Do I know the anatomy of the lip? Implications for a successful filling

Conheço a anatomia labial? Implicações para o bom preenchimento

ABSTRACT

The lips are important anatomical units for perfect facial aesthetic balance. A number of methods can be used to improve lip appearance, including chemical and physical peels, botulinum toxin, cosmetic surgery and the use of cutaneous fillers. In the face of the already widespread and yet still growing use of fillers worldwide, the need for precise anatomical knowledge arises as an important tool to prevent complications. The objective of the present study is to shed light on the anatomical peculiarities of this facial topography and review recommendations linked to best practices with cutaneous fillings.

Keywords: Anatomy; Esthetics; Hyaluronic acid; Lip; Lip products

RESUMO

Os lábios representam unidades anatômicas importantes para a harmonia estética facial. Inúmeros métodos podem ser utilizados para a melhoria da estética labial, incluindo os peelings químicos e físicos, a toxina botulínica, cirurgias estéticas e o uso de preenchedores. Dada a grande e crescente utilização desses preenchedores mundialmente, surge a necessidade de preciso conhecimento anatômico para a prevenção de intercorrências. O objetivo deste trabalho é trazer informações sobre as peculiaridades anatômicas nessa topografia, além de recomendações relacionadas à boa prática de preenchimento.

Palavras-chave: Ácido hialurônico; Anatomia; Estética; Lábio; Produtos para lábios

INTRODUCTION

Lips are anatomical units of extreme aesthetic importance. Their contour and dimensions connote youth, sensuality, and beauty. Like the skin, they are subject to extrinsic and intrinsic factors that are responsible for aging.1,2

There are several possible approaches for improving the aesthetic quality of the lips, predominantly chemical and physical peels, which in the latter category includes ablative or non-ablative lasers, mechanical abrasions, botulinum toxin, and different surgical techniques—all examples of treatment modalities.2

This paper will focus on the cutaneous filling technique as a resource to improve the aesthetics of this area. A fundamental prerequisite for its appropriate use is the knowledge of lip anatomy—a determining factor for the correct implementation of this invasive procedure.3

Complications from the use of fillers include ecchymosis, edema, erythema, infections, herpes reactivation, nodules, grani-
Anatomy for lip filling

Lipomas and those resulting from vascular damage, which include bleeding, necrosis and embolization – complications that are very relevant to the topic discussed. The objective of the present paper is to provide essential information regarding the labial arterial supply, including recommendations to minimize these potential acute complications.

LABIAL ARTERIAL SUPPLY

Figure 1 shows the arterial supply of the lips, including its relationship with the major vessels of the central portion of the face. The facial vessels constitute a wide vascular network. Damage caused in a particular artery can be compensated by its contralateral pair and/or anastomoses.

Upper lip

The arteries responsible for the arterial blood supply of the lips originate in the facial artery (FA). The main artery of the upper lip is the superior labial artery (SLA), and its subalar (SAA) and septal (SA) branches are sometimes additional to this process.

According to Al-Hoqail et al., Crouzet et al. and Ricbourg, based on the dissection of cadavers fixed in formalin, in most cases the SLA originates above the labial commissure and in fewer than 25% of cases its origin coincides with it (Figure 1). Tansatit et al. determined that the distance from the SLA’s origin to the labial commissure ranges from 5-9 mm.

Regarding the diameter of the SLA, Park et al. identified a diameter of 1.2 mm at its origin, while Crouzet et al. identified an average diameter of 1.0 mm and Magden et al. 1.3 mm. Al Hoqail et al. found an average diameter of 1.8 mm and Pinar et al., 1.6 mm. Tansatit et al. came to a value of 1.1 + 0.3 mm.

Although the labial artery is commonly bilateral, it varies widely according to the pattern in the dominant side, tortuosity, and path. Interestingly, Al-Hoqail et al. and Magden et al. demonstrated the unilateral existence of the SLA in 36% of cases and Tansatit et al. in 23% of cases.

