem excelentes resultados, com efeitos colaterais reduzidos.*

***Objetivos:*** *Avaliar o rejuvenescimento facial, utilizando-se o lasers fracionados não ablativos 1340nm em alta energia com passagem única e em média energia com passagem tripla, mediante estudo prospectivo e comparativo.*

***Métodos:*** *20 pacientes com envelhecimento facial foram tratadas com duas ou três sessões do laser a cada quatro semanas: a hemiface direita com lasers fracionados não ablativos 1340nm com fluência 90mJ, duração de pulso 5', 100mtz/cm2, três passadas; a esquerda com fluência 120mJ, duração de pulso 5', 100mtz/cm2 e passada única. As variáveis avaliadas foram manchas, rugas, porfirinas e aparência global.*

***Resultados:*** *As pacientes (n = 20) foram avaliadas a intervalos de seis a 24 meses. As análises fotográficas demonstraram melhora significativa das manchas no lado direito e das rugas de ambos os lados. Das 20 pacientes 18 apresentaram satisfação com o tratamento.*

***Conclusão:*** *O lasers fracionados não ablativos 1340nm demostrou-se alternativa atual, segura e eficaz para o rejuvenescimento facial. Para as manchas, o protocolo de energia média e passagem tripla demonstrou resposta superior. Nas rugas, entretanto, não houve diferença entre energia alta com passagem única e média com passagem tripla.*

***Palavras-chave:*** *laser; rejuvenescimento; envelhecimento facial; face*

## INTRODUCTION

The rejuvenating techniques have been perfected not only due to technological advances, but also due to the concern of the population with health and physical appearance, as well as longevity.[1] Some studies suggest that the facial changes due to aging begin at around 30 years of age[2] and are clearly noticed from 40 years of age, when there is a reduction in the estrogen levels and collagen fibers, making the skin thinner and more sensitive, with pigment changes and the appearance of wrinkles, telangiectasias and lentigos. The formation of wrinkles, irregularities, reduction of elasticity and firmness of the facial skin are the most expressive signs of the biologic age.[3] In chronological aging, the thickness of the dermis reduces due to biochemical and structural changes of the collagen and elastic fibers, as well as the ground substance.[4,5] There is reduction in the production of collagen and increased degradation due to the elevated levels of collagenase. The cutaneous amount of collagen reduces 1% per year on average throughout adulthood, beginning between 30 and 40 years of age in women and somewhat later, between 40 and 50 years in men. Remaining collagen fibers are disorganized, more compact and fragmented. Elastic fibers are reduced in number and diameter. The amount of mucopolysaccharides in the ground substance is reduced, especially hyaluronic acid. These changes have a negative influence on the skin turgor and the collagen.[6] Skin aging is a natural and multifactorial process that results in cutaneous deterioration, sagging and wrinkles. The extension of aging is determined by factor related to genetics, skin pigmentation and thickness, as well as external factors, such as sun exposure, smoking and quality of nutrition.[7,8]

The conservation of youth was always fascinating and there has been an increase in demand for non-invasive treatments to control facial aging.[9] Some people invest time and money in rejuvenation techniques, many of which do not have their efficacy proven.[10] According to survey by the American Society for Dermatologic Surgery in 2014, around 150 thousand laser resurfacing procedures were performed. More directed studies are needed with each device to try to evaluate the role of different parameters and their standardization.[11]

Cutaneous laser rejuvenation has shorter operation and recovery times, with more natural result when compared to traditional surgery.[12,13] Non-ablative lasers and other sources of electromagnetic energy represent the new approaches to improve photoaged skin. Since the degree of collagen remodeling is not as high as seen with other techniques, that are more destructive and ablative, the non-ablative technique is appropriate for the treatment of persons who aim at improving the quality of their skin, with no downtime.[14] The main indication for the non-ablative fractional laser is mild to moderate photoaging, because the neocollagenesis with this technique is limited. Removal of epidermal and superficial dermal pigmentation is a second indication.[15] For decades, devices and peels were used for facial rejuvenation and for the treatment of skin damage. In the last few years, new laser systems were developed, including ablative and non-ablative fractional, that can provide good results with less side effects.[16] Non-ablative rejuvenation uses laser to improve the skin appearance and reduce the number of wrinkles, blemishes and scars by generating heat in the dermis, keeping the epidermis intact. The fractional approach allows the skin to recover much quicker than the non-fractional. This approach reduces recovery time and the number of possible complications. In most cases, multiple sessions are needed.[17]

## OBJECTIVE

The objective of the present study was to evaluate and compare facial rejuvenation with non-ablative fractional laser (LFNA) 1340nm with a single pass and high energy to triple pass and medium energy.

## METHODS

For this clinical, prospective, single-center and comparative study, 20 female patients, aged 40 to 70 years, Fitzpatrick phototypes I to IV and Glocau's aging index of moderate to severe were recruited from the Dermatology Outpatient clinic of the Faculdade de Medicina de Jundiaí (SP). It was conducted in accordance to the Helsinki Declaration and according to the CNS Resolution n. 466/12 of the Anvisa, according to Good Clinical Practice (Document of the Americas and ICH E6: Good Clinical Practice). The patients were informed about the objective, methodology, duration, advantages and clinical restrictions related to the study. The participants confirmed their interest, signing a consent form. Technical documentation of this study will be kept in file for five years.

Exclusion criteria were infection on the site to be treated, history of keloid scarring, known connective tissue or autoimmune diseases Raynaud phenomenon or circulation changes, pregnancy or lactation, presence of suspicious lesion for malignancy on dermoscopy, history of allergy to anesthetics agents and unrealistic expectations for the treatment.

All patients were prepared for the treatment with the application of topical anesthetic with lidocaine 4%, 30 minutes before the session. Fifteen patients had three laser sessions for the face and other five patients, due to scheduling problems, had two sessions, 4 weeks apart. The treatment platform used was ETHEREA-MX® (VYDENCE Medical®, São Carlos, SP, Brazil), and its handpiece ProoDeep – non-ablative fractional laser Nd:YAP (Neodimiun:Ytrium Aluminum Peroviskita) of 1340nm. The right side of the face was treated with LFNA 1340nm with the fluence of 90mJ, pulse duration of 5', 100mtz/cm², three passes and skin cooling with the device SIBERIAN (VYDENCE Medical®, São Carlos, SP, Brazil) for comfort during and after the procedure. The left side of the face was treated with LFNA 1340nm with the fluence of 120mJ, pulse duration of 5', 100mtz/cm², single pass and cooling identical to the other side of the face.

The patients received instructions to avoid topical agents on the treated area for the duration of the study and to report adverse cutaneous or systemic reaction after laser. They were contacted between 6 and 24 months after the last session. Clinical efficacy of the treatment was performed by three blinded

dermatologists, through photographic analysis before and after the treatment. Besides analyzing the photographs, the results were evaluated with the device Visia. The parameters used for the clinical evaluation before and after the treatment were: blemishes, wrinkles and porphyrins.

After the procedure, the patients were advised to avoid sun exposure and use sunscreen daily on the treated area, with a large UVA and UVB protection spectrum (solar protection factor 50), until fully recovered. Besides, they were advised to avoid contact with substances that could irritate ou sensitize the area in the first week after the procedure.

The statistical analysis of the results was performed using the software Grafhpad Prism 7. Scores of 0 to 4 were created to evaluate and grade the improvement, with 0 corresponding to the category "None", 1 to the category "Little", 2 to the category "Medium", 3 to the category "Large" and 4 to the category "Excellent". The quantitative variables were described by the mean and standard deviation and compared by the Student T test for matched samples. We considered the significance level of 5%.

## RESULTS

The patients (n = 20) were assessed in a period of 6 to 24 months between the first treatment and the last clinical assessment. Upon examination of the results of the photographical analysis (Figure 1), evaluated and quantified the parameters blemishes, wrinkles and porphyrins, before and after the treatment, with the device Vísia, there was a statistically significant improvement of the blemishes on the right side of the face ($p < 0.05$ Student t test), wrinkles on the right and left sides ($p < 0.05$ Student t test). Regarding porphyrins, there was no statistically significant improvement ($p > 0.05$, Student t test). The photographic analysis demonstrated treatment efficacy and the possibility of reaching a unique benefit in a short time. Figure 1 illustrates wrinkle improvement on both sides of the face.


**FIGURE 1:** Improvement in a 45-year-old patient, whose right side of the face was treated with medium energy and 3 passes, and the left, with high energy and single pass

In the evaluation of the percentage and statistical results performed by the blinded dermatologists (A1, A2 and A3) (Table 1), we observe the statistically significant clinical efficacy of the wrinkle treatment tratamento by examiner 1 (A1). Regarding the assessment of the other examiners, there was no statistically significant difference between matched samples ($p > 0.05$).

Global rejuvenation (global appearance), analyzed in percentages, showed that the variables "Large" and "Excellent" were higher. In the subjective evaluation of the patients, 90% (18/20 patients) demonstrated a higher satisfaction rate with the treatment given. The level of satisfaction was evident after 30 days of the first reassessment, before the second session, with the manifestation of interest to continue the treatment. The patients

**TABLE 1: Percentage and statistical analysis of the assessing dermatologist**

| Variables | Right side | Left side |
|---|---|---|
| **Wrinkles** | | |
| None | 15% | 5% |
| Little | 45% | 25% |
| Medium | 65% | 35% |
| Large | 45% | 20% |
| Excellent | 30% | 15% |
| **Vessels** | | |
| None | 60% | 40% |
| Little | 35% | 45% |
| Medium | 5% | 10% |
| Large | 0% | 0% |
| Excellent | 0% | 0% |
| **Pigmented Lesion** | | |
| None | 0% | 0% |
| Little | 20% | 25% |
| Medium | 55% | 55% |
| Large | 25% | 20% |
| Excellent | 0% | 0% |
| **Global Appearance** | | |
| None | 0% | 0% |
| Little | 15% | 15% |
| Medium | 25% | 45% |
| Large | 45% | 25% |
| Excellent | 15% | 15% |

Data shown as percentages

Matched samples were compared by Student t test, considering significance level of 5%

Statistically significant difference P>0.05 in the other variables analyzed

reported improvement on the skin for up to 6 months after the last session.

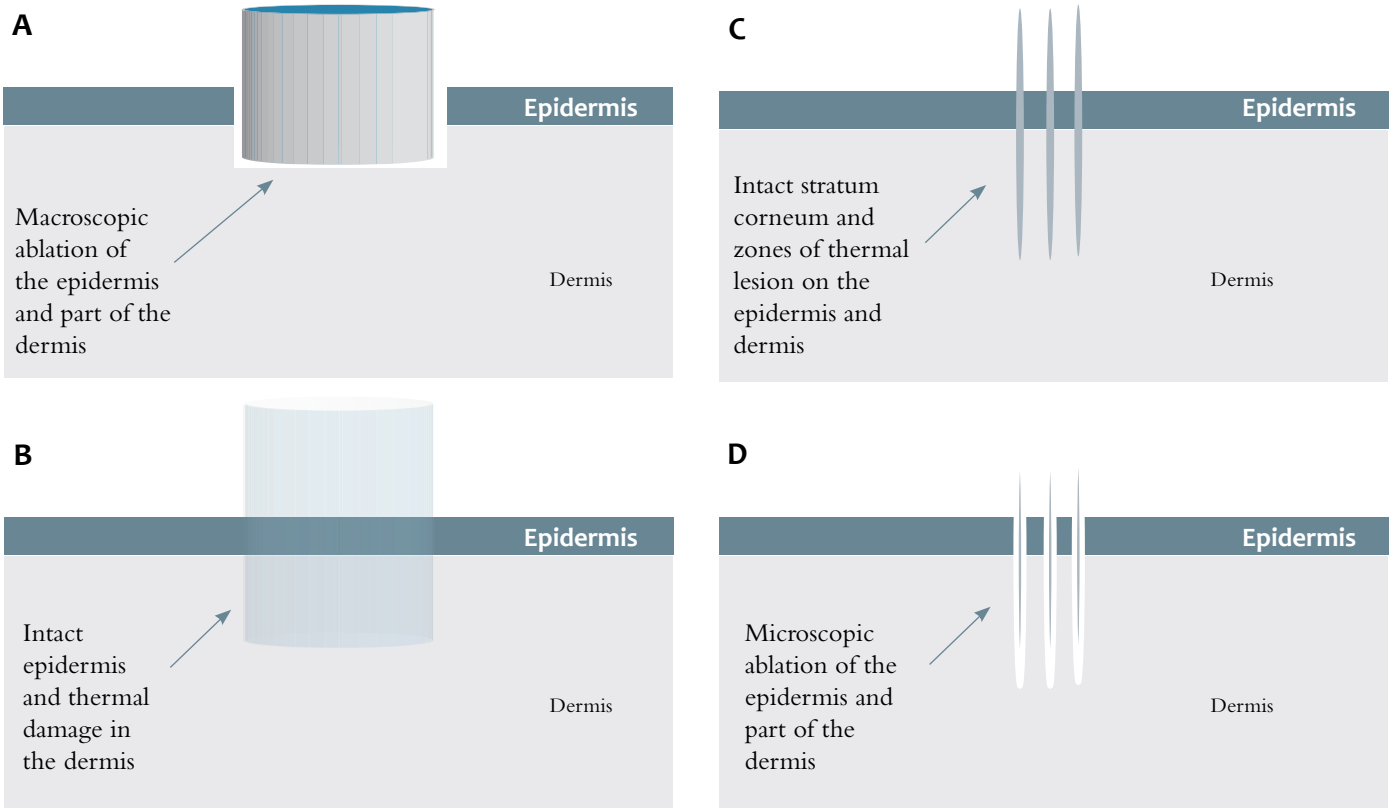
The side effects reported were erythema and edema immediately after the session, with similar intensity on both sides of the face, that disappeared spontaneously in the first 48 hours; no other side effect was seen after that.

## DISCUSSION

Innovative treatments for facial rejuvenation are in constant evolution, in particular with the use of non-ablative laser. However, no studies were published on its efficacy or the specifications of Nd:YAP 1340nm laser for this indication.

Inevitable changes occur on the skin with chronologic aging, including loss of elasticity, texture and color changes.[18] The modification of the thickness of the dermis occur via biochemical and structural changes in the collagen and elastic fibers and in the ground substance, with reduction of the collagen synthesis and increased degradation due to the elevation in the levels of collagenase The elastic fibers are reduced in number and diameter, and the amount of mucopolysaccharides in the ground substance is also reduced, and of the hyaluronic acid in particular, which influences negatively the skin turgor and also on the deposition, direction and size of collagen fibers.[19]

The market of non-surgical, energy-based facial rejuvenation techniques increased exponentially since lasers were first used for this indication. The advance is this area lead to a wide range of products that demand a great repertoire of knowledge from the modern doctor.[20] Since the advent of high potency pulsed ablative carbon dioxide laser for the reduction of wrinkles and treatment of photoaging in the mid-1990s, laser resurfacing became the standard treatment for rejuvenation of facial skin. In the beginning, this technique was popular. Even though the results are impressive, the discomfort, the prolonged recovery and the high risk for complications lead to patient dissatisfaction and it became gradually less popular. Although this laser continues to be the treatment of choice for the skin with severe photoaging, the use of non-ablative laser also imporves lines and wrinkles in mild to moderate aged skin, with a minimal risk of




Explanation of the mechanism of action of multiple lasers.[15]

**A**: Conventional ablative laser (non-fractional): removes all epidermis and dermis.

**B**: Non-ablative laser: does not remove the epidermis and causes thermal damage in the dermis.

**C**: Non-ablative fractional resurfacing: spares the epidermis and generates rows of coagulation in the dermis.

**D**: Fractional ablative laser: forms rows of epidermal and dermal ablation.

**Figure 2:** Mechanism of action of multiple lasers

complications and without the downtime associated to ablative laser techniques. With the advances in laser technology, multiple non-ablative lasers for facial rejuvenation became available. The results of the treatment with these devices were reported by various researchers.[21,22]

In the present study, high-energy 1340nm non-ablative fractional laser with a single pass and medium energy with a triple pass proved to be an effective treatment for facial rejuvenation. There was a slight overall improvement, with an obvious global rejuvenation, not as dramatic as what is seen with ablative laser treatment.[23,24] None of the patients in this study reported any side effect after 48 hours of treatment.

Non-ablative fractional laser rays generate rows of coagulation in the skin, maintaining an intact, non-ablated epidermis (Figure 2). In this row, there is a process of reconstitution of all the area that was coagulated, from the dermis to the epidermis, after a few hours and with months' duration. Collagen and fractions of pigment and vessels that were coagulated are slowly eliminated through the epidermis.[15] The penetration of the rays varies depending on the fluence. The literature shows that the higher the energy released, the deeper the action and the greater the neocollagenesis, allowing for a modulation of the desired result.[25] In this study, the use of higher energies with a single pass was not more effective in the reduction of wrinkles than the treatment with medium energy and three passes.

Despite the fact that melanin and hemoglobin are not the targets of this lasers, the ray row coagulates part of pigments and/or vessels that are reached by it upon penetration in the skin. Thus, even indirectly, there is removal of superficial epidermal and dermal pigments and also of some smaller blood vessels. There was no significant reduction of the vessels. Regarding lentigos, the side treated with a triple pass and medium energy had a higher reduction than the side treated with a single pass and higher energies. This is the first study of the use of Nd:YAP 1340nm laser for facial rejuvenation, so more studies are needed to compare with the efficacy of other well-established lasers.

## CONCLUSION

Even with a small number of patients in this clinical study, the treatment with 1340nm non-ablative fractional laser with high energy and single pass versus medium energy and three passes proved to be safe and effective for facial rejuvenation, becoming an alternative for the face. The technique of triple pass and medium energy showed a better reduction in lentigos than the single pass with higher energies; however, there was no difference regarding the reduction of wrinkles with the two techniques. An approach with the identification of the degree of aging will certainly improve the efficacy of the treatment, possibly achieving even better results. The proposed treatment ended with satisfied patients, who had more beautiful skin and a younger look.