Philtrum

Figure 3 shows the philtrum’s arterial supply, carried out by the arch formed by the central artery of the philtrum (CAP), the left and right lateral ascendant arteries of the philtrum (LLAAP and RLAAP, respectively) and the left and right accessory arteries of the philtrum (LAAP and RAAP, respectively).

The anatomical study conducted in cadavers by Garcia de Mitchell et al. demonstrated the existence of a fat compartment superficial to the orbicularis oris muscle. In addition, it is important to note that the arteries that make up this arch in the philtrum are located above the orbicularis oris muscle (Figure 4).

Lower lip

The lower lip is supplied by the FAs, the inferior labial artery (ILA) and the labiomentonian artery (LMA). The LMA may have horizontal branches (called the horizontal labial artery - HLA), and vertical branches (called vertical labial artery - VLA). With a role similar to that played by the SLA, the ILA is primarily responsible for the lower lip’s arterial supply. Although there is a dominance of the VLA over the HLA, there is an alternating pattern in the HLA and VLA.

Many anatomy textbooks and researchers have described the ILA as originating at the level of the labial commissure. However, Al-Hoqail et al. identified its origin below the labial commissure in 42.9% of cases, at the commissure level in 35.7% of cases, and above the commissure in 21.4% of cases. In

![Figure 1: Central portion of the main arteries of the face](image1.png)

![Figure 2: Position of the superior labial artery (SLA) and its relationship with the orbicularis oris muscle and the vermillion. The branches of the cutaneous, mucosa, and vermillion branches can be observed](image2.png)
addition, its origin in a branch shared with the SLA occurred in 28.6%, while Tansatit et al. \(^5\) identified this pattern in 11.5% of the cases (Kawai’s type B).

By studying the origin of the ILA, Kawai et al. \(^12\) demonstrated the existence of three patterns: Type A) originally described as the most common (Figure 5). On the other hand, Al-Hoqail et al. \(^3\) demonstrated Type B (42.9%) as the most common type, followed by Type A (35.7%) and Type C (21.4%), respectively. Other origin and path patterns for the ILA were described by Al-Hoqail et al. \(^3\)

In turn, Tansatit et al. \(^5\) found that the ILA more commonly originates in the FA, forming common branch with the LMA. In 30.8% of cadavers, the FA sends another small transverse branch of the LMA – from one or both sides – before the formation of the main branch. Pinar et al. \(^10\) and Tansatit et al. \(^5\) found a diameter of roughly 1.3 mm for the ILA.

### RECOMMENDATIONS FOR THE FILLING PROCEDURE

#### General

Lazzeri et al. \(^13\) provide important general recommendations for the use of cutaneous filling substances:

- Prefer using micro cannulas with blunt tips in areas where there is a greater chance of arterial damage, in order to prevent direct injection into the vessel with a conventional needle.
- Move the blunt tip micro cannula gently in order to avoid tearing and to stimulate temporary vasoconstriction of the vessels.
- Choose needles/micro cannulas of a smaller caliber, for although greater initial pressure is necessary to inject the product, this choice favors a lower injection speed and reduces the likelihood of vascular occlusion or blockage of the peripheral flow.
- In order to facilitate the insertion of the cannula, a subcision or pre-tunneling can be performed using an 18G needle. This is safer than carrying out the dissection procedure with the filler substance itself.
- Aspirate before injecting the product in order to verify that the needle/micro cannula is not inserted in an artery or vein.
- Avoid the path of a large caliber (>0.5 mm) artery; alternatively use a 25G cannula parallel to that artery in order to minimize the risk of accidental vascular perforation.
- Inject only small volumes at a time, thereby decreasing the damage, because if a plunger occurs, it will most likely be subclinical.
- Avoid injection of large volumes in less distensible planes, thereby preventing high pressure locally.
• To carry out an anesthetic block and/or topical anesthesia promotes arterial vasoconstriction. This is potentially beneficial due to the fact that it minimizes the risk of perforation or cannulation, which occurs more often in vasodilated arteries.

• Avoid performing the filling procedure associated with other procedures, such as rhytidoplasty and liposuction in the same site, for the risk is higher in tissues that have previously been traumatized.

DeJoseph[4] also offers the following suggestions:

• The fingers of the hand that is not being used to inject must be employed to stabilize the skin and assist the progression of the cannula.

• Less massage is necessary when the filling substance is injected deeply into the tissues.

Recommendations specific to the lips

Tansatt et al.[5] bring contributions to the use of filler to the region of the lips:

• The injection of lips at a depth greater than 3 mm beneath the vermilion can be deemed safe for the projection of the lips.

• The vermilion’s border is a safe area for creating the “cupid’s bow” with 30G microcannulas or 27G needles.

• An injection that is carried out in deeper planes using 27G microcannula, being inserted longitudinally in the middle of the lip with an aim at increasing its volume, can be deemed safe, for the SLA is not usually located in the more central portion of the lip.

• Compression of the SLA at about 1 cm above the oral commissure, a point at which it passes near the oral angle, is recommended.

• Injection in the border of the lower lip is safer. The ILA’s path runs close to the alveolar border, outside the lower lip’s vermilion. Most labial branches cross into the vermilion perpendicularly, and the marginal arteries that connect with these terminal branches in the vermilion are of a very small caliber. In about only 4% of cases the ILA assumes an aberrant path, running more superiorly and much closer to the vermilion.

THE PHYSICS OF FILLING SUBSTANCES

For a better understanding of the practical parameters, such as the pressure exerted on the syringe’s plunger, the effect of the caliber of the microcannula’s/needle’s length and the product’s viscosity, it is important to briefly discuss the dynamics of fluids.

Through the contributions of outstanding researchers, such as Bernoulli and Darcy–Weisbach, a behavioral equation was formulated for an ideal incompressible fluid in linear flow (in the absence of turbulence and/or vortices) in a circular pipe.14 In the present paper, the fluid being analyzed is the cutaneous filling substance.

\[ P = f \times \frac{L}{D} \times \frac{V^2}{2g} \]

where:

- \( P \) = pressure exerted in the syringe,
- \( f \) = Darcy–Weisbach’s friction factor,
- \( L \) = pipe’s length,
- \( D \) = pipe’s diameter,
- \( V \) = fluid’s speed within the pipe (m/s), and
- \( g \) = local acceleration due to gravity.

The equation shows that the diameter of the needle/microcannula and the syringe has a direct effect on the amount of pressure required to promote the filler’s flow. It also shows that greater pressure is needed to make the filler flow through a smaller caliber and for longer distances.

In addition, the friction factor is closely related to viscosity. The denser the filler the greater the pressure gradient required in order for it to flow. The use of Darcy–Weisbach’s equation allows the immediate understanding of important variables applied to the cutaneous filling technique.

DETERMINING FACTORS OF VASCULAR OCCLUSION

The literature describes the considerably intuitive fact that the injected volume directly influences the severity of vascular occlusion.5 Other factors are also determining: The artery’s diameter, the degree of vasoconstriction, the applied pressure gradient, the blood flow through the anastomotic network (toward the eyes or the mouth), and the size of the puncture made in the artery’s wall (in the absence of direct channeling via the needle) are hemodynamic conditions that influence the degree of vascular occlusion. There are a variety of filling techniques: serial and linear punctures, injections in deposit or in layers, and their variants.15 Since they influence the manner and the amount of injected product, as well as the tissular damage in the filled region, it is reasonable to consider the role of these techniques in the occlusion process.

FINAL CONSIDERATIONS

As a part of the aging process—which is aggravated by the effects of gravity—there is a widening of the cutaneous portion of the upper lip (an increase in distance between the nasal base and mucocutaneous transition line) and a decrease in its thickness. Furthermore, the process includes philtrum deletion, reversal of the vermilion, an obstructed view of the incisor teeth during major facial incursions, and a horizontal flattening of the vermilion. Perioral wrinkles arise concomitantly.