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Original Articles

# Percutaneous induction of collagen with needles (IPCA®) associated with Pulsed radiofrequency with multineedles (RFPM®) in the management of depressed acne scars: treatment protocol

*Indução percutânea de colágeno com agulhas (IPCA®) associada a radiofrequência pulsada com multiagulhas (RFPM®) na condução de cicatrizes de acne deprimidas: protocolo de tratamento*

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## ABSTRACT

**Introduction**: Depressed acne scars always arise as a therapeutic challenge. Fractional lasers, surgical approaches and chemical peels have attempted to offer acceptable aesthetic results, however it is still difficult to determine the ideal treatment.

Objective: To evaluate the efficacy of Percutaneous Collagen Induction with needles (IPCA®) associated with Pulsed Radiofrequency with Multineedles (RFPM®) in depressed acne scars.

**Methods**: Retrospective study of the safety and effectiveness of the technique through the evaluation of results based on a satisfaction questionnaire answered by the patients and the clinical and photographic assessment carried out by a dermatologist.

**Results**: Thirteen patients (aged between 21 and 37 years) who had undergone the combination treatment were evaluated. All (100%) reported satisfaction with the outcomes, while in the comparative evaluation of photographs yielded an improvement rate of 50% in 2 patients and of 70% in 6 patients.

**Conclusion**: This new therapeutic proposal arises as an alternative in the treatment of depressed acne scars.

**Keywords**: scars; pulsed radiofrequency treatment; collagen

## RESUMO

***Introdução**: As cicatrizes de acne deprimidas apresentam-se sempre como um desafio terapêutico. Lasers fracionados, abordagens cirúrgicas e peelings químicos têm tentado oferecer resultados cosméticos aceitáveis, mas continua difícil a escolha do tratamento ideal.*

***Objetivo**: Avaliar a eficácia da indução percutânea de colágeno com agulhas associada a radiofrequência pulsada com multiagulhas em cicatrizes de acne deprimidas.*

***Métodos**: Estudo retrospectivo da segurança e efetividade da técnica mediante avaliação dos resultados por aplicação de questionário de satisfação aos pacientes e julgamento clínico e fotográfico pelo dermatologista.*

***Resultados**: Foram avaliados 13 pacientes com idade entre 21 e 37 anos, submetidos à associação, 100% dos quais relataram satisfação com os resultados, enquanto na avaliação comparativa das fotografias o índice de melhora foi de 50% em dois pacientes e de 70% em seis pacientes.*

***Conclusão**: Essa nova proposta terapêutica se apresenta como alternativa ao tratamento de cicatrizes de acne deprimidas.*

***Palavras-chave:** cicatrizes; tratamento por radiofrequência pulsada; colágeno*

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## INTRODUCTION

Depressed acne scars always present as a therapeutic challenge. We commonly see significant changes in color, texture and relief due to an inflammatory process that causes destruction of the epidermis, dermis and, sometimes, with important consumption of the subcutaneous tissue.[1] Surgical techniques and technologies have been used in the management of these difficult-to-treat lesions, however, due to the different presentations, we do not have a gold-standard therapeutic option.[1] Percutaneous collagen induction (PCI) with needles proposes the substitution of the cicatricial collagen for a new collagen at the same time that it preserves the epidermis of the area treated. The scars are broken down by a roller with 192 microneedles on average that, after many passes on the area of interest, results in the formation of micro channels, bleeding and an inflammatory cascade that induces the remodeling of the scar tissue.[2-4] With the intention to optimize the results obtained with PCI, the author has been using the combination of other techniques before the use of the needle roller. Based on the findings from treatment of eyelid laxity and in old stretch marks, the author initiated an investigation looking for the applicability of fractional radiofrequency micro-needling (FRM) in depressed acne scars.[5,6] In FRM, the random fractional, high frequency energy applied on the skin results in dermal regeneration at the level of the interface papillary-reticular, through the stimulation of fibroblasts with subsequent synthesis of collagen and elastic fibers, as well as epidermal regeneration generated by keratinocyte migration. This study is the result of the observation of the association of PCI and FRM. Here, it is proposed an innovative approach for the treatment of depressed acne scars, based on the sub-ablative energy, with electrodes with multiple needles connected to a radioelectrosurgery device. This technique, performed accurately and isolated, does not compromise the tissue surrounding the vaporized micropoints and causes a significant impact on the tissue, enabling the stimulus for a new collagen (Figure 1). Electrodes known as Lima 2, Lima 4 e Lima 8 are needed for the execution of FRM, named after the author, made up of two, four or eight tungsten needles, respectively, with a diameter of 100 thousandth of millimeters, identical weight and length and oriented in a parallel fashion, with the objective of reaching the same depth. With a length of 2.5mm, these needles pass through the epidermis and act in the dermis, stimulating the contraction and the renovation of the collagen.

## METHODS

In this retrospective study of the safety and efficacy of the combined techniques, the records of 13 patients with depressed acne scars on the face, treated at Santa Casa de Misericórdia do Recife with the combination of PCI and FRM, performed in the outpatient setting by the same physician, using the same protocol, between January and December 2016 were. Photographic records were done with the same digital camera in identical environmental conditions, immediately before and two months after a single treatment. The study was conducted according to the ethical criteria of the Helsinki declaration. After disinfection with chlorhexidine 1%, the area was infiltrated with lidocaine 2% without vasoconstrictor 1:2 saline 0.9% solution, respecting the maximum safe dose according to the weight of each patient. Then protocol was initiated with FRM. For its execution, the device FRAXX® (Loktal Medical Electronics, São Paulo, Brazil Anvisa n. 10362610008) was used in the single pulse mode. The patients in this group were treated with the setting CUT, with potency 30 and Active 30', using the electrode Lima 8 following the trajectory of the scars, without overlapping. Subsequently and on the same surgical step, PCI was performed using a 2.5mm roller (Dr. Roller®-Moohan Enterprise CO., Gyeonggi-do, South Korea, Anvisa n. 80669600001) looking for a uniform purpura pattern.

## RESULTS

Seven female patients and six male patients, aged 21-37 years, were included in this investigation. The phototypes were III to V, according to the classification of Fitzpatrick. All patients were satisfied with the results, shown in the questionnaires as good and very good, according to the norms proposed. In the clinical and comparative evaluation of the photographs from before the treatment and two months after, the improvement rates were: 50% = good in 2 patients and 70% = very good in 6 patients (Figure 2). Pain during treatment was considered bear-

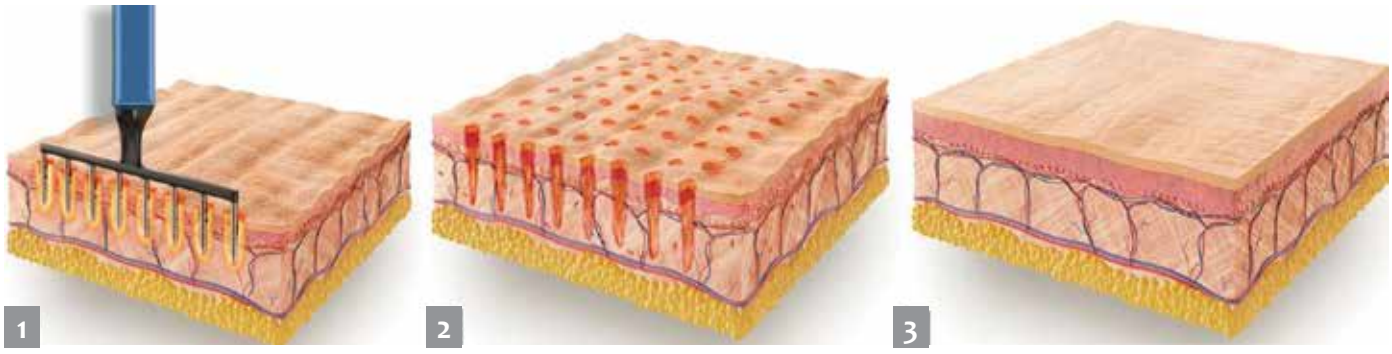


**Figure 1:** 1. Electrode Lima 8 acting on the skin 2. Immediately after fractional radiofrequency micro-needling 3. Regeneration of the skin 30 days after treatment

able, and tissue regeneration was seen between 5 to 7 days, with return to normal activities in the same time.

There was no infection, dyspigmentation or unsightly scars observed in this group after the treatment. Edema and erythema were as expected for a surgical intervention, with spontaneous regression between 7 to 10 days.

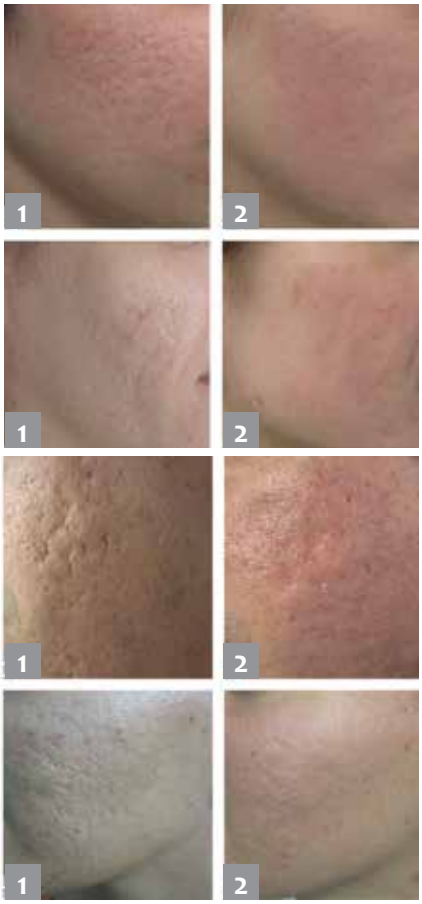


**Figure 2:** Patients before the combination treatment with PCI and FRM (1) and 60 days after the treatment (2)

## DISCUSSION

Even with the wide range of therapeutic options currently available for the treatment of scars, we still see mild or dissatisfactory improvement in many patients. Micro-needling has been offering promising results for the correction of acne scars, stretch marks, laxity and wrinkles.[7,8] In this investigation, we proposed the combination of two techniques that use microneedles in an innovative intervention, following a protocol by the author for the correction of difficult-to-treat scars. The results obtained allow us to conclude that:

FRM is a promising therapy for the treatment of depressed acne scars, when associated to PCI.

The results obtained are reproducible by qualified professionals using the methodology described in this article.

The quick return to normal activities and the few side effects seen in the group assessed encourage the author to recommend the inclusion of this new proposition in the wide therapeutic arsenal already available.

The procedure demands training and is essentially operator-dependent. The operator needs to be adequately trained and have all the basic knowledge to achieve the best results.

We suggest the evaluation of the protocol here established in other groups to confirm the results and conclusions here presented.

## DECLARATION OF PARTICIPATION:

**Emerson Vasconcelos de Andrade Lima**
Study conception and planning. Preparation and wording of the manuscript. Data collection, analysis and interpretation.

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Original Articles

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# Analysis of the profile of patients and dermatoses treated in a dermatologic surgery public campaign: the importance of the dermatologist in public health

## *Análise do perfil dos pacientes e das dermatoses abordadas em mutirão de cirurgia dermatológica: a importância do dermatologista na saúde pública*

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## ABSTRACT

**Introduction**: In the Brazilian public health system, the current demand for dermatological procedures is greater than the offer, resulting in a waiting list of patients bearing dermatoses to be treated surgically. Aimed at reducing that waiting list, a collective effort of surgical procedures was carried out in the tertiary public health service. The corresponding data on the patients and lesions is disclosed in the present study.

**Objective**: To assess the profile of the patients – and respective skin lesions – who are awaiting to undergo dermatological procedures.

**Methods**: A simple descriptive profile analysis of the patients, treated dermatoses and procedures performed was carried out.

**Results**: Thirty-one patients (aged between 21 and 95 years, mean = 63.7 years). Seventeen (54.83%) were women and 14 (45.17%) were men. Thirty-eight lesions were treated: 21 neoplastic (carcinomas and melanomas), 8 pre-neoplastic (actinic keratoses) and 9 non-neoplastic (nevi, keloid and neurofibroma).

**Conclusions**: The present article is relevant due to the fact it identifies cases and patients awaiting dermatological surgical procedures in the public health system. Based on it, a better planning of public health strategies in the dermatological field should be possible. Also, it highlights the importance of the dermatologist physician's action in the public health, diagnosing and treating pre-neoplastic and neoplastic lesions.

**Keywords**: dermatology; ambulatory health services; health centers; population studies in public health; public health; public health administration; neoplasms; melanoma; carcinoma; carcinoma, basal cell

## *RESUMO*

***Introdução:*** *A saúde pública no Brasil apresenta demanda de procedimentos dermatológicos superior à atual oferta, resultando em fila de espera de pacientes com dermatoses a abordar cirurgicamente. Foi realizado mutirão de procedimentos cirúrgicos em serviço terciário de atendimento público para reduzir essa fila, sendo os dados dos pacientes e suas lesões aqui apresentados.*

***Objetivo:*** *Analisar o perfil dos pacientes que aguardam a realização de procedimentos dermatológicos bem como suas dermatoses.*

***Métodos****: Realizou-se análise descritiva simples do perfil dos pacientes, de suas dermatoses abordadas e dos procedimentos realizados.*

***Resultados:*** *Foram atendidos 31 pacientes com idade entre 21 e 95 anos (média de 63,7 anos), sendo 17 (54,83%) do sexo feminino e 14 (45,17%) do sexo masculino. Foram abordadas 38 lesões, sendo 21 neoplásicas (carcinomas e melanoma), oito pré-neoplásicas (queratoses actínicas) e nove não neoplásicas (nevos, queloide e neurofibroma).*

***Conclusões:*** *Este artigo torna-se relevante por identificar casos e pacientes que aguardam procedimentos cirúrgicos dermatológicos no serviço público. Com ele, estratégias de saúde pública na área dermatológica podem ser mais bem programadas, além de destacar a importante ação do dermatologista na saúde pública diagnosticando e tratando lesões pré-neoplásicas e neoplásicas.*

**Palavras-chave:** *dermatologia; hospitais de dermatologia sanitária de patologia tropical; administração em saúde pública; estudos populacionais em saúde pública; saúde pública; neoplasias epiteliais e glandulares; melanoma; carcinoma basocelular; carcinoma*

## INTRODUCTION

Public health in Brazil offers a universal and free service to all inhabitants. However, the demand in the population surpasses the number of bookings offered by health systems in all three levels of complexity: primary, secondary and tertiary.[1]

In dermatology, aging of the population over the past years associated to a gradual increase in the incidence of cutaneous neoplasias, reinforces the higher demand for surgical procedures in the public health setting. Such factors lead to a known waiting list of patients, either for consultations with dermatologists or to undergo dermatologic surgical procedures.[1-3]

Skin cancer is the most frequent cancer in Brazil and corresponds to 30% of all malignancies recorded in the country. They are more common in persons older than 40 years and have high cure rates if detected early. Among skin tumors, non-melanoma type has the highest incidence and lowest mortality. It is estimated for 2016 a total of 175,760 new cases, 80,850 being in men and 94,910 in women.[2-4]

Currently, in the city of São Paulo, 16 thousand dermatology consultations are requested every month, with the suspicion of skin cancers. The consultation capacity in the city is of about 10 per month, generating a waiting line for consultations of 65 thousand cases, that wait on average for 6 months[1], not always requiring immediate surgical attention.

In the attempt of reducing the waiting time for the patients with a diagnosis of skin cancer that are waiting for a surgical procedure, collective efforts are organized in one day with a high number of dermatological procedures. In August 2017, one was made in a tertiary hospital in the city of São Paulo. The patient's and their condition's profile s were identified in order to better characterize the waiting list aspects and improve the performance of public health in dermatology.

## METHODS

It is a cross-sectional descriptive study analyzing patients seen on a day of collective effort in August 2017 in a tertiary hospital in the city of São Paulo. All patients had been examined by dermatologists previously and had their lesions diagnosed clinically and/or histopathologically. They were on a waiting list for a surgical procedure. The first 31 patients on the surgical procedure waiting list of that particular hospital were invited by phone. More complex cases were not invited in this collective effort since they would require the participation of other specialties, non-outpatient operating theater and longer stay in the operatory and post-operatory recovery rooms.

All cases were treated in an outpatient surgical center by two dermatologists and seven residents and interns in the dermatology program of the hospital, that took turns in three operating rooms (Figure 1). All patients signed a surgical consent form, were discharge straight after the end of the procedure and a post-operatory follow-up for removal of sutures and dermatology consultation was scheduled. All patients progressed with no post-operatory complications during follow-up.

## RESULTS

In total, 31 patients with ages from 21 to 95 years of age (mean of 63.7), being 21 (67.74%) older than 60 years were booked in; 17 (54.83%) were female and 14 (45.17%) male. These patients had 38 lesions to be treated, 21 one them being malignancies. These malignancies were 18 (47.36% of all lesions treated) basal cell carcinomas (BCC), two (5.26%) squamous cell carcinomas (SCC) and one (2.63%) malignant melanoma. Eight (21.05%) pre-cancerous lesions were also treated, all of them actinic keratosis (AK). Nine non-malignant lesions were also surgically treated: seven nevi (18.4%), one neurofibroma and one keloid (2.63% each). The lesions measured between 0.3 and

**Figure 1:** Dermatology team performing surgery in a collective effort

3cm and most of them were on photoexposed areas, with only 4 lesions on covered areas (Figures 2 and 3).

Of the procedures performed, 26 (68.42%) were complete excision: 18 with safety margins, of which 23 with primary and direct closure with interrupted stitches, one with secondary intention healing (granulation) and only one with flap. Ten curettages were performed (26.31%), seven of them with complementation of the technique with electrocautery or cryotherapy with liquid nitrogen in the bed of the wound. For the keloid, a debulking surgery was performed (2.63%), and one patient with actinic keratoses was treated solely with cryotherapy (2.63%) (Figure 4). All specimens from the patients, except for the keloid, were sent to histopathology.

The detailed data are present in table 1.

## DISCUSSION

The epidemiological profile of the patients seen identified mostly elderly, with a slight predominance of females. Upon verification that most of the lesions treated were neoplastic (63.15%) we concluded that patients waiting for surgical procedures cannot wait for a long time for treatment, since the progression of these lesions is unfavorable over the months. Many times, a lesion treated not too long after the diagnosis with a minor procedure can progress in an unfavorable fashion, and later require a procedure that not only leads to disfiguration, but also evolves with metastasis.