In 2008, according to data from the American Society of Plastic Surgery, 1.26 million treatments with hyaluronic acid were performed, 123,000 with apatite hydroxide, 58,000 with collagen, and about 32,000 with poly-L lactic acid. It is believed that these statistics are underestimated, as a result of the fact that only dermatologists, plastic surgeons, and otorhinolaryngologists with recognized qualifications were included.10

The widespread use of these techniques, combined with potential complications due to poor practice, justifies the need for prior in-depth knowledge of the anatomy of the area to be treated. Such conduct is expected in order to prevent serious
diseases, including acute vascular occlusion.

The anatomical focus of this lip’s topography has other implications, even for surgical planning, transcending its purpose related to the best use of fillers. For example, the recognition of the possibility of anatomical variation of the SLA, with unilateral origin, has a predictive value for the survival of single-pedicled axial flaps, such as the Estlander, McGregor, and Abbe among others, widely used in the treatment of lip carcinomas.3

The wide variety of anatomical presentations revealed by the various studies carried out with cadavers have shown that the vessels of the labial region have numerous individual configurations. Alterations in the diameter, path, dominance, and symmetry were found in a series of analyses of cadavers.8, 5, 6, 7, 10 It is important to recognize the relevance of the data contained in the basic sources of anatomy for the advancement of learning. Nevertheless, given its impact on daily practice, it becomes impossible to disregard these relevant anatomical variations.

Avoiding intersections with the path of the lip’s vessels is of great importance.3 Regarding the ILA, the recognition of the types proposed by Kawai et al.12 allows for the best choice of the needle/microcannula’s insertion, as well as the identification of its possible path (Figure 5). Although with less apparent variations, such reasoning also applies to the SLA in the upper lip.

Another anatomical peculiarity mentioned is in regards to the region of the philtrum. The understanding of the philtrum’s anatomy is valuable, since this area is subject to many cosmetic procedures, such as cutaneous fillings. It is possible to observe that this region’s arteries are superficial to the orbicularis oris muscle, in a symmetrically opposite location regarding the SLA (Figure 4).13 This superficial layout explains the common occurrence of bleeding verified when performing a filling of the philtrum’s pillars.

In fact, it is believed that alterations resulting from angiogenesis in the philtrum have participation as a causal or predisposing factor of congenital lip defects, including the cleft lip.11

Regarding complications, the formation of a centralized database containing essential information, such as topography, product type, injected volume per region, complications observed, and duration and reversibility of complications would be of great statistical value. Medical specialty societies could promote such an initiative, encouraging the dissemination of statistical results obtained from their analysis, which would guide professionals to act based on the best evidence of these complications.

The damage or vascular occlusion caused by fillers is rare, however it can be poorly reported or not recognized, which interferes with an accurate reporting of its prevalence.7 This reinforces the recommended creation of the database. Diagnosis and early management are challenging. The vascular injection occurs when the filling substance causes the vessel’s occlusion. Another possible form of vascular occlusion results from the increased external pressure exerted by the volume of the filling substance, paralyzing the blood flow. Such occlusion can be arterial or venous, with the first being described as being associated with sudden and intense pain, leaving the skin pale or purplish in color. Another possibility is induced and persistent vasospasm.4, 17

It is worth noting that the diameter of the main arteries in the lips is large enough to allow the implementation of microsurgical anastomoses.1 Their dimensions can be greater than that of the diameter of the needles/microcannulas, making intra-arterial injections physically feasible. Regarding the microcannulas, it is interesting to note that, if on the one hand a 25G cannula allows for the injection of a greater quantity of the substance in bolus, on the other hand its larger caliber implies a lesser risk of causing a perforation in the arterial wall when compared to a thinner cannula, such as 30G.3