After the histologic reports, we observed a diagnostic discrepancy in five lesions that were treated with curettage: two that were considered AKs were actually SCCs, and one considered to be SCC turned out to be an AK. The chosen procedure for these cases was curettage in view of the patients' age and comorbidities, that hindered other approaches, considering that


**Figure 2:** Some of the lesions treated: **A, B, C:** basal cell carcinomas excised with safety margins. **D:** keloid after debulking

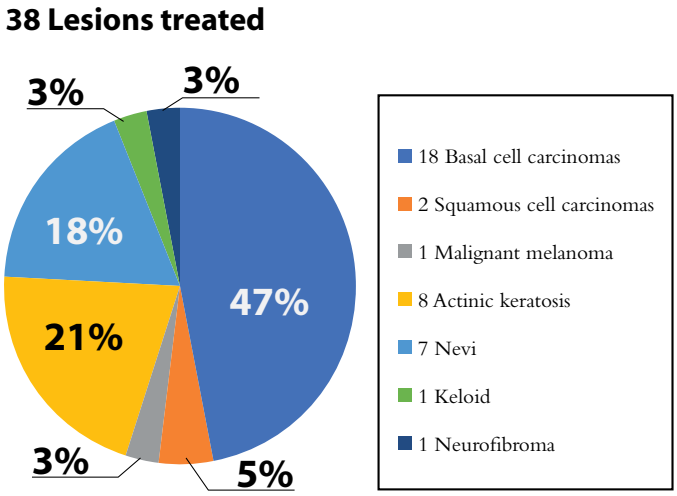


**Figure 3:** Listing of the lesions surgically treated

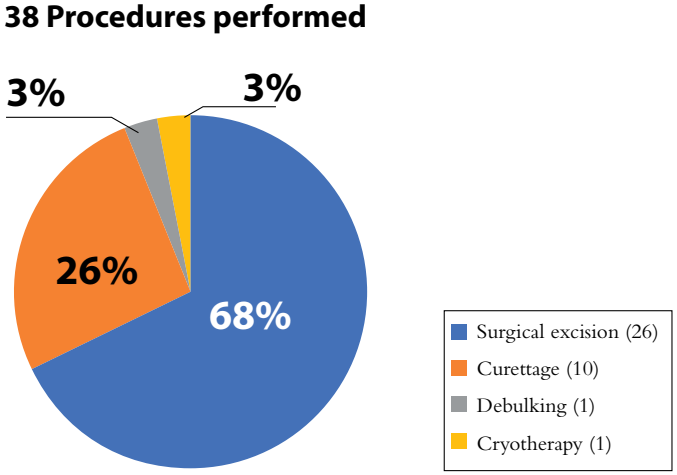


**Figure 4:** Listing of the procedures performed by the dermatologic surgery team

all will continue with outpatient follow-up that will help detect a subsequent early recurrence. Besides those lesions, there was one collagenoma for a lesion that was considered to be a nevus; since it is a benign lesion that was completely excised, there are no further considerations for this case. There was also a suspected BCC that was excised with safety margins and had a histological diagnosis of AK.

It must be taken into consideration that due to the fact that the present study was performed in a tertiary hospital, the cases with surgical indication do not come only from this service, but are also referred from other services of primary and secondary care in the area. This increased demand is not compatible with the availability of the dermatologic surgical team, leading

**Table 1: Listing of the patients seen and lesions treated**

| PATIENT | SEX | AGE | DIAGNOSIS | AREA | SIZE | PROPOSITION | HISTOPATHOLOGIC |
|---|---|---|---|---|---|---|---|
| 1 | F | 71 | BCC | L Pre-auricular L NLF | 0.4cm | Excision with margins, interrupted stitches | BCC |
| 2 | F | 82 | BCC | R Infraorbital | 0.5cm | Excision with margins, island flap repair | BCC |
| 3 | F | 77 | BCC | L lateral cervical | 0.8cm | Excision with margins, interrupted stitches | BCC |
| 4 | M | 48 | BCC | R malar | 1cm | Excision with margins, interrupted stitches | BCC |
| 5 | F | 49 | BCC | L medial canthus | 2cm | Excision with margins, interrupted stitches | BCC |
| 6 | M | 66 | BCC | L parietal | 0.7cm | Excision with margins, granulation | BCC |
| 7 | F | 47 | BCC | R mid dorsum | 0.5cm | Excision with margins, interrupted stitches | BCC |
| 8 | M | 50 | Melanoma | L lateral dorsum | 1.3cm | Excision with margins, interrupted stitches | Melanoma |
| 9 | M | 56 | BCC | R malar | 0.6cm | Excision with margins, interrupted stitches | BCC |
| 10 | F | 76 | BCC | L clavicular Postauricular Abdomen | 3cm | Excision with margins, interrupted stitches | BCC |
| 11 | F | 62 | BCC | R upper chest L nose | 3cm | Excision with margins, interrupted stitches | BCC |
| 12 | M | 46 | Keloid | Upper lip | 2cm | Debulking | - |
| 13 | F | 21 | Nevus | L face and arm | 0.5cm | Excision without margins, interrupted stitches | Nevus |
| 14 | F | 71 | BCC | L temporal | 0.4cm | Excision with margins, interrupted stitches | BCC |
| 15 | M | 74 | BCC | R arm | 0.5cm | Excision with margins, interrupted stitches | BCC |
| 16 | F | 66 | BCC | R Pre-auricular | 0.7cm | Excision with margins, interrupted stitches | BCC |
| 17 | M | 89 | AK | Chest | 0.4cm | Curettage + Cryotherapy | SCC |
| 18 | M | 67 | SCC | R postauricular | 0.8cm | Curettage + Electrocautery | AK |
| 19 | M | 71 | BCC | R temporal | 1.5cm | Curettage + Electrocautery | BCC |
| 20 | F | 66 | AK | L nasal ala | 0.9cm | Curettage + Electrocautery | AK |
| 21 | F | 43 | Nevus | R and L Pre-tibial | 0.4cm | Excision without margins, interrupted stitches | Nevus |
| 22 | M | 50 | Neurofibroma | R dorsum hand | 2cm | Excision without margins, interrupted stitches | Neurofibroma |
| 23 | M | 61 | AK | L shoulder | 0.6cm | Curettage + Electrocautery | AK |
| 24 | F | 87 | BCC | R temporal | 0.3cm | Curettage | BCC |
| 25 | F | 92 | QA | L temporal | 0.9cm | Curettage | BCC |
| 26 | F | 60 | Nevus | Chest | 0.4cm | Excision without margins, interrupted stitches | Nevus |
| 27 | M | 67 | BCC | Ombro E | 0.4cm | Excision with margins, interrupted stitches | AK |
| 28 | M | 72 | BCC | Temporal E | 0.5cm | Excision with margins, interrupted stitches | BCC |
| 29 | M | 58 | AK | Temporal D | 0.4cm | Cryotherapy | |
| 30 | F | 36 | Nevus | Tórax anterior | 0.4cm | Excision without margins, interrupted stitches | |

F: female, M: male, BCC: basal cell carcinoma, AK: actinic keratosis, SCC: squamous cell carcinoma, NLF: nasolabial fold

to a current waiting list of 165 patients that wait for at least three months for a surgical procedure. With the fact that more than ¾ of all lesions treated were malignant or pre-cancerous, it becomes clear the importance of the role of the dermatologist in cutaneous oncology, area of sanitary dermatology that also comprises occupational dermatoses, Hansen disease and sexually transmitted infections.

Some actions have been developed to reduce the waiting list for dermatological consultations in public health, such as teledermatology, that combines communication and computing technologies to dermatological practices in order to reduce the need of face-to-face encounters with the patient, offering an effective health planning.[5,6] Surgical approach of patients, however, cannot be done through this route, and the dermatologist must be physically present. Hiring more dermatologists to incorporate the clinical body of the public sector is essential for the resolution of this issue, besides providing a physical infrastructure, paramedics and adequate instruments for the procedures. In the absence of this, which is costlier for the State, collective efforts are a way of reducing the waiting list for dermatological procedures.

The fact that all procedures are performed in an outpatient setting, under local anesthesia, demonstrates that there is no need to use central surgical theaters to perform most of the dermatological surgeries, reducing considerably the institution's costs and expediting the surgical bookings for the service.[3]

## CONCLUSIONS

This study becomes relevant because it identifies the cases of patients that await dermatological assistance in the public system in the city of São Paulo. With this, public health strategies for dermatology can be organized, besides highlighting the important role of the dermatologist in public health, diagnosing and treating malignant and pre-malignant lesions.

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Study conception and planning, Actual participation in guiding the research, Intelectual participation in propaedeutic and/or therapeutic of the cases studied. Approval of the final version of the manuscript.

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# Photoprotectors profile in Brazilian sunscreens

## *Perfil dos filtros solares utilizados nos fotoprotetores no Brasil*

Original Articles

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### ABSTRACT

**Introduction**: Photoprotectors are the active ingredients of sunscreens with the capability of protecting the skin against UV radiation. An increasing number of such photoprotection ingredients have been launched in the marketplace, causing sunscreens' formulas to become increasingly varied.

**Objective**: To list the main active photoprotection ingredients contained in formulations commercially available in Brazil, as well as to document the presence of other ingredients contained in sunscreens.

**Methods**: The authors inspected four drugstores in the city of Rio de Janeiro, Brazil, and analyzed the formulas of the SPF 30 sunscreens available. The active photoprotector substances found in all formulations were listed and the percentage of each of them was compared to those contained in all sunscreens evaluated. The presence of plant extracts and antioxidants was also documented.

**Results**: Thirty commercially available SPF 30 sunscreens were found in different drugstores, having their formulas analyzed. Within this sample, there were 17 different active photoprotection principles, of which titanium dioxide was the most frequently found, followed by bis-ethylhexyloxyphenol methoxyphenyl triazine.

**Conclusion**: The present study lists the profiles of photoprotection active principles found in the main sunscreens on sale in Brazil and provides data for further evaluation of changes in these profiles over time, as new sunscreens are launched in the marketplace.


**Keywords**: photoprotectors; sunscreens; photoprotection; ultraviolet rays


### *RESUMO*

***Introdução:*** *Filtros solares são os ingredientes ativos dos protetores solares capazes de promover proteção contra as radiações ultravioleta. O mercado tem oferecido um número crescente desses ingredientes, tornando a fórmula dos fotoprotetores cada vez mais variada.*

***Objetivo:*** *Listar os principais filtros solares que fazem parte das formulações à venda no Brasil, assim como registrar a presença de outros ingredientes dos protetores solares.*

***Métodos:*** *Os Authors visitaram quatro farmácias da cidade do Rio de Janeiro, (RJ), Brasil, e analisaram as fórmulas dos protetores solares com fator de proteção solar 30 encontrados. Os filtros solares encontrados nas formulações foram listados, e o percentual de cada um deles foi avaliado em relação ao total de todos os filtros presentes. A presença de extratos vegetais e antioxidantes também foi anotada.*

***Resultados:*** *Foram encontrados 30 fotoprotetores à venda com FPS 30 nos diferentes estabelecimentos, e todos foram analisados em sua composição. Neles havia 17 filtros solares, sendo o mais frequente nas formulações o dióxido de titânio, seguido pelo bis-ethylhexyloxyphenol methoxyphenol triazine.*

***Conclusão:*** *Este estudo apresenta o perfil dos filtros solares utilizados nos principais fotoprotetores à venda no Brasil e fornece dados para posterior avaliação de mudanças desse perfil ao longo dos anos, à medida que novos filtros solares sejam introduzidos no mercado.*


***Palavras-chave:*** *filtros solares; fotoprotetores; fotoproteção; raios ultravioleta*


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## INTRODUCTION

Sunscreens are molecules or molecular complexes that promote photoprotection against types A and B ultraviolet radiation, and visible light, according to their spectrums of action.

Sunscreens are products whose formulas are based on the combination of photoprotecting agents – deemed as the active photoprotecting ingredients – with vehicles such as hydroalcoholic lotions, oils, aerosols, creams, emulsions and gels. This combination yields several compounds, with different action spectra against solar radiation, texture and photo-stability, among other aspects. [1,2]

The habit of using sunscreens has been increasing in the last few decades. A seven-fold increase in the sales of these products between 1992 and 2002 corroborates this fact. [1] People are increasingly becoming aware of the importance of photoprotection in the prevention of photoaging and pre-malignant and malignant photoinduced lesions. [2]

As a result, manufacturers have been investing in the development of new formulations, offering a growing number of new sunscreens. [1]

The constant emergence of new photoprotecting agents implies that the sunscreens' formulations have been changing over the years. While stronger and more photo-stable photoprotecting agents are introduced in the formulations, others used in the past are suppressed, for instance, for being less effective, for containing allergenic potential or providing poor aesthetic effect regarding the formulation. In addition, ingredients deemed as antioxidants have often been included in current formulations of sunscreens.

In light of these facts and the necessity to gain knowledge about the profiles of the photoprotecting agents used in the formulations of some of the main sunscreens on sale in the Brazilian market, the present study is aimed at listing the active photoprotecting ingredients present in the major formulations that are commercially available. This knowledge can provide data for later analysis and changes in those profiles.

## METHODS

The authors surveyed four drugstores – two large and two small – in the city of Rio de Janeiro, Brazil.

All products identified as SPF 30 (Sun Protection Factor 30) sunscreens had their formulations evaluated based on the information contained in the labels provided by the manufacturers.

Based on data related to the ingredients contained in the package, the photoprotecting agents listed in the formulations were segregated from the remaining substances contained in each of the analyzed sunscreens. Finally, the percentage of each photoprotective agent was calculated for all products.

Also, the presence of antioxidants and vegetable extracts in the formulations was evaluated.

Lips sunscreens or moisturizers containing SPF were not included in the assessments.

## RESULTS

A total of 30 different SPF 30 sunscreens were found, which contained 17 different types of photoprotecting agents in their formulations.

The photoprotecting agents found in the formulations, as well as their percentage, are depicted in Figure 1.

The most commonly found photoprotecting agent in the sunscreens' formulations was the titanium dioxide (present in 70% of the products analyzed), followed by the bis-ethylhexyloxyphenol methoxyphenyl triazine (anizotriazine), which was present in 66.6% of the products.

Disodium phenyl dibenzimidazole tetrasulfonate and isoamyl p-methoxycinnamate were the less frequently found active photoprotecting ingredients (3.3%).

The number of the active photoprotecting ingredients in the researched sunscreens ranged from 2 to 9, with an average of 6.

The concentration of the photoprotecting agents could not be evaluated, given that this data is not provided on the products' labels.

## DISCUSSION

The choice for analyzing products with SPF 30 was based on the recommendations of the American Academy of Dermatology, which compiled studies showing that the use of sunscreens with SPF below 30 are ineffective, since the amount of the product applied to the skin by the population in general is smaller than that recommended in tests measuring the sunscreens' FPS. [3] In addition, the assessment of products that have the same FPS makes the comparisons and the study more homogeneous and reliable.

Of the 17 sunscreens found, 16 were approved for use by ANVISA[4] and 10 by the FDA[3] (Table 1). [3,4,5,6,7,8,9] The disodium phenyl dibenzimidazole tetrasulfonate, present in 3.3% of the analyzed sunscreens, was the only photoprotecting agent without ANVISA approval.

The authors did not find similar research reports in Brazil, which precludes static and time series comparisons of the sunscreens' profiles. However, it was possible to compare the data found with the data related to the formulation of sunscreens marketed in the European Union (EU), where some differences could be observed.

In European study performed by Kerr,[10] in 2011, 19 photoprotecting agents were found in the sunscreens' formulations. Of these, 18 are approved by AVISA and 9 were approved by the FDA. The sample of sunscreens analyzed in this study was larger and not limited to products with SPF 30. The average SPF of all sunscreens analyzed in this study was 30. The average number photoprotecting agents found in the formulations was 5 (min =1, max = 8).

The photoprotecting agent found most frequently in the EU sunscreens was the butyl methoxydibenzoylmethane (96.4%). This finding corroborates the necessity and effort of the European pharmaceutical companies to provide adequate protection against UVA, as well as adequate efficacy against UVB.[10] According to the findings of the present study, (Figure 1) it is the fourth most frequently used photoprotecting agent in SPF 30 sunscreens in Brazil, along with ethylhexyl methoxycinnamate

**Table 1: INCI, USAN and trademark nomenclature, action spectra, marketing approval according to ANVISA and FDA and maximum percentage concentrationfor use of the photoprotecting agents found [3-9]**

| Nomenclature Inci | Nomenclature Usan | Trade mark® | Manufacturer | UVA action | UVB action | ANVISA | FDA | Maximum allowed concentration (%) |
|---|---|---|---|---|---|---|---|---|
| Titanium dioxide | | Neo Heliopan E 1000 | Symrise | + | + | + | + | 25 |
| Bis-Ethylhexyloxyphenyl methoxyphenol triazine | Anisotriazine | Tinosorb S | BASF | + | + | + | - | 10 |
| Octocrylene | | Eusolex OCR | Merk | + | + | + | + | 10 |
| | | Neo Heliopan 303 | Symrise | | | | | |
| | | Uvinul MC 80 | BASF | | | | | |
| Ethylhexyl (ou Octyl) methoxycinnamate | Octinoxate | Parsol MCX | DSM | - | + | + | + | 10 |
| | | Eusolex 232 | Merk | | | | | |
| | | Uvinul MC 80 | BASF | | | | | |
| Butyl methoxydibenzoylmethane | Avobenzone | Eusolex 9020 | Merk | + | - | + | + | 5 |
| | | Neo Heliopan 357 | Symrise | | | | | |
| | | Parsol 1789 | DSM | | | | | |
| | | Uvinul A Plus | BASF | | | | | |
| Ethylhexyl triazone | Octyl triazone | Uvinul T150 | BASF | - | + | + | - | 5 |
| Methylene bis-benzotriazolyl tetramethylbutylphenol | Bisoctrizola | Tinosorb M | BASF | + | + | + | - | 10 |
| Ethylhexyl salicylate | Octisalate | Eusolex OS | Merk | - | + | + | + | 5 |
| | | Neo Heliopan OS | Symrise | | | | | |
| Homosalate | | Eusolex 232 | Merk | - | + | + | + | 15 |
| | | Neo Heliopan 357 | Symrise | | | | | |
| Benzoaphenone-3 | Oxybenzone | Eusolex 4360 | Merk | + | + | + | + | 10 |
| | | Neo Heliopan BB | Symrise | | | | | |
| Phenylbenzimidazole sulfonic acid | Ensulizole | Eusolex 232 | Merk | - | + | + | + | 8 |
| | | Neo Heliopan Hydro | Symrise | | | | | |
| Terephthalylidene dicamphor sulfonic acid | Ecamsule | Meroxyl SX | L`Óreal | + | + | + | + | 3 |
| Diethylamino hydroxybenzoyl hexyl benzoate | | Uvinul A Plus | BASF | + | - | + | - | 10 |
| Drometrizole trisiloxane | | Meroxyl XL | L`Óreal | + | + | + | - | 15 |
| Zinc oxide | | Zinc Oxide Neutral | Symrise | + | + | + | + | 25 |
| Disodium phenyl dibenzimidazole tetrasulfonate | Bisdisulizole disodium | Neo Heliopan AP | Symrise | + | - | - | - | 10 |
| Isoamyl p-methoxycinnamate | Amiloxate | Neo Helipan E 1000 | Symrise | - | + | + | - | 10 |

(53.3%). Nevertheless, based on the analysis performed in the present study, it was possible to conclude that the Brazilian pharmaceutical companies also demonstrate an interest in providing effective protection against UVA and UVB radiations. Bis-ethylhexyloxyphenol methoxyphenyl triazine, and octocrylene, two combined photoprotecting agents (with action against both radiations spectra), constitute the first and second organic photoprotecting agents most frequently found in the formulations (66.6% and 56.6%, respectively).

There has been an increase in the percentage in the use of these two photoprotecting active ingredients in sunscreens in the EU.[10]

Titanium dioxide, the most frequently used photoprotecting agent in the analyzed formulations in Brazil (70%), was present in only 49% of Europeans sunscreens. Its low allergenic potential in addition to the action spectrum against UVA, UVB and visible light can justify the high percentage of use of this photoprotecting agent in sunscreens.[2] While zinc oxide, another example of inorganic photoprotecting agent, was present in 6.6% of the Brazilian formulations, it was absent in the European formulas, since its use is not allowed in the EU.[10]

Allergic reactions, contact and photocontact dermatitis triggered by the use of photoprotecting agents are rare. Contact photoallergies are more related to benzophenone-3 (oxybenzone).[2] Despite this possible adverse effect, this active photoprotecting ingredient was found in 23.3% of the sunscreen formulations marketed in Brazil. This percentage is smaller in the European Union (15.1%).[10]

Current reports of octocrylene as an emerging photoallergenic ingredient suggest a possible increase of photoallergy cases related to this photoprotecting agent.[10] While in 2005 it was the fourth most used photoprotecting active principle in European sunscreens, its presence increased by 23% in 2010, meaning it is currently the second most frequently used active photoprotecting agent in European formulations.[10] This increase may be responsible for an increase in the number of cases of photoallergy in the EU. In Brazil, it is the third most commonly used photoprotecting agent in the sunscreens analyzed (present in 56.6% of them), nevertheless it was not possible to evaluate the progression of its presence in the formulations due to a lack of comparative data. Notwithstanding, it is important to warn dermatologists that this photoprotecting agent is emerging as a potential cause of photoallergic reactions related to sunscreens and, in case this correlation becomes evident, its concentration in subsequent formulations will tend to decrease. A similar situation occurred with the photoprotecting agent PABA. It was the most frequently used photoprotecting active principle in the 70s' sunscreens formulations. Nonetheless, PABA, amyl dimethyl PABA and benzophenone-10 were proven to be allergenic, with sales being interrupted.[2]

Another interesting finding of the present study was the presence of plant extracts in a significant number of sunscreens.

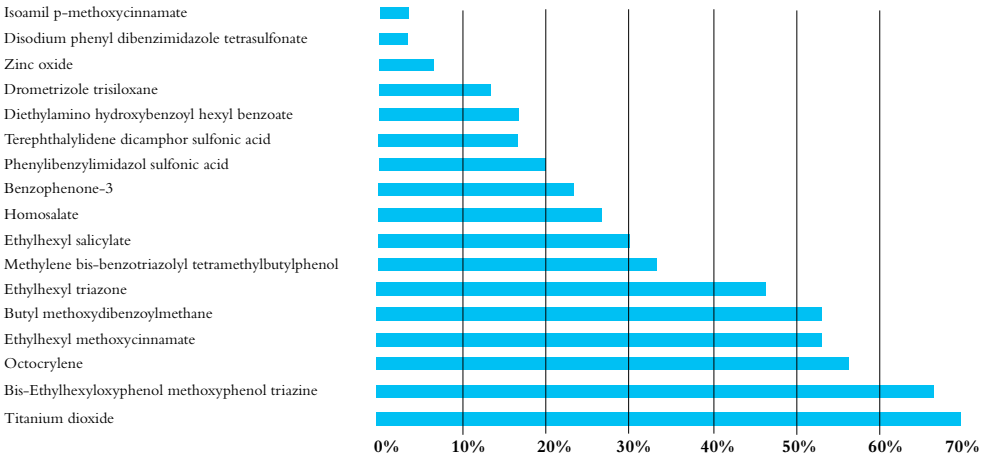


**Figure 1:** Profile of photoprotecting molecules found in the commercial solar formulations analyzed

Among them, *Camellia sinensis* (green tea extract) was the most frequently present in the formulations. It has a powerful antioxidant and photoprotecting effect against photoaging and photoimunossupression.[11,12,13] *Polipodium leucotomos* was found in only one of the studied sunscreens. Scientific evidence suggests its topical or systemic use has a photoprotective effect. [13]

Others plant extracts found in the studied sunscreens were *Aloe barbadenses* (aloe vera), daucos carota oil (carrot oil), chamomile, *Glyciriizia inflata, Calendula officinales* (calendula), *Zinger oficinalles, Citrus vulgaris, Cucurbita pepo* seed oil (pumpkin seed oil), *Prunus Cerasus* (cherry), *Malphiguia pruncifolia* fruit extract and *Cassia alata* leaf extract. These plant extracts act as protectors against free radicals generated by UV radiation, which participate in the photoaging process and carcinogenesis. Another component with antioxidant effect found in 66% of the studied products was tocopherol (vitamin E).[14]

As with titanium dioxide and zinc oxide, talc is considered an inorganic photoprotecting agent,[15] being found in only one of the 30 analyzed sunscreens.

## CONCLUSION

The present study allows to draw a profile of the photoprotecting active principles found in the composition of the main SPF 30 sunscreens marketed in Brazil, providing a foundation for further analysis of the progression of the formulations as new active photoprotecting ingredients are introduced and new sunscreen formulations are created and marketed. ●

**DECLARATION OF PARTICIPATION:**

**Mariana Marteleto Godinho:**
Data collection at pharmacies, data analysis and drafting of the manuscript

**Bryan Hudson Hossy:**
Data analysis, preparation of the table and figure, drafting of the manuscript

**João Paulo Niemeyer-Corbellini:**
Data analysis, drafting and final review of the manuscript

**Márcia Ramos-e-Silva:**
Drafting and final review of the manuscript

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# Skin flap alternatives for dermatological lesions on the leg

## *Alternativas de retalhos cutâneos para lesões dermatológicas na perna*

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**ABSTRACT**

The use of skin flaps for covering lesions is a better option than skin grafts, due to the diversity of the receptor area after the tumor's resection and the greater degree of safety. For better results, the lesion's location and extent, as well as the safety of the vascularization, should also be taken into account. Three resections were performed, with different coverage techniques. The patients had excellent development, without necrosis or dehiscence.
Keywords: reconstructive surgical procedures; surgical flaps; free tissue flaps; plastic surgery; skin diseases

**RESUMO**

*A utilização de retalhos de pele para a cobertura de lesões é melhor opção do que o enxerto de pele, considerando-se a heterogeneidade do leito receptor após a ressecção do tumor e a maior segurança oferecida. Para melhor resultado devem ser levados em consideração também o local e a extensão da lesão, além da segurança da vascularização. Foram realizadas três ressecções com diferentes técnicas de cobertura. Os pacientes apresentaram excelente evolução, sem necroses ou deiscências.*
***Palavras-chave:*** *procedimentos cirúrgicos reconstrutivos; retalhos cirúrgicos; retalhos de tecido biológico; cirurgia plástica; dermatopatias*

## INTRODUCTION

Leg lesions may arise from diverse etiologies, from traumatic to infectious, and even neoplastic. They may present as superficial or deep, with muscle and/or bone involvement, where severe infections may exist. Depending on the etiology, the evolution, the type of lesion and the anatomical characteristics of the leg, different reconstructions are proposed, with different structures involved, such as muscles, fascia, septum and skin, or a combination.[1] The site and size of the lesion are also important factors when considering the reconstruction. Due to the superficial anatomical vascular characteristic of the leg, where a great part of blood distribution occurs through musculocutaneous perforating vessels originating from deep vessels, the cutaneous flaps used for reconstruction in this region are based on the areas vascularized by this type of vessels.[2]

The incidence of skin cancer has been increasing over the last decades. The chances of developing skin cancer during a person's life is multifactorial, for instance due to sun exposure, skin type and phenotype, and family history.[3] Skin cancers have a higher incidence in areas that are more exposed to the sun, and



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are represented by the basal cell carcinoma, squamous cell carcinoma and melanoma. Basal cell carcinomas account for 65% of all epithelial neoplasias, the face being the most affected area. In turn, the squamous cell carcinoma represents 15% of all epithelial neoplasias, with 64% of them also present in the face.[4,5] Melanomas have an incidence of 3% to 4%, accounting for the smallest among skin tumors. However, they present the highest mortality rate among all skin tumors.[6]

## OBJECTIVE

The objective of this article was to present alternatives to skin flaps for cutaneous lesions in lower limbs.

## METHODOLOGY

Three tumors were resected in three patients, using different coverage techniques. The options for cutaneous leg flaps are: circular rotation flap (small rotating arc), circular rotation flap (large rotating arc) and rectangular rotation flap. These options will be detailed below. In the first case, the skin tumor was located in the medial region of the lower third of the right leg, presenting 2.5cm in diameter, with clinical aspect compatible with basal cell carcinoma. In this patient the first option was chosen: circular rotation flap (small rotation arc). The tumor was marked [taking into consideration safety margins, and the planned skin flap to be performed (Figure 1). After the circular removal of the tumor, the rotation flap was designed, starting circularly on the lateral side of the tumor's perimeter, and extending cranially in the form of a hook, as a flap diameter similar to that of the tumor (Figure 2). A musculocutaneous perforating vessel (Figure 3) made it possible to mobilize the flap, even with a small arc of rotation. The donor area was then closed (Figure 4) after adjustment and release of the surrounding tissues.

In the second case, the skin tumor was located on the lateral posterior side of the right leg, presenting a 5cm diameter and clinical aspect compatible with basal cell carcinoma. The second option was chosen for this patient: circular rotation flap (large rotation arc). The surgical marking took into consideration safety margins and the cutaneous flap to be performed (Figure 5). After the circular removal of the tumor, the rotation flap was performed (Figure 6). It started circularly at the most distal area of the tumor perimeter and was extended cranially, with a diameter greater than that of the tumor. Its vascularization was based on a musculocutaneous artery. Due to the size and shape of the flap, it was easily and safely mobilized toward the receiving area. The primary closure of the donor area was performed after adjustments and release of the surrounding tissues (Figure 7).

In the third case, the tumor was located in the mid-third of the right leg, on the posterior face, presenting 3cm in diameter, with clinical aspect compatible with basal cell carcinoma. In this patient the third flap option was chosen: the rectangular rotation flap. The tumor was marked taking into consideration safety margins, and the cutaneous flap to be performed (Figure 8). After circular removal of the tumor, the rectangular flap was designed, starting rectangularly at the distal extremity of the tumor perimeter, and extending 4cm laterally and 5cm cranially, with measurements larger than those of the tumor. Its vascularization was based on a musculocutaneous artery (Figure 9). Due to the shape of the flap, it was mobilized easily and safely towards the recipient area. The primary closure of the donor area was performed after adjustments and release of the surrounding tissues (Figure 10).

## DISCUSSION

The option of using the skin flap to cover the recipient area overlaps the use of the skin graft, since the latter is a thin and often vulnerable cover, especially when localized on

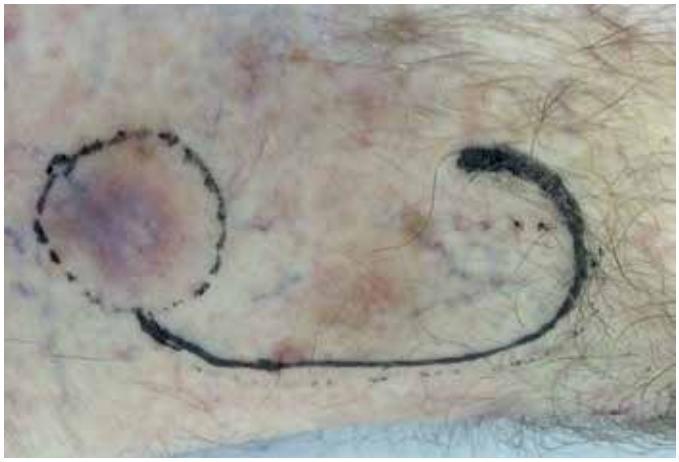

**Figure 1:** Planning of the skin flap rotation of the skin tumor in the medial lateral area of tibia, beginning at the center of the lesion

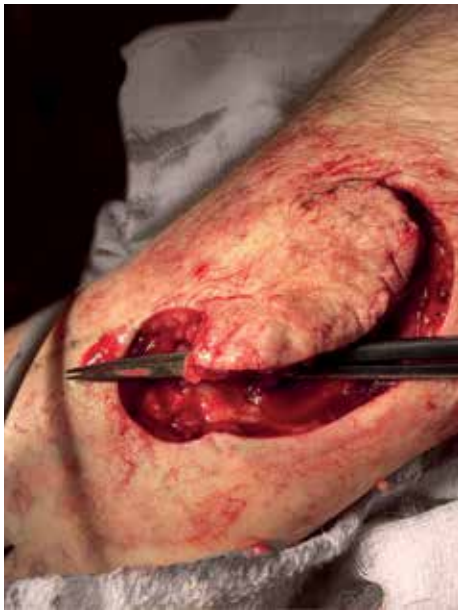

**Figure 2:** Location and dissection of perforating vessel

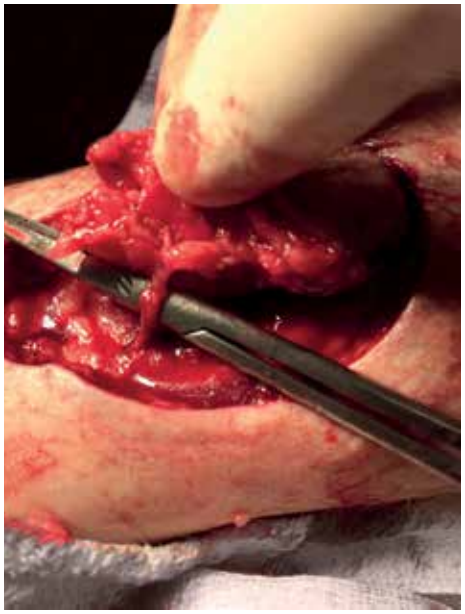

**Figure 3:** Isolation of the perforating vessel

**Figure 5:** Planning of the rotation flap with the large rotational arc (beginning at the most distal end of the skin tumor perimeter on the right calf

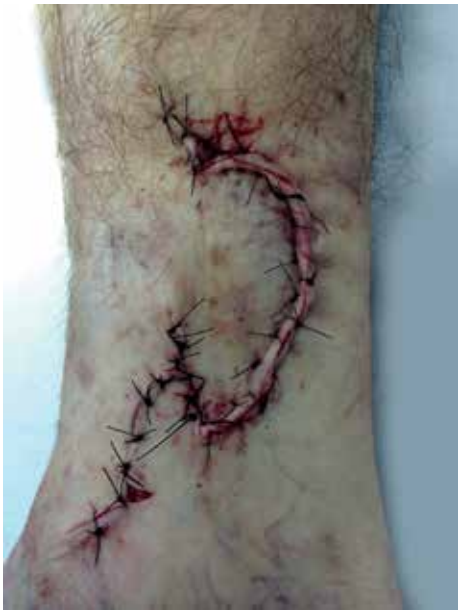

**Figure 4:** Final appearance after flap rotation with leftover skin adjustments

**Figure 6:** Resection of the tumor and confection of the skin flap, and elevation of the flap with preservation of the perforating vessel

the bone tissue. In addition, for good graft integration, a homogeneous receptor area is needed, different from that found after the resection of tumors.[7] The flap transfer should take into consideration the location of the lesion: whether on the anterior or posterior side of the leg. The amount of skin on the anterior face, that is, on the pretibial area, is smaller than that on the calf, which means increased difficulty in rotating the flap and/or closing the donor area. The inclusion of the regional perforating vessel in the flap, regardless of its design, means a safe vascularization.[8] Its inclusion, however, must be planned prior to surgery, either by anatomical knowledge or by locating it through a vascular Doppler test.[2] The latter is more frequently used when the flap is mobilized in a helical form.[9] The planning of a flap at the lower extremity without the location of the perforator does not impair its use, but limits its extension and the arc of rotation, which becomes more vulnerable to tension and eventual necrosis. Cutaneous flaps used in superficial reconstructions of the lower limb may vary in size depending on the size of the lesion. Sometimes, depending on the location of the lesion, the amount of skin may not suffice to cover the recipient area and to close