The embolization of the retinal artery causes blindness.13, 17 In a review of cases of blindness, fat was the most commonly used type of filling substance, and in fact, occurred when the filling procedure was carried out in the lower third of the face. A case of temporary loss of visual acuity was described with the use of corticosteroid in the scalp for the treatment of alopecia areata, and other cases of blindness linked to the use of intranasal injections and in angiomatous. That study did not conclude that blindness resulted from the use of artificial fillers used only in the lip region – however it should be noted that, despite this conclusion, it does not mean that it cannot happen. Finally, the authors warn about the threat of such a situation and the high probability of permanent sequel, even when all necessary measures are taken.13, 17

Although they did not provide a mathematical exemplification, Lazzeri et al.13 found that a shorter distance from the retinal artery’s origin implied a greater risk of blindness. This correlation can be easily verified by the Darcy-Weisbach’s equation, which shows that less pressure is needed when the vessel’s length is shorter, unfortunately making the occurrence of this condition easier. It is also important to note that the degree of exerted pressure can be intense to the point of promoting the retrograde flow of the filler up to the internal carotid, a point at which cerebral embolization would take place. This represents a situation with even more serious consequences, and whose symptoms will depend on the involved area of cerebral ischemia.17, 18

Finally, despite the great diversity of filling techniques, there is no consensus on which would be the best one.19 It is also worth noting that there is no consensus among experts regarding this matter or as to the type of product to be injected into a specific region.20 In consideration of this, well-conducted, prospective studies would be valuable for elucidating these issues.21
REFERENCES


Questions for continuing medical education - CME

1- Regarding labial filling, check the correct alternative:
   a) The filling procedure is extremely versatile, with applications in all alterations resulting from labial aging.
   b) Its use associated with botulinum toxin is absolutely contraindicated.
   c) Embolization is an acute event, however the pain referred always occurs later.
   d) Knowledge of labial anatomy is essential for a successful filling procedure.
   e) Embolization can occur in an artery or vein.

2- Regarding the superior labial artery (SLA), it is correct to state that:
   a) the upper lip’s supply is carried out solely by the SLA.
   b) anatomical variations of the SLA are rarely found.
   c) the distance from the SLA to the labial commissure ranges from 5-9 cm.
   d) the SLA’s path is anterior to the orbicularis oris muscle.
   e) the SLA may have a unilateral arrangement.

3- Choose the correct alternative:
   a) The SLA and the right and left ascendant lateral arteries of the philtrum (RALAP and LALAP) have the same position in relation to the orbicularis oris muscle.
   b) The philtrum’s arch is composed of the central artery of the philtrum (CAP), RALAP, LALAP, accessory arteries and left and right oblique arteries.
   c) The CAP is the most important artery for the filling of the philtrum’s pillars.
   d) The SLA is anterior to the orbicularis oris muscle, while the philtrum’s arch’s arteries are posterior to it.
   e) The superficiality of the philtrum’s arch favors the risk of vascular damage.

4- Regarding the ILA, it is wrong to state that:
   a) the ILA can have more than three patterns with respect to its origin.
   b) there is disagreement among authors regarding the most common pattern described by Kawai et al.
   c) the ILA’s diameter may be greater than 1 mm.
   d) the ILA’s origin is at the level of the labial commissure, with a path similar to that of the SLA.
   e) the labiomental artery (LMA) may have vertical and horizontal branches.

5- Regarding the recommendations for the use of filling procedures, it is correct to state that:
   a) the use of the microcannula is sufficient to prevent vascular damage.
   b) aspiration prior to the injection of the filling substance has little use due to the high viscosity of the latter.
   c) prior anesthetic block induced vasoconstriction can have a favorable effect.
   d) the association of the filling procedure with facial liposuction and rhytidoplasty should be encouraged to take advantage of the fact that the patient is sedated.
   e) only vessels of more than 1 mm in diameter are potentially cannalized.