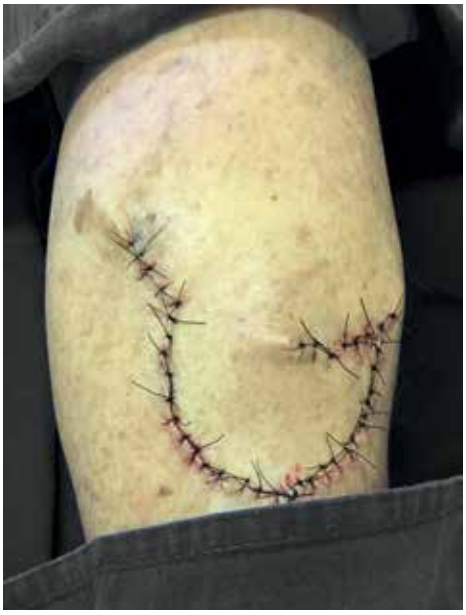

**Figure 7:** Final appearance after flap rotation with leftover skin adjustments

**Figure 9:** Tumor resection and flap elevation, and dissection and isolation of perforating vessel

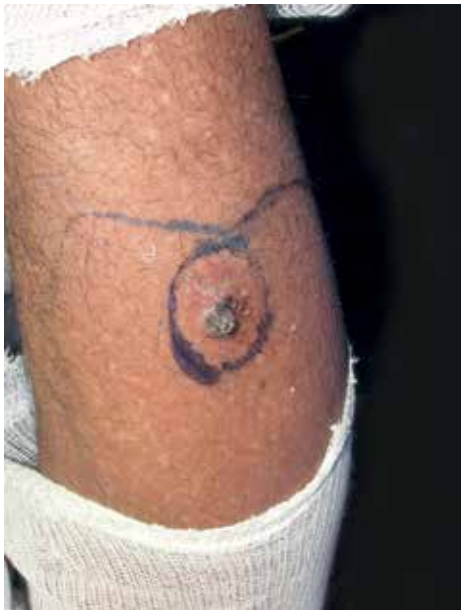

**Figure 8:** Skin tumor on the calf and planning of the rectangular rotation flap design (beginning at the most distal end of the tumor perimeter)

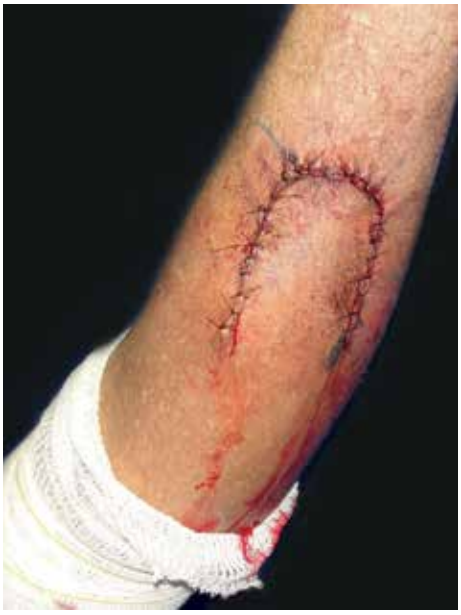

**Figure 10:** Final appearance after rotation of the rectangular flap with leftover skin adjustments

the donor area. Thus, skin grafts can be used in the donor areas. In regard to the shape of the flap, it should be chosen according to the location of the reconstruction.[2] The circular flaps have the advantage of being able to be rotated bilaterally, if necessary. The rotation of the skin flap that is based distally, however, leads to an increased risk of necrosis, especially in the most distal area of the leg.

## CONCLUSION

The options presented for skin flaps for the leg are safe and easy to perform, being that circular flaps may be added with additional opposing flaps when necessary. ●

**DECLARATION OF PARTICIPATION:**

**Douglas Haddad Filho:**
Conception and planning of the study. Effective participation in the orientation of the research. Elaboration and final revision of the manuscript

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Drafting and revision of the manuscript

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Diagnostic imaging

# High-frequency ultrasonography (22MHz) for identification and removal of a rayfish stinger

## *Ultrassonografia de alta frequência (22MHz) na identificação e remoção de ferrão de arraia*

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ABSTRACT

The presence of foreign bodies located on the skin, their size, constitution and precise location are often not perceptible on dermatological clinical examination. Despite their benign nature, the presence of foreign bodies in the skin is associated to high morbidity. High frequency ultrasonography has been widely used in different areas of Dermatology. Technological development and the introduction of devices offering high frequency and high resolution makes this method useful in identifying and guiding the removal of foreign bodies located in the skin. The authors describe a case where high frequency ultrasonography was used to identify and remove a rayfish stinger.

**Keywords**: ultrasound; ultrassonography; foreign body; surgery

*RESUMO*

*A presença de corpos estranhos localizados na pele, sua dimensão, constituição e exata localização muitas vezes não são perceptíveis ao exame clínico dermatológico. Apesar de seu caráter benigno, a existência de corpos estranhos à pele provocam alta morbidade. A ultrassonografia de alta frequência tem sido amplamente utilizada nas diferentes áreas da Dermatologia. O avanço tecnológico com a introdução de aparelhos de alta frequência e resolução torna esse método útil na identificação e orientação da remoção de corpos estranhos localizados na pele. Apresentamos caso em que a ultrassonografia de alta frequência foi utilizada na identificação e retirada de um ferrão de arraia.*

***Palavras-chave:*** *ultrassom; ultrassonografia; corpo estranho; cirurgia*

## INTRODUCTION

Different methods of imaging based diagnosis, such as radiography, computerized tomography (CT), magnetic resonance imaging (MRI) and ultrasound are used to detect the presence of foreign bodies (FB) in the soft parts of the body.[1] However, the FB's constitution, size and depth at which it is located can significantly influence the accuracy of the imaging method. In this way, it is crucial to choose the proper imaging technique for identify a FB.

Brazil has an extensive coastline, which is home to a diverse wildlife. Bathing in the sea is a common habit, entailing that people are more susceptible to exposure to the aquatic fauna. The authors of the present article describe a case in which high frequency ultrasound (HFUS) was used to diagnose a persistent skin disorder after trauma caused by a stingray, detecting the presence of a stinger, determining its exact location and shape, and serving as a guide for a surgical removal procedure.

## CASE REPORT

A 72 year-old Brazilian male patient, had swelling and complained of pain in the third left toe developed two months before, after having been stung by a stingray on the dorsum of the left foot, and treated with topi-

cal antiseptic (Figure 1). The patient did not report anything relevant regarding the medical or family history. The physical examination revealed edema with limitation of motion of the interphalangeal joint of the third left toe and pain on palpation. No alteration in the integrity of the skin of the toe in question could be observed (Figure 2).

Ultrasonography was performed with a linear transducer using a 22MHz frequency at the location of the scar on the dorsum of the foot and of the third left toe, showing no considerable alterations.

The examination carried out in the plantar region of the toe in question suggested the presence of an hyperechoic structure with elongated triangular shape, measuring 1.3 cm in its greater length, with one of the sides showing a linear profile and the other a serrated profile (Figure 3).

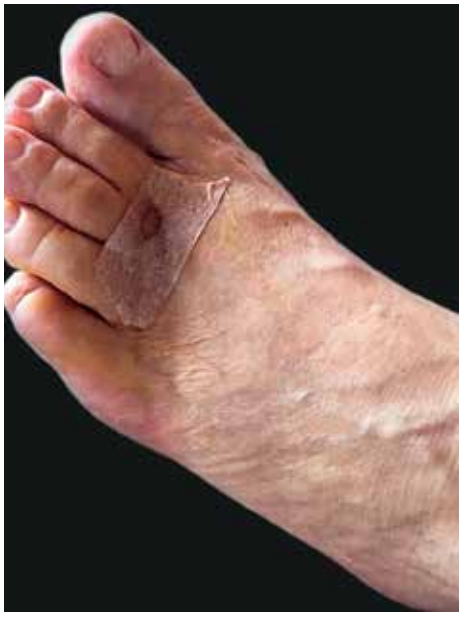

**Figure 1:** Dorsum of the left foot after trauma caused by stingray

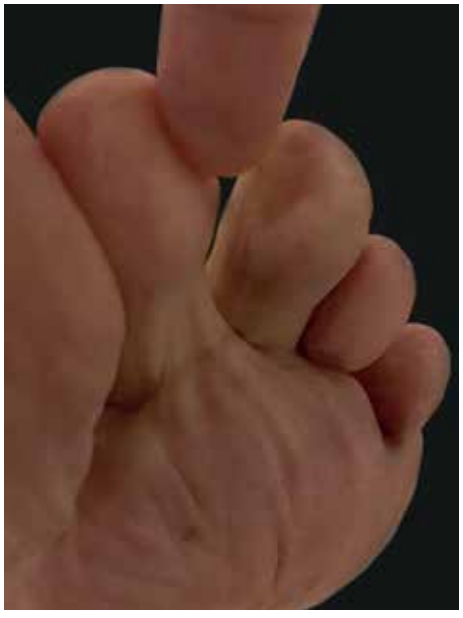

**Figure 2:** Third left toe without loss of continuity solution

The patient underwent the removal of the FB (Figure 4) through a small incision made in the plantar region with guidance of the ultrasound examination, under local anesthesia. Systemic antibiotic was administered (Cefadroxil, 500mg, 12/12 hours, for 7 days). The post-operative coursed without events.

## DISCUSSION

Foreign body is any objetct originated outside the body. When located in the soft parts of the body, it might have been originated by trauma or piercing. Foreign bodies can be inert or irritating to the body. If irritant, they are capable of promoting inflammation, secondary infection, abscess formation in addition to pain and discomfort. Therefore, identifying it is crucial.[2]

Symptoms related to accidents with stingrays can have traumatic origin – resulting from the penetration of the stinger, which has a serrated shape – or toxic origin – secondary to the poison produced by glandular structures on its tail.[3] In the present case, the patient did not have systemic manifestations

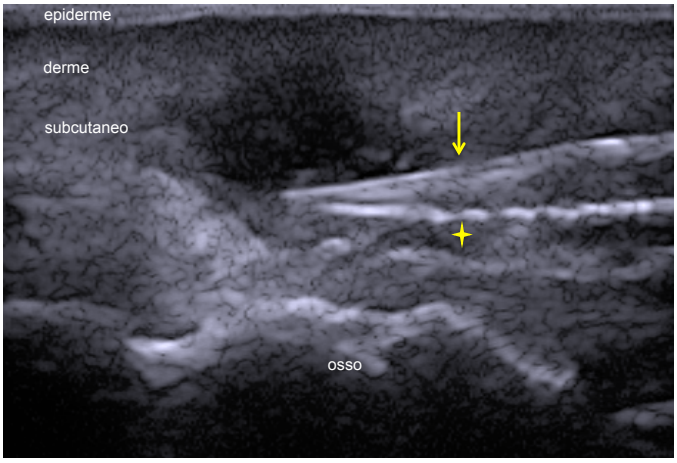


**Figure 3:** 22MHz HFUS. Hyperechogenic image with triangular shape, one side with linear structure **A**, and the other with serrated structure **B**

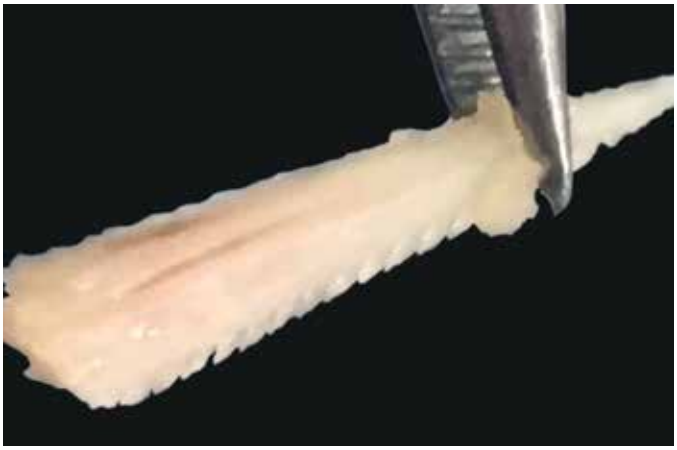

**Figure 4:** Stingray's stinger. Serrated aspect in detail seen using 22 MHz HFUS

suggestive of poisoning and only realized something was wrong 2 months after the accident with the stinger. Therefore, there was not certainty about the presence of a FB in the foot, which is the most commonly affected site by this type of accident, according to the literature. The penetration of the stinger occurred in the dorsum of the left foot, and the symptoms were felt in the ventral face of the third left toe.

Different diagnostic imaging methods are used to identify the presence of FB – which, depending on their nature, can be radiopaque or radiolucent – in soft tissues. Magnetic resonance imaging appears to be the less indicated technique, since most of the FBs have materials with low signal to that kind of technology, entailing that they might be mistaken with calcifications, and scars or tendons. Moreover, metallic materials can move due to the strong magnetic field.[4] A study comparing the effectiveness of CT and ultrasonography (USG) for identifying FBs composed by different materials have shown that USG has the best accuracy with radiolucent materials and when they are located on the skin's surface. [2, 5]

Ultrasonography is a painless and non-radioactive imaging based diagnostic method which is based on the reflection of sound waves through the tissues. According to the anatomical structure, vascularization and density, the ultrasonic waves are reflected back to the transducer, which translates them into a scale of gray that can be observed on a monitor. The higher the frequency of the waves emitted by the transducer, the greater the spatial resolution and resulting visualization of structures close to it. The introduction of transducers with frequencies higher than 15 MHz gave rise to the high frequency ultrasound (HFUS). The shorter wavelength obtained with this frequency allowed better evaluation of superficial structures, meaning their use in dermatological disorders significantly increased.[6]

Devices with frequencies higher than 15MHz allow the analysis of the skin and its appendages, as they are capable of distinguishing the cutaneous layers and structures. Nevertheless, devices with frequencies higher than 20 MHz offer the best resolution for studying superficial structures.[6] In this manner, HFUS allows a better visualization of the FB located in soft parts, yielding information that is useful for their removal (e.g. as exact location, shape and composition) and providing a detailed analysis of the tissue and adjacent structures.

Ultrasonographically, most of the FBs are seen as hyperechogenic structures with a posterior acoustic shadow. Depending on the duration of its permanence in the tissue, it is possible to observe the presence of a hypoechoic area around the FB, that can possibly correspond to edema, abscess or granulation tissue.[5] Foreign bodies made of wood are initially hyperechogenic, however can lose their echogenicity over time. [4] Stones arise as hyperechogenic areas with the presence of posterior acoustic shadow, while metals and glasses are hyperechoic and present, as an artifact, reverberation. [2] Foreign bodies that are rich in calcium, as in the case described in the present article, are hyperechogenic.

Ultrasonography allows three-dimensional access (longitudinal axis X transversal axis x depth) to the FB in addition to being an examination carried out in real time, [5] enabling the acquisition of anatomical knowledge of the affected area and exact location of the FB, allowing the surgeon to precisely remove it, minimizing the damage to vital structures, such as nerves and vessels.

The sensitivity to and specificity of HFUS are limitations of the method, and just like as those of other imaging based diagnostic methods, depend on several factors, such as the FB's composition, size and location, the transducer's frequency, the image's resolution and the examiner's experience.

The authors of the present article conclude that, despite the limitations described, HFUS is a useful method in the screening of FBs located on the surface of the human body, allowing detection and acquisition of knowledge related to their composition and exact location. This analysis provides important parameters to guide the surgical approach. ●

**DECLARATION OF PARTICIPATION:**

**Elisa de Oliveira Barcaui:**
Bibliographic research and drafting of the manuscript

**Carlos Batista Barcaui:**
Bibliographic research, drafting and review of the manuscript

**Antonio Carlos Carvalho:**
Review of the manuscript

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# Cryosurgery as an adjuvant treatment in sporotrichosis: a three-case report

## *Criocirurgia como tratamento adjuvante na esporotricose: relato de três casos*

Case report

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ABSTRACT

Sporotrichosis is a disease caused by the dimorphic fungus Sporothrix spp. The number of cases has been increasing, notedly in the city of Rio de Janeiro, Brazil, where it is now considered a public health problem. The recommended treatment employs antifungals, however in case of persistence of the lesions or when there is contraindication, cryosurgery is an option, since the fungus is sensitive to extreme temperatures. The authors report 3 cases of sporotrichosis treated for longer than 6 months with itraconazole and/or potassium iodide, all yielding incomplete response and where cryosurgery was successfully used as an adjuvant treatment.

**Keywords**: sporotrichosis; opportunistic infections; cryosurgery

*RESUMO*

*A esporotricose é doença causada pelo fungo dimorfo Sporothrix spp., e o número de casos vem aumentando, principalmente na cidade do Rio de Janeiro, onde hoje é considerada um problema de saúde pública. O tratamento recomendado é com antifúngicos, mas em caso de persistência das lesões ou quando houver contraindicação, a criocirurgia é opção, pois o fungo é sensível a temperaturas extremas. São relatados três casos de esporotricose tratados com itraconazol e/ou iodeto de potássio durante mais de seis meses com resposta incompleta, nos quais a criocirurgia foi usada com sucesso como tratamento adjuvante.*

***Palavras-chave:*** *esporotricose; infecções oportunistas; criocirurgia*

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## INTRODUCTION

Sporotrichosis is a disease caused by the inoculation of the dimorphic fungus *Sporothrix spp.* on the skin, usually as a result of handling contaminated soil and vegetables. [1,2] In addition to the rural manifestation, currently it is often urban, with the transmission occurring through infected cats, which is the most important source of contamination in the Brazilian city of Rio de Janeiro. [2]

Of the clinical forms of sporotrichosis – extracutaneous, localized/fixed, and lymphocutaneous – the latter is the most frequent in humans and emerges with nodules and gums along the lymphatic vessels, progressing to ulceration in the affected body areas. [1,2] The main tests for diagnosis are the mycological (mainly culture), the histologic and molecular biology. [1]

Different drugs have been used in the treatment of sporotrichosis. The choice of the medicament depends on the clinical form, patient's morbidity, side effects and drug

interactions. The objective of the present study is to describe 3 cases of sporotrichosis, confirmed by mycological test and treated with itraconazole and / or saturated solution of potassium iodide (KI) for longer than 6 months, in which cryosurgery with liquid nitrogen (LN) was used as an adjuvant treatment.

## CASE REPORT

Case 1: A 53-year old male patient residing in the Brazilian city of Rio de Janeiro presented a nodular lesion with 1cm in diameter on the dorsum of the left hand, and a rounded erythematous plaque on the left elbow. After 10.5 months of treatment with 200 mg/day itraconazole, the lesions had little regression (Figures 1A and 1B), with cryosurgery having been indicated. The device used was the Cry-Ac® (Brymill, Ellington, USA), with the intermittent spray technique, tip A, central solid pattern, with a 0.5 cm margin, two cycles of freezing and thawing observing a 4-minute interval between them (Figure 1C). After 2 weeks, the lesion showed healing (Figure 1D). The patient completed 13 months of use of itraconazole and moved to another city, with the follow up having been lost.

Case 2: A 15-year old male patient, student, residing in the Brazilian city of Rio de Janeiro, area of Belford Roxo described the reappearance of nodules with crusts on the third, fourth and fifth fingers and dorsum of the left hand over cicatricial lesions of sporotrichosis (Figure 2A) one month after the completion of treatment with KI, followed by 200 mg/day itraconazole for six months. Itraconazole was reintroduced and 3 sessions of cryosurgery with LN carried out observing intervals of one month, using the Cry-Ac® deice, intermittent spray technique, nozzle B, central solid pattern with 2 cycles of freezing and thawing, with 4-minute intervals between the cycles (Figure 2B). Also, the use of itraconazole was recommended for an additional month, making for a total of 10 months. Two months after the procedure, the patient presented scars (Figure 2C). The patient remains free of active lesions of the disease during 3 years of follow-up.

Case 3: Cryosurgery was indicated for a 59-year old female patient, maid by occupation, residing in the Brazilian city of Rio de Janeiro. The indication ensued the use of itraconazole for one year and seven months (100 mg/day for 7 months, and 200 mg/day during the remaining of the period) for the treatment of a resistant ulcerated lesion, without signs of healing (Figure 3A). One session of cryosurgery was carried out with the Nitrospray® device (Criotécnica, Campinas (SP, Brazil), contact probe with 2 cm in diameter, two cycles of freezing and thawing observing a 4-minute interval between the cycles, after total thawing (Figure 3B). The lesion receded (Figure 4A) and after 3 months showed a scar (Figure 4B).

## DISCUSSION

Sporotrichosis is a subcutaneous mycosis with universal distribution and increasing number of cases. [1] Since 1997, the State of Rio de Janeiro is going through an zoonotic epidemic / endemic with more than 5,000 human cases having been di-

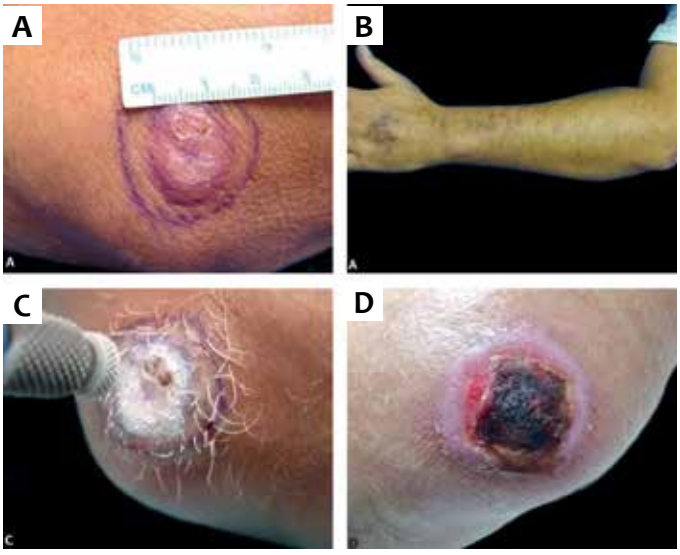


**Figure 1: A:** Erythematous plaque of 1.5 cm in diameter with a central crust, located on the left elbow. **B:** Presence of lymphatic cord from the dorsum of the left hand up until the lesion in the left elbow. **C:** Cryosurgery with the device Cry-Ac® / Brymill -USA, spraying technique, tip A. **D:** Ulcerated crusted lesion 2 weeks after cryosurgery

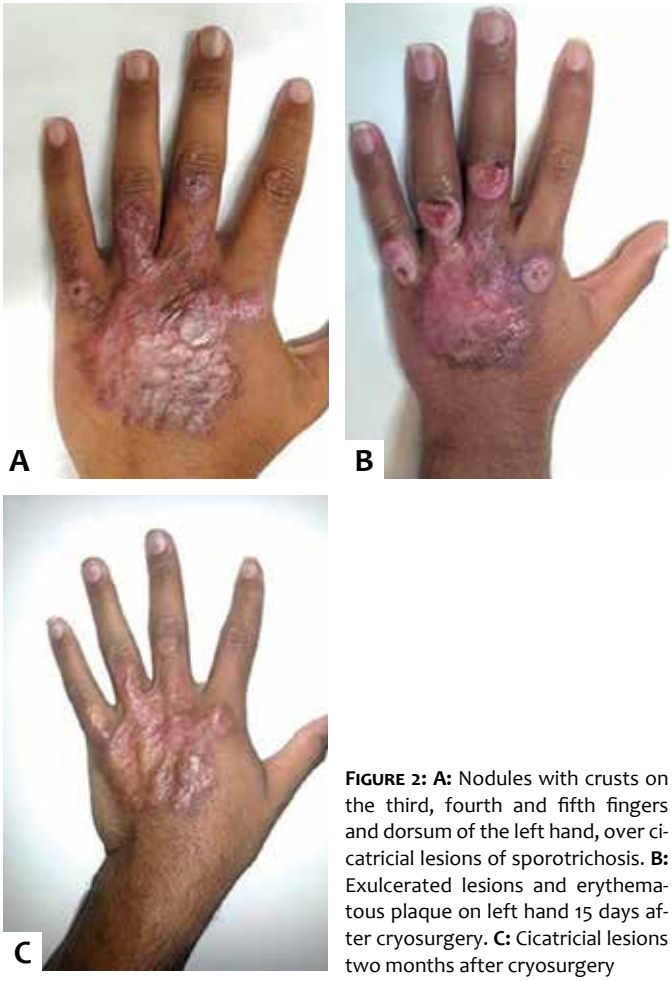


**Figure 2: A:** Nodules with crusts on the third, fourth and fifth fingers and dorsum of the left hand, over cicatricial lesions of sporotrichosis. **B:** Exulcerated lesions and erythematous plaque on left hand 15 days after cryosurgery. **C:** Cicatricial lesions two months after cryosurgery

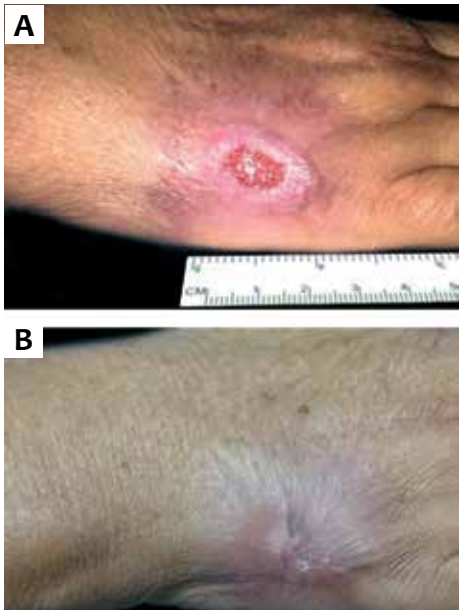


**Figure 3: A:** Ulcer with clean and erythematosus background, and 2.5cm in diameter, on the back of the right hand **B:** Cryosurgery with the device Nitrospray® (Criotécnica, Campinas (SP), Brazil), contact probe, two cycles of freezing and thawing, 4mm margin

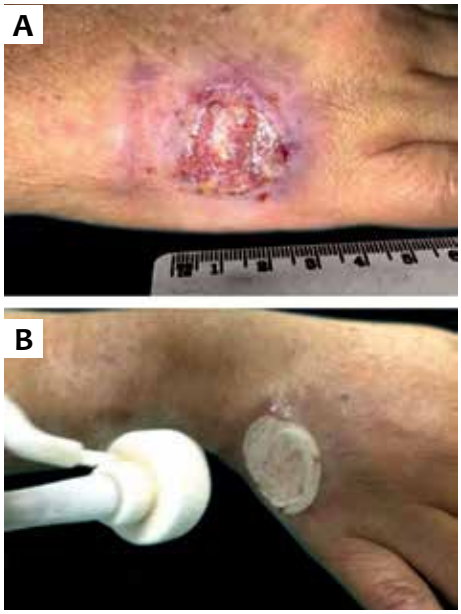


**Figure 4: A:** Healing ulcerated lesion with granulation tissue two months after cryosurgery. **B:** Scar three months after cryosurgery

agnosed at the National Institute of Infectious Diseases Evandro Chagas, a REFERENCES center in the city.[2] Reporting the disease is compulsory.

Itraconazole is the treatment of choice for sporotrichosis, however other substances can also be used: saturated KI solution, terbinafine, fluconazole, ketoconazole and amphotericin B. [1,3] The average duration of treatment is 3 months, and the criterion for cure is clinical, corresponding to the healing of the lesions and the disappearance of erythema and crusts. [3] *Sporothrix spp.* is sensitive to temperature, both to excessive heat and cold. As a result, cryosurgery with LN can be used as an adjuvant to traditional treatment.

Cryosurgery is effective in the treatment of various benign, pre-malignant and malignant cutaneous diseases. It can be used as an isolated treatment or as an adjuvant to conventional or medicated surgical treatments, as in fungal infectious diseases. [4-6] This form of treatment is based on the selective destruction of cells or tissues through freezing, which depends on the minimum temperature reached during cryogenic injury. In order to obtain a severe injury, the freezing process is maintained for a longer period, reaching -20°C to -30°C, resulting in necrosis. The cryosurgery application techniques depend on the lesion's type, shape, size and location, as well as on the cryosurgeon's experience. [4,6] The following techniques can be used in sporotrichosis: intermittent spraying with central solid pattern and tips A or B (Cry-Ac®) and tips 8, 9 and 10 (Nitrospray®); confined spraying using open cones for deepening the freezing process without causing lateral damage to the round lesions; and the solid contact technique, which uses previously frozen solid tips (probes) of varying diameters, in flat areas and ulcerated lesions. The lateral margin ranges from 3mm to 4mm, and the freezing time varies depending on the size of the lesion. Two cycles of freezing and thawing (in the minimum duration ratio of 1:3) are recommended, with a 4-minute interval between the cycles, and sessions every 30 days or with healed lesions.

Ferreira *et al.* described 9 patients with lymphocutaneous and localized sporotrichosis treated with LN (two cycles of 15 seconds and an average of 2.2 sessions at monthly intervals) after having undergone prior treatment with KI, itraconazole (isolated or combined with terbinafine) (Table 1). [7] Moraes *et al.* cited a case of resistance to the use of KI and itraconazole that experienced regression of signs of the disease activity and good development of healing after cryosurgery (Table 1). [4] Bargman also reported 3 cases of the fixed form that experienced cure (Table 1). [8] The present article describes 3 patients who had active sporotrichosis lesions for over 6 months after previous treatment with KI and / or itraconazole, experiencing therapeutic success after undergoing cryosurgery (Table 1).

The combination of cryosurgery with itraconazole for the treatment of feline sporotrichosis lends effectiveness and swiftness to the therapy. Souza *et al.* found clinical cure in 84.6% of cats treated with the combination therapy for an average duration of 32 weeks, decreasing the cost and side effects of antifungals. [9]

It is worth noting that the accessories used in cryosurgery, such as probes and open tips, must be sterilized in autoclave or ethylene oxide.

Furthermore, the fact that sporotrichosis is a zoonosis with a larger number of cases caused by infected animals, implies that the disease should be diagnosed and treated early with a view to stop the epidemiological chain.

**Table 1: Profile of the cases with sporotrichosis treated with cryosurgery**

| Author,Year | Gender | Age (years) | Clinical form | Medication, Total duration | N umber of cryosurgery sessions | Follow- up without recurrence |
|---|---|---|---|---|---|---|
| Bargman, 1995 | M | 60 | fixed | KI, 8 weeks | 11 | 24 Months |
| | F | 12 | fixed | Absence of previous treatment | 12 | 24 Months |
| | F | 58 | fixed | Absence of previous treatment | 4 | 18 Months |
| Moraes *et al*, 2008 | M | ND | fixed | Itraconazole and KI, NA | 1 | ND |
| Ferreira *et al*, 2010 | 7 F 2 M | 45 | Lymphocutaneous and fixed | 5 Patients:itraconazole weeks 28.8 * | 2,2 | ND |
| | | | | 1 patient: KI 12 weeks | | ND |
| | | | | 3 Patients :itraconazole 21.2weeks *;andterbinafine,16 weeks * | | ND |
| Secchin *et al* | M | 53 | lymphocutaneous | Itraconazole,52 weeks | 1 | ND |
| | M | 15 | fixed | KI, 4 weeksand Itraconazole,40 weeks | 3 | 36 Months |
| | F | 59 | fixed | Itraconazole,76 weeks | 1 | 3 Months |

M: male, F: female, NA: not available, * Mean KI: potassium iodide

## CONCLUSION

Indications and outcomes of treating sporotrichosis with cryosurgery still need even better definitions. The scarce literature on the subject and the observation of the three reported cases suggest it is useful in cases of lymphocutaneous or localized / fixed forms of the disease that were not resolved with the use of itraconazole and / or KI for a period exceeding 6 months. ●

## DECLARATION OF PARTICIPATION:

**Pedro Secchin:**
Study design and planning

**Giselle Ribeiro Pereira Seabra:**
Clinical evaluation of cases and indication of cryosurgery, definition of parameters to be used in the procedure (lesion location, tips, freezing and thawing time control, safety margins), patient follow-up, evaluation and indication of additional sessions

**Cleide Eiko Ishida:**
Research study design and guidance, preparation and final review of the manuscript

**David Rubem Azulay**
Participation in research orientation and final text revision

**Nurimar Conceição Fernandes**
Participation in research orientation and final text revision

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# Beard alopecia caused by deoxycholic acid for the treatment of submental fat

*Alopecia em barba causada por desoxicolato para tratamento de gordura submentoniana*

DOI: http://dx.doi.org/10.5935/scd1984-8773.2017931037

ABSTRACT

Second case report in the literature regarding beard alopecia observed after the third session of injections of 1% deoxycholic acid for reduction of submental fat.

**Keywords**: alopecia; subcutaneous fat; deoxycholic acid

*RESUMO*

*Segundo relato de caso da literatura de alopecia em região de barba observada após terceira sessão de injeções de desoxicolato a 1% para redução de gordura submentoniana.*

***Palavras-chave:*** *alopecia; gordura subcutânea; ácido desoxicólico*

A report describing alopecia after ATX-101 injections for submental fat reduction was recently published, calling attention for the possibility of this aesthetic side effect, which was detected in a study of a single case in the post-marketing period, phase IV of the Kybela® product (Allergan, USA), in the United States of America. The study described a one-year follow-up period of permanent alopecia after a single session of the substance.' Despite the number of patients studied in the pre-sales period in a controlled environment, the actual safety profile of a medication becomes evident with the continued vigilance, based on voluntary reports of adverse effects.[2] Case reports are extremely important for the detection of side effects not covered by the designs of phase II and III studies, promptly alerting the industry to actively assess the actual risk of the event: in the present case, in a male patient with beard in the submental area. There is also the need to include this possible side effect in the physician's practice's terms of consent.

A very similar case occurred at the private practice of the author of the present report (Figure 1), observed by the patient himself one month after the third 1% deoxycholate injections session. The injection was prepared in a sterile vial containing 22ml of distilled water with 0.9% benzyl alcohol (Bacteriostatic Water 30ml, Hospira), adding up 1ml of 2% lidocaine with 1:200,000 epinephrine (Xylestesin, Critália, São Paulo, Brazil), 6.1ml of 4.75% deoxycholate (sodium deoxycholate, Pineda®, São Paulo, Brazil). The injection was carried out with a 3ml syringe (Luer Lok™, Becton Dickson) and 0.3x13mm

## Case report

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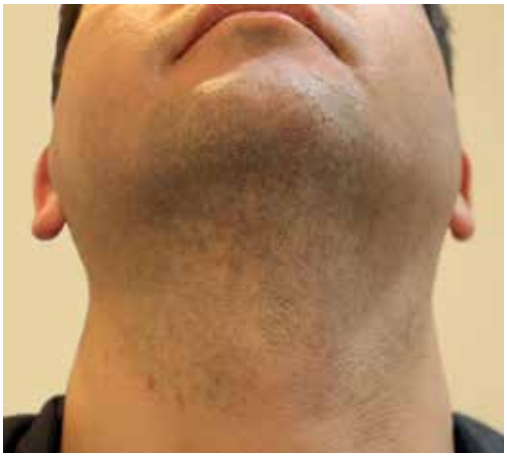

**Figure 1:** Alopecia in the area treated with 1% deoxycholate

needle (30G 1/2, Becton Dickson), and a volume of 0.2ml per point in the pre-platysmal fat (needle inserted between 2/3 and its complete length, perpendicularly to the skin, pinched and tractionned with the opposite hand). The marking of the points is performed every 1cm in an area limited by the following anatomical landmarks: upper margin at 1.5cm caudally from the mandibular margin, lower margin at 1cm cranially from the hyoid bone, lateral margins at 1cm medially to the platysmal band that inserts into the area termed "jowl". Despite the fact that the submental alopecia persisted on each return for a new session in the previous three months, the patient decided to continue the treatment due to the excellent progressive results in the reduction of submental fat. Alopecia was also observed in the Adam's apple region, however it was not injected.

Given that none of the reported cases underwent biopsy, it is only possible to speculate about the possible mechanisms of this apparently non-cicatricial alopecia. The diffusion of deoxycholate solution in the subcutaneous tissue can promote its direct chemical reaction on the cellular walls of the bulbs and follicular papillae in the superficial subcutaneous tissue. The inflammation and subcutaneous fibrosis triggered by lyses of adipocytes could also affect the hair cycle. There is also possibility of diffuse alopecia areata, triggered by the inflammation of the underlying chemical panniculitis. The possibility of inadvertent injection of medical silicone, which lubricates the plungers of the syringes for decreasing the attrition with the inner wall of the tubes, is not ruled out. Since the position of the syringe during the submental injection is tilted upwards, in case of the solubilization of the silicone, due to its lower density relative to that of the water, it may migrate to the upper portion of the liquid to be injected. The lubricant used in syringes, when injected into the subcutaneous tissue, can cause fibrosing lipogranuloma with resulting alopecia.

The product ATX-101 (Kybella®/Belkyra®) is not yet available in Brazil and the only products containing deoxycholate are purchased from dispensing pharmacies specializing in injectable substances, with a heightened concern about higher potential risk of mycobacterial infection as compared with that relative to large scale industrialized products. Unfortunately, Brazilian dermatologists who pioneered the field of the effectiveness of injections containing deoxycholate for treating fatty deposits [3,4] still await for the responsible laboratory to make the product commercially available.

Taking into consideration the possibility of alopecia in patients who wear facial beard or those who do not tolerate the edema caused by the deoxycholate, there is the alternative of indicating the "cosmetic lipoatrophy", proposed in 2009 by Hexsel,[5] using minimal quantities of triamcinolone as the active substance, with lasting effect, nevertheless apparently momentary, and with capillary growth as a possible side effect. ●

**PARTICIPATION IN THE ARTICLE:**

**Carlos Gustavo Wambier:**
Drafting and critical review

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# Herpes zoster ophthalmicus after onabotulinumtoxin for cosmetic treatment: a case report

## *Herpes-zóster oftálmico apos injeção de onabotulinotoxina para tratamento cosmético - Relato de caso*

DOI: http://dx.doi.org/10.5935/scd1984-8773.201793840

ABSTRACT

Herpes zoster outbreaks following minor procedures have been documented recently in literature. Since the use of botulinum toxin is nowadays spread in several medical areas for different purposes, it is crucial to study its side effects and complications. Literature review revealed 65 cases of zoster reactivation following minor procedures, and three cases related to BTA injections (two for facial lines treatment and one for chronic migraine). In our case, a 43 year old healthy woman had herpes zoster on the face and scalp after receiving BTA injections for cosmetic purpose, with complete recovery after anti-viral treatment.

**Keywords**: herpes zoster ophthalmicus; herpes zoster; botulinum toxins, type a; dermatologic surgical procedures

*RESUMO*

*Episódios de herpes-zóster após procedimentos têm sido documentados recentemente na literatura. Uma vez que o uso da toxina botulínica atualmente se faz presente em diversas especialidades médicas, é crucial o estudo de seus efeitos colaterais e complicações. Uma revisão da literatura mostrou 65 casos de reativação de zóster após procedimentos, sendo três relacionados a injeções de toxina botulínica tipo A (dois para tratamento de rítides faciais e um para migrânea crônica). Em nosso caso, uma mulher de 43 anos previamente hígida apresentou herpe-zóster na face e couro cabeludo após injeções de toxina botulínica tipo A com fins estéticos, tendo recuperação completa após tratamento antiviral.*

***Palavras-chave:*** *Herpes-zóster oftálmico; herpes-zóster; toxinas botulínicas tipo a; procedimentos cirúrgicos dermatológicos*

## CASE REPORT

A healthy, 43 year-old woman with absence of history of herpes, received botulinum toxin type A (OnabotulinumtoxinA) for cosmetic treatment. A total of 40 units were injected in the frontal, glabellar and periorbital regions, without any immediate side effects. After three days, the patient complained of pain and paresthesia on her left eyelid and the left frontal area, which then disseminated to the ipsilateral parietal and temporal regions, accompanied by a burning sensation on the left eye and preserved visual acuity. Twelve hours after these first symptoms, the condition progressed with an edema and erythematous papules; she was treated with antibiotics orally, after the diagnostic hypothesis of cellulitis. On the fourth day, the edema and the erythema worsened, with the appearance of some vesicles on her forehead, glabella and the left side of her scalp, followed by superficial

Case report

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erosions and periorbital edema (Figure 1). Five days afterwards, the patient was examined by a dermatologist, who diagnosed her with herpes-zoster on the first branch of the left trigeminal nerve. The patient was treated with 1g of valacyclovir hydrochloride three times a day for seven days, ophthalmologic ointment acyclovir to be applied four times a day for seven days, and 40 mg/day of prednisolone to be taken orally for five days. After ten days, the signs and symptoms had almost completely be resolved, however, the patient was still complaining about pain and edema on her left eyelid, which was treated with an antibiotic typical for blepharitis for seven more days (Figure 2). The ophthalmological exams showed no other changes.

## Literature Review

### BOTULINUM TOXIN

Botulinum Toxin Type A (BTX-A) blocks acetylcholine by the cleavage of the Synaptosome-Associated Protein 25, which participates in the formation of the exocytic receptor of the Soluble N-ethylmaleimide Sensitive Attachment Protein (SNARE) essential for the fusion of vesicles containing acetylcholine to the presynaptic membrane. The blockage results in the selective chemical denervation of the muscles. The local peripheral injection of Botulinum Toxin Type A also results in the reduction of several substances that sensitize nociceptors, such as the substance P and the calcitonin gene-related peptide, which performs a significant role in neurogenic inflammation.1 The Food and Drug Administration (FDA) has approved the usage of BTX-A for strabismus in 1979, for blepharospasm in 1985, for hemifacial spasm in 1989, and, finally, for glabellar dynamic wrinkles in 2003.2

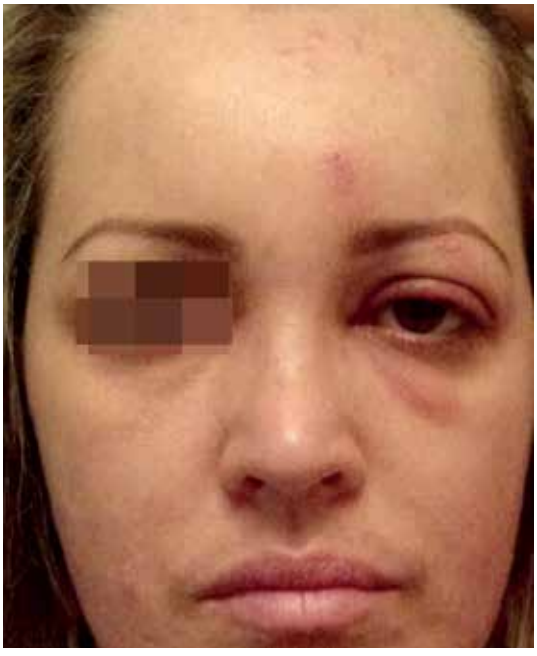

**Figure 1:** Edema, erythema, vesicles and erosions on the region innervated by the ophthalmic branch of the trigeminal nerve

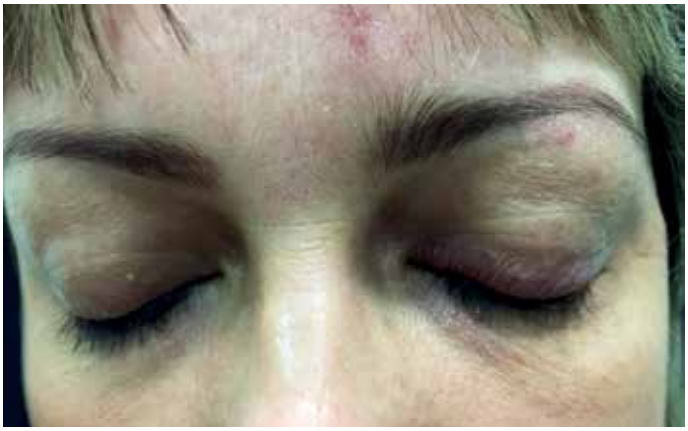

**Figure 2:** After ten days, remaining left eyelid pain and edema were treated as blepharitis for 7 more days, with full resolution

In reviewing the literature, 65 cases of herpes zoster reactivation were found following procedures, most of them in young patients without any specific risk factors, which suggests that the presence of herpes zoster related to trauma is not uncommon. There are only three reported cases of herpes zoster following the application of BTX-A. In a controlled study, Thomsd et al. have shown the presence of increased risk of an outbreak of herpes zoster in the site related to the trauma during the month subsequent to the procedure.[3] Juel-Jensen reported 38 herpes zoster outbreaks related to the trauma in a series of cases involving 100 patients who were herpes zoster carriers.[4] In a wide review of the literature, Gadient et al.[5] have indicated several causes associated to the reactivation of herpes zoster, such as: radiotherapy for breast cancer (41 patients), dental treatment and orofacial surgery (six patients); placement of central venous catheter (two patients); liposuction of the back and flank; surgical repair of orbital fracture; intra-articular injection of corticosteroids; laser surgery for myopia; cryosurgery for actinic keratoses; hepatic biopsy for hepatitis C; skin graft following burns; thoracic sympathectomy; axillary nerve block; breast reconstruction under intercostal nerve block; and endotracheal intubation for esophagogastrostomy.[5]

### HERPES ZOSTER

Subsequent to the primary infection (varicella), the varicella zoster virus (VZV) remains dormant in the dorsal root ganglion; its reactivations causes herpes zoster, clinically characterized by the sudden onset of vesicles in a specific dermatome, unilaterally, more commonly appearing on the thoracic and cranial distributions, generally being followed by prodromal symptoms such as pain, dysesthesia, malaise and pruritus.[6]

### BOTULINUM TOXIN AND HERPES ZOSTER

The mechanism of reactivation of VZV is not clear. The primary risk factors for herpes zoster reactivation are immunosuppression, advanced age, systemic diseases, and certain malignancies. VZV is not uncommon after major surgeries due to im-

mune stress. After small procedures, reactivation of the varicella is likely related to localized trauma or inflammation.[3, 6, 7] *In vivo* studies show that specific cytokines, such as IL-6 and alpha-TNF, as well as the VP16 viral protein, are related to the reactivation of the Herpes Virus Simplex Type 1, while VZV can be triggered in similar ways.[5,8] Gadient et al.[5] suggested that stress-generating agents (radiation, laser, chemical, thermal and mechanical agents) exert local epigenetic influence on viral transcription, allowing their reactivation.

As reported by Gadient and Graber,[5, 6] it is suspected that repeated administration of BTX-A causes reactivation of VZV. On the other hand, no cases of herpes zoster were reported in another study with 513 subjects who were treated with BTX-A for chronic migraine (patients were followed up for 56 weeks).[9]

## DISCUSSION

According to the literature, the present report describes the fourth case of a herpes zoster outbreak after a BTX-A injection. Until then, only three cases had been attributed to this procedure (two following cosmetic treatment with BTX-A on the forehead, glabella and periorbital areas;[6] and one after BTX-A was used to treat chronic migraine).[5] In the cosmetic case, herpes zoster was diagnosed after one week[6] and in the migraine case, 48 hours after treatment.[5]

In one case, a 55-year-old female with no previous history of herpes zoster or any risk factors received 50 units of onabotulinum toxin type A for the treatment of facial expression lines in the glabellar, frontal and periorbital areas.[6] The patient had undergone eight previous treatments with BTX-A. Differently from our case, in which the patient had undergone the treatment for the first time; seven days after the injections, the patient complained of swelling, itching and pain in the left frontal region and glabella, presenting poorly demarcated erythema and edema, with superficial erosions in the region, not exactly in the same place of the injections. In the present case report, the lesions occurred three days afterwards in the left frontal region and glabella, as in the aforementioned patient. After the diagnosis of herpes zoster ophthalmicus, the patient received 1g of valacyclovir hydrochloride three times a day for ten days, which resulted in complete resolution of symptoms after one week. Six months later, the BTX-A treatment was repeated for the same purpose (cosmetic), and the patient received oral antivirals, with no recurrence of herpes zoster.[6]

The same study also reports the case of a 48-year-old woman with no history of herpes zoster nor any risk factor, nor previous use of botulinum toxin of any kind, as in the present case report. The patient was treated with BTX-A in the glabellar, frontal and periorbital areas.[6] Six days after the treatment, she presented with paresthesia in the right outer ear, constant headache on the right side and, on the seventh day, vesicles developed on the glabella and on the right side of the frontal region. The clinical signs and symptoms were similar to those of the present case report, except for the fact that the contralateral area was affected. Orally-administered treatment with valacyclovir was successful.

The third case, reported by Gadient et al.,[5] was that of a 72-year-old woman who received BTX-A injections every three months for three years to treat chronic migraine, absent of incidents. It was the first published report on herpes zoster after the use of BTX-A to treat chronic migraines. Two days after the procedure, the patient developed a periorbital edema and a possible cellulitis, was treated with oral antibiotics, just as in the present case report. Herpes zoster was diagnosed only one week later and, therefore, the patient was not treated with antivirals.

## CONCLUSION

Although the exact mechanisms for VZV reactivation remain unknown, this condition has been reported following minor procedures and related to localized trauma or inflammation. Herpes zoster outbreaks following BTX-A have recently been documented in the literature, not only for cosmetic purposes but also for the treatment of chronic migraine. Since the application of BTX-A is a very common procedure, it is important that dermatologists are attentive, thus avoiding diagnostic errors.[1]

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# Vulvar lichen sclerosus: description of 5 cases successfully treated with the 2,940nm Erbium-YAG laser

*Líquen escleroso vulvar: descrição de cinco casos de sucesso com laser Erbium-YAG 2940*

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ABSTRACT

Lichen sclerosus is a chronic dermatosis, usually anogenital and mainly affecting pos-menopausal women. The use of topical corticosteroids is the mainstay of medical treatment. Other treatments are topical testosterone, calcineurin inhibitors, photodynamic therapy, cryotherapy, antibiotic therapy and laser therapy. In this article, five patients with vulvar lichen sclerosus which had no response to treatment with topical clobetasol, had good results when treated with fractional Erbium:YAG laser 2940.

Keywords: laser therapy; vulvar lichen sclerosus; 17-Hydroxycorticosteroids

*RESUMO*

*Líquen escleroso é dermatose crônica com predileção pela região genital. Acomete, principalmente, a raça branca, sendo mais frequente em mulheres. O tratamento-padrão é feito com corticosteroides tópicos de alta potência. Tratamentos com propionato de testosterona, imunomoduladores tópicos, terapia fotodinâmica, crioterapia, antibioticoterapia e laserterapia são citados na literatura. Neste artigo são relatados cinco casos de pacientes com liquen escleroso vulvar, sem sucesso com o clobetasol tópico, submetidas ao tratamento com Laser Erbium YAG 2940 fracionado. Os resultados foram bastante satisfatórios, sugerindo a laserterapia como opção no tratamento do líquen escleroso, incluídos casos de insucesso com o uso corticoides tópicos.*

***Palavras-chave:*** *líquen escleroso vulvar; corticosteroides; terapia a laser*

## INTRODUCTION

Lichen sclerosus (LS) is a chronic and benign dermatosis that affects the genital and extragenital region. Vulvar involvement is predominantly observed in premenopausal and menopausal women, and may cause pruritus, pain, dyspareunia and sexual dysfunction (1,2).

Autoimmune and genetic factors are implicated in its etiology. Association with other autoimmune diseases corroborates this theory (3). The participation of the spirochaete *Borrelia Burgdorferi* is still controversial (1).

Clinically, it affects the perineum, labia majora and minora, clitoris and perianal region. It is characterized by hypochromic plaques, fissures, as well as causing a buried clitoris and fusion of the labia majora and minora. The main complaint is *pruritus vulvae,* associated or not with dysuria, dyspareunia and burning sensation. Lesions can also be observed lesions in genitocrural folds, thighs and buttocks (4).

Histologically the epidermis is scarce with hyperkeratosis, homogenization of collagen between the dermis and the epidermis, and lymphocytic infiltrate (4).

## Case report

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Some cases of LS can progress to squamous cell carcinoma, requiring the control and clinical follow-up of these patients (5).

Many patients respond to treatment with the abolition of signs and symptoms, but in other cases the signs remain and the symptoms are intermittent (6).

Currently, the treatment is done with a high-potency topical corticosteroid (clobetasol) with good results. Other options are topical immunomodulators (tacrolimus and pimecrolimus), photodynamic therapy, cryotherapy, antibiotic therapy and laser therapy (7). The use of laser in the treatment of lichen is recent and few studies have used the fractional $CO_2$ laser (8,9,10); none have used the fractional 2,940 Er:YAG fractional laser.

The purpose of this study was to evaluate the efficacy of the 2,940 Er:YAG fractional laser in the treatment of LS in cases where other treatments were not successful in relieving symptoms.

We have described in this article five cases of patients with LS confirmed by histological exams, resistant to the use of clobetasol who underwent five sessions of 2,940 Er:YAG fractional laser (Solon Platform – LMG, MG, Brasil) every 21 days, with an important improvement of lesions and pruritus. The parameters used are shown in Table 1.

**Table 1: Treatment Protocol with 2,940 Er:YAG fractional laser**

| | Mode | Fluence (J/cm2) | Pulse Width (ms) | Number of passes |
|---|---|---|---|---|
| Mucous Membrane | Ablative / Coagulative | 17 | Auto | 2 |
| Skin | Ablative | 10 | 1.0 | 2 |

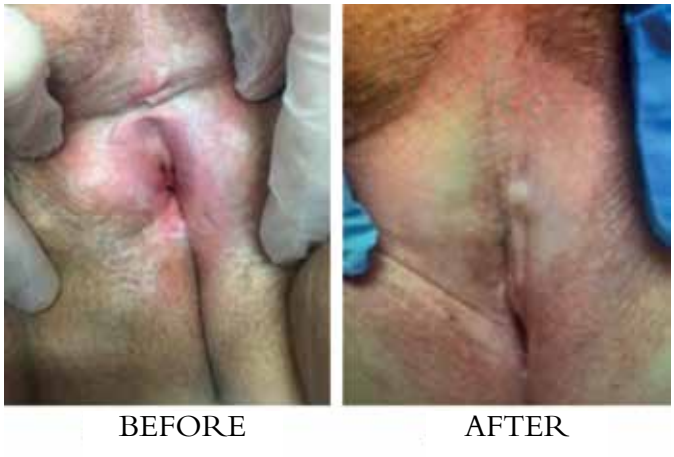


**Figure 1:** Case 1, photographs before and two months after the last session

**Case 1**

MSNL, 68 years old, Caucasian, underwent menopause 13 years previously, with clinical and anatomopathological diagnosis of LS for 8 years, intense vulvar pruritus without improvement with clobetasol 0.5 mg/g daily. At the examination presented with a loss of the vulvar architecture, hypopigmentation, whitish plaques and excoriations (Figure 1).

Two months after the last session the patient reported complete improvement of pruritus and that she was no longer using the topical clobetasol. During the clinical examination, presented improvement of skin texture and areas of repigmentation (Figure 1).

**Case 2**

MAV, 69 years old, Caucasian, underwent menopause 24 years previously, complaint of intense vulvar pruritus for 2 years. Clinical and anatomopathological diagnosis of LS, using clobetasol 0.5mg/g daily without improvement of pruritus. At examination, vulva with hypopigmentation and areas of leukoplakia mainly on the clitoral hood. (Figure 2).

Two months after the end of treatment, the patient reported improvement of 70% of pruritus and that since the last consultation she had not used the topical clobetasol. During the clinical examination, presented significant improvement of leukoplakia and areas of repigmentation (Figure 2).

**Case 3**

ERN, 70 years old, Caucasian, underwent menopause 25 years previously, presenting intense vulvar pruritus and little re-


**Figure 2:** Case 2, photographs before and two months after the last session

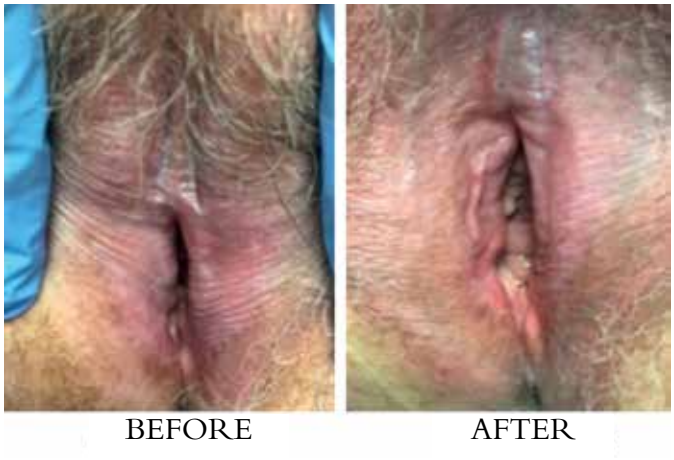


**Figure 3:** Case 3, photographs before and two months after the last session

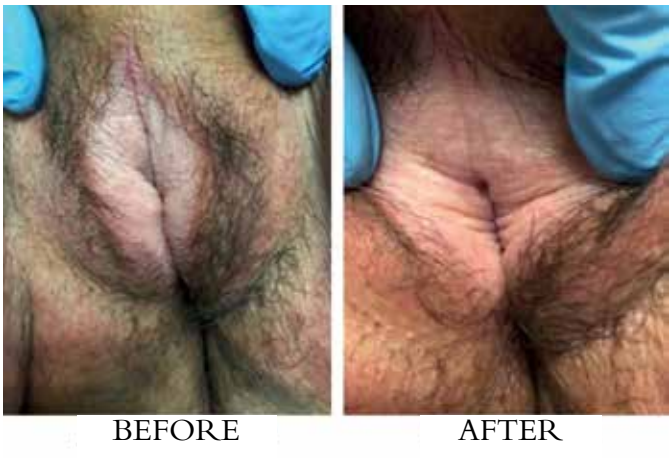


**Figure 4:** Case 4, photographs before and two months after the last session

sponse to daily use of clobetasol 0.5mg/g. Upon examination, presented with a loss of the vulvar architecture, erythematous and atrophic mucosa, and fusion of the labia minora (Figure 3).

Two months after the end of the treatment, the patient reported improvement of 80% of pruritus and that since the last consultation she had used the topical clobetasol only when she had pruritus (once a week). During the examination, presented improvement of texture and separation of the labia minora (Figure 3).

**Case 4**

VES, 60 years old, Caucasian, underwent menopause 6 years previously, reported vulvar pruritus for over 1 year, using clobetasol 0.5mg/g twice a day since then, with little improvement. Upon examination, were observed loss of the vulvar architecture, hypopigmented and atrophic mucosa and whitish plaques (Figure 4.1).

Two months after the end of the treatment, the patient reported improvement of 100% of pruritus and that since the last consultation had not used the topical clobetasol. During the examination, presented improvement of the texture and color of the vulvar mucosa (Figure 4.2).

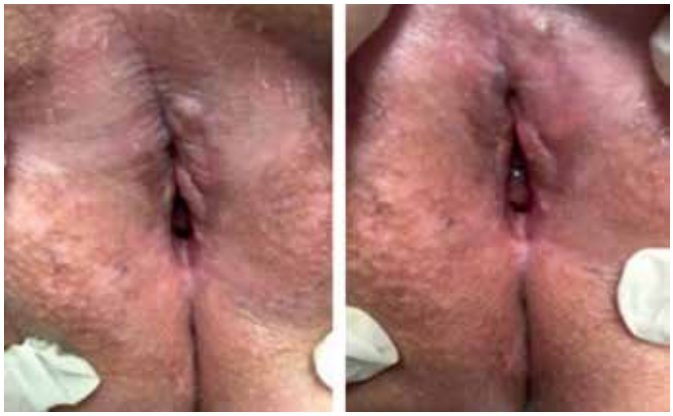

**Figure 5:** Case 5, photographs before and two months after the last session

**Case 5**

JGP, 67 years old, Caucasian, underwent menopause 24 year previously, presenting vulvar pruritus for over 23 years. She has used several topical medications without clinical improvement and underwent surgery for debridement in the clitoral region one year previous due to phimosis and abscess formation. Has been using clobetasol 0.5mg/g for 6 months, once a day with little response. During the clinical examination presented loss of the vulvar architecture, hypopigmented and atrophic mucosa (Figure 5).

Two months after the end of the treatment, the patient reported improvement of 100% of the pruritus and that she had not used the topical clobetasol. During the examination, presented improvement of the texture and pigmentation of the vulva (Figure 5).

## DISCUSSION

Lichen Sclerosus can occur at all ages and both genders, but it is more frequently seen in postmenopausal women (11). Pruritus is the main complaint, often important, causing discomfort and even social isolation. Dyspareunia and loss of vulvar architecture are also common (12). Severe pruritus was reported by all patients, even with daily clobetasol use prior to the start of the treatment. After the third session there was a significant improvement in pruritus (of at least 50%) and a decrease in the frequency of daily corticosteroid application to once a week or less.

The pain during laser application was reported by all patients as moderate in the first session and mild in the following. We believe that the fear of the unknown towards the treatment, in its first session, was responsible for the greater intensity of the pain, because in the subsequent sessions it was less intense, without change to the parameters that were used. The topical anesthetic may ease the pain during the application.

Godoi et al., in 2015 (2) compared tissue biopsies with and without lichen sclerosus and found in patients with LS decreased elastic fibers in the upper layer of the dermis, associated with the increase of type V collagen and decreased expression of extracellular matrix protein 1, the latter two probably due to poor tissue repair due to the disappearance of the elastic fibers. As demonstrated in other areas of the body, laser induces remodeling of connective tissue through the production of collagen and elastic fibers (13). This process involves the interaction of the heat shock proteins 43, 47 and 70 that induce local increase of cytokines such as TGF-$\alpha$ (transforming growth factor alpha) that stimulates proteins in the matrix such as collagen, FGF (fibroblast growth factor) that stimulates angiogenic activity, EGF (epidermal growth factor) that stimulates reepithelialization, PDGF (platelet-derived growth factor) that stimulates fibroblasts to produce the components of the extracellular matrix and VEGF (vascular endothelial growth factor) that regulates angiogenesis (14). We believe that the remodeling promoted by the laser may play an important role in the reorganization of elastic fibers and consequently in the treatment of lichen sclerosus, bringing hope that a more stable treatment, with better results may be used in these patients.

Our subjective (pruritus) and objective (aspect of the vulva) results corroborate with our hypothesis; however, studies with more patients are necessary.

## CONCLUSION

The 2,940 Er:YAG fractional laser has shown promise in the treatment of vulvar lichen sclerosus, even in resistant cases to topical treatment with clobetasol. ●

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# Repigmentation pattern in a vitiligo patient after autologous stem cells implantation

*Padrão de repigmentação em um paciente com vitiligo após a utilização de células tronco*

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ABSTRACT

Vitiligo is a hypopigmentation disorder that is characterized by macules and selective destruction of functional epidermal melanocytes. It is characterized by defilements and circumscribed depigmented patches. Vitiligo affects around 0,5% about 0.5% -2% of the general population worldwide, and is not observed pREFERENCES for sex and ethnicity. The goals of treatment are repigmentation of vitiligo and stabilization of depigmentation process. We report the case of a 53-year-old female patient who underwent underwent experimental stem cell therapy with autologous biologically expanded stem cells isolated from hair follicle, holding three sessions with three months apart. The vitiligo affected area was relatively decreased in density with a rare repigmentation pattern.

**Keywords**: stem cells; vitiligo; therapeutics

*RESUMO*

*Vitiligo é desordem de hipopigmentação caracterizada pela destruição seletiva de melanócitos epidérmicos funcionais e por máculas e manchas despigmentadas circunscritas. Vitiligo afeta de 0,5% a 2% da população e não é observada preferência por sexo e etnia. Os objetivos do tratamento são repigmentação das lesões e estabilização do processo de despigmentação. Relatamos o caso de uma paciente de 53 anos de idade submetida à terapia experimental com células-tronco autólogas isoladas do folículo piloso e expandidas biologicamente. Foram realizadas três sessões com três meses de intervalo. A área afetada apresentou repigmentação importante.*

***Palavras-chave:*** *células-tronco; vitiligo; terapêutica*

## INTRODUCTION

Vitiligo is an acquired idiopathic disorder characterized by the selective destruction of functional epidermal melanocytes. Melanocytes disappear from the skin surrounded by mechanisms that have not yet been fully identified.[1,2] Vitiligo affects 0.5% to 2% of the general population worldwide, with no distinction for gender or ethnicity. It can occur at any period of a person's life, with the mean age of onset being 20 years old.[2] The disorder is characterized by circumscribed depigmented patches that vary in number and size. The disease can be classified according to the distribution of the lesions as: localized (focal, segmental and mucosal) and generalized (acrofacial, vulgaris and universalis). The physiopathological mechanism of vitiligo is not yet clearly understood. It is a multifactorial disorder related to genetic and non-genetic factors. Studies suggest that vitiligo is a non-Mendelian, polygenic inheritance disease, with recurrence of 20% to 30% among first-degree relatives. Among the known non-genetic hypotheses, the most important are: autoimmune destruction

Case report

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of melanocytes, intrinsic defect in the structure and function of melanocytes, imperfect defense against free radicals, and reduction of melanocyte survival.[3] The objectives of the treatment are the repigmentation and the stabilization of the depigmentation process. Among the repigmentation therapies are the Narrow Band UVB, psoralen photochemotherapy, topical and immunosuppressant corticosteroids, surgical therapies and micropigmentation.[4-6] The treatment of vitiligo is difficult and long since, despite the available therapeutic arsenal, the disease can progress with incomplete repigmentation depending on the affected area. Thus, new therapeutic approaches are emerging, being that stem cell therapy has a vast and unexplored potential in the treatment of patients with vitiligo. Stem cells are characterized by being undifferentiated, capable of proliferation and regeneration after tissue injury, presenting several subpopulations, and have been studied in the research on vitiligo. The skin, in particular, is a rich source of different types of stem cells: epidermal, hair follicles, sebaceous and sweat glands, as well as dermal mesenchymal with regenerative properties, which are increasingly being explored in vitiligo management strategies.

## CASE REPORT

A 53-year-old female patient presented with vitiligo lesions four years previously, starting on the front, back of the hand, abdomen, and external genitalia (Figure 1). She was submitted to 30 sessions (three times a week) of PUVA Treatment (psoralen + UVA phototherapy) during the first year after the onset of the lesions. Due to the poor response to treatment, she dropped out of therapy and remained for the past three years without any oral or topical medication.

A circular 5mm fragment of skin from the left posterior region of the scalp was obtained from a punch and sent to the laboratory at the Cellular Technology Center - CCB - ISO N7. The various types of stem cells present in the skin sample were isolated and expanded using the biological method of stem cell expansion (Figure 2). After expansion, 1.5x106/ml cells (second passage) were placed in a physiological solution (0.09% NaCl), in a syringe, and applied to the affected area. Thousands of stem cells are transplanted into the vitiligo areas with each procedure. The number of procedures required depends on the size of the affected area. The patient was submitted to experimental therapy with stem cells in December of 2015 (three sessions with three months interval). The images show the patient before the therapy, at the end of the treatment (last session) and four months after the last session (Figures 3 and 4).

The patient has not undergone any therapy for the improvement of her vitiligo lesions between the last session of the treatment in question and the time at which this article was prepared.

## DISCUSSION

Vitiligo affects millions of people around the world, and the melanocytes, cells that give color to skin, play an important role in repigmentation. There is a theory that suggests that melanocytes are responsible for repigmentation in vitiligo, dividing and migrating to the surface along the epidermis. Nishimura et al. demonstrated that the stem cells in the bulge region could migrate towards the surface to the epidermis, resulting in repigmentation in animal models. Chemical and physical stimuli may promote the migration of precursor melanocytes involved in the repigmentation of vitiligo lesions.[7, 8] Phototherapy can be used to accelerate this process, but success is not guaranteed, and sometimes there is no pigmentation after the procedure. The shade of the new pigmentation may be lighter, darker or more irregular than the surrounding normal skin. The technical aspect of the procedure, performed exclusively by the authors of this article, is the application of a mixture of biologically expanded autologous stem cells in the lesion of vitiligo. The cells are harvested from a painless biopsy on the scalp, expanded *in vitro* (Figure 2) and then transferred to the affected area with the aim of replacing the missing pigment cells, restoring the patient's natural skin color. Repigmentation begins with the appearance

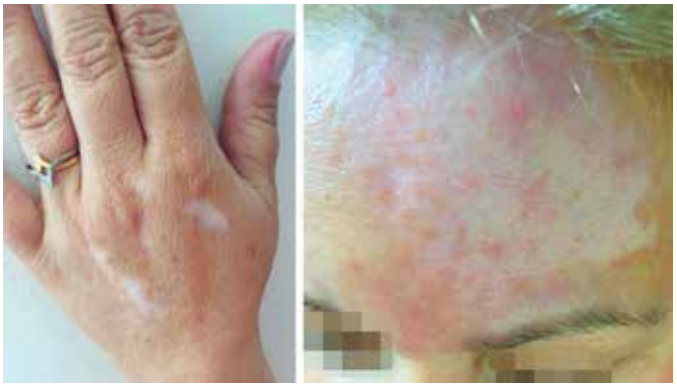

**Figure 1:** Initial clinical picture of the hand and front in December 2015

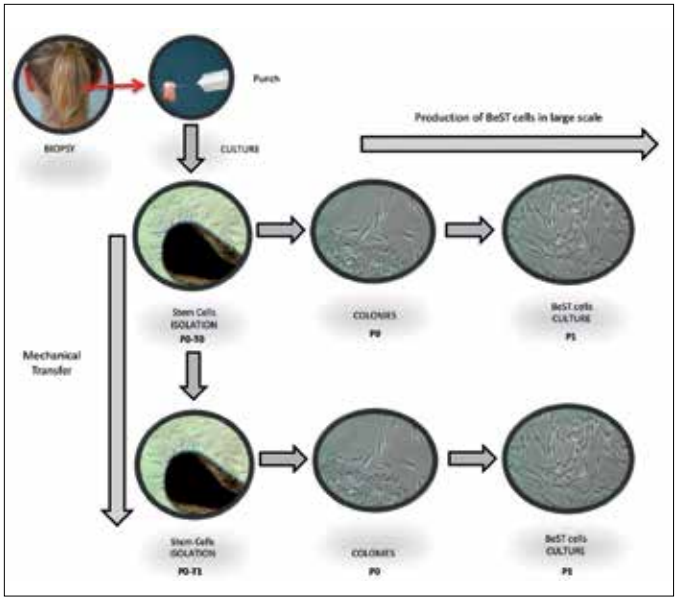


**Figure 2: CCB-**Patented Biological Expansion Method Of Stem Cells

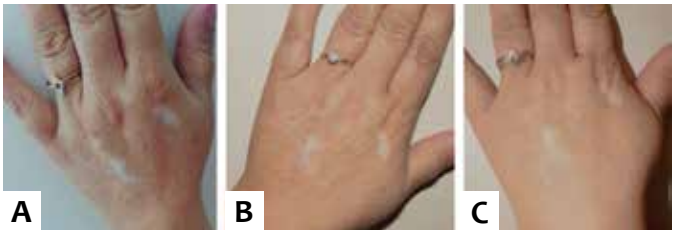


**Figure 3:** Decreased density of white color in the depigmented area was observed on the dorsum of the hand. **A** - Dec. 2015; **B** - Apr. 2016; **C** - Jul. 2016

of dotted or drop-like spots in the follicular ostia within the patch or in the centripetal direction from the edges (Figures 3 and 4). Pigmentation occurs due to the application of stem cells, which promotes the proliferation and migration of melanocytes from hair follicles to the basal layer of depigmented skin. The authors of the present article demonstrated the presence of evident decrease in the density of the area affected by vitiligo, with exceptional repigmentation. The usual treatment of vitiligo is difficult and long since, despite the available therapeutic arsenal, the disease can advance and complete repigmentation does not occur. Thus, in order to achieve success in the treatment of vitiligo, personalized stem cell therapy should also be considered as a way to provide adherence to treatment even when therapeutic failures occur.


**Figure 4:** Decreased density of white color in the depigmented area was observed on the forehead. **A** - Dec. 2015 **B** - Apr. 2016 **C** - Jul. 2016

## CONCLUSION

By the present report, a relative decrease in the density of the area affected by vitiligo was observed, with a rare repigmentation pattern. These findings indicate the need for further studies on stem cell therapy for the treatment of vitiligo. The clinical efficacy of the stem cell transplantation in the studied patient suggests the existence of potential for the treatment of patients with vitiligo.

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