6- Regarding the physics of the filling substances, it is correct to state that:
   a) the Torricelli equation is often used to evaluate the flow of fluids.
   b) the Darcy-Weisbach’s equation can be applied to fluid with turbulence within a non-stationary regimen.
   c) the diameter of the cannula has no effect on the pressure exerted during the filling procedure.
   d) the friction factor depends on the viscosity of the product.
   e) in practical terms, the cannula’s dimensions are irrelevant for the filling procedure.

7- Choose the correct alternative regarding the factors that influence the vascular occlusion:
   a) retroinjection is accepted as the only technique capable of preventing vascular occlusion.
   b) the injected volume has little influence on the occlusion.
   c) the pressure required in order for the injected substance to reach the carotid system cannot be achieved with standard syringes.
   d) blood flow is easily predictable in a network of anastomoses.
   e) the mechanical stimulus generated by the cannula can have a beneficial vasoconstrictor effect.

8- Mark what is true about labial aging:
   a) the deletion of the philtrum is not related to the loss of fat superficial to the orbicularis oris muscle.
   b) in labial aging, filling substances are indicated more often for the correction of the lip’s vermilion, avoiding the necessity of vermilionectomy.
   c) with aging, the reduction of the lower lip is greater than that of the upper lip.
   d) the “gull’s wing” excision technique can be used to correct the widening of the cutaneous portion of the upper lip caused by aging.
   e) the alterations in the alveolar processes do not have an influence on the lip’s appearance.

9- It is wrong to state that:
   a) the apatite hydroxide-based filler is the second most used filling substance.
   b) statistics regarding the total number of filling procedures performed are underestimated.
   c) the lip’s anatomy varies among individuals and influences the results of filling procedures.
   d) anatomical variations do not have an influence on the viability of labial flaps.
   e) alterations in the diameter, path, symmetry, and dominance are found in studies with cadavers.

10- Is it true that:
    a) the Darcy-Weisbach’s equation does not help in understanding how the pressure and the dimensions of the vessels take part in acute vascular occlusion.
    b) due to the fact that it is autologous, fat decreases the risk of embolization.
    c) embolization in the carotid system cannot be achieved with standard syringes.
    d) the use of cannulas prevents the patient from developing blindness.
    e) it would be interesting if the medical specialties societies had a database documenting the risk of complications and which practices were adopted.

Gabarito

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

As respostas devem ser encaminhadas diretamente pelo site www.surgicalcosmetic.org.br.
A data limite para responder ao questionário constará por e-mail que será encaminhado com o link direto para acessar a revista.
ABSTRACT

**Introduction:** The treatment of keloids and hypertrophic scars are an everyday challenge for the dermatologist. Despite the existence of a large therapeutic armamentarium, a variable rate of effectiveness, side effects, and recurrences make it difficult to achieve satisfactory results. As an isolated or in-combination therapy, 5-fluorouracil has the potential to be a part of the treatment paradigm for keloid and hypertrophic scars.

**Objective:** To evaluate, during 12 years, the outcomes of the use of 5-FU (50 mg/ml) in a ratio of 9:1 with triamcinolone acetonide (20 mg/ml) in patients bearing keloids and hypertrophic scars.

**Methods:** Retrospective study of 32 patients with keloids, hypertrophic scars, and cicatricial fibrosis who underwent 1 to 17 intralesional injections of a combination of 5-FU and triamcinolone acetonide in fortnightly intervals. A visual analog scale (VAS) was employed to evaluate the pain/discomfort caused by the lesion, as well as to assess the patient’s perception of the scar when seeing it in the mirror.

**Results:** In the comparison of the visual analogue scales (VAS) after the treatment, there was a significant reduction in the level of pain/discomfort (VAS pain) \((p = 0.001)\) and in the assessment of the scar’s appearance in the mirror (VAS mirror) \((p <0.001)\). Three patients \((9.4\%)\) had complications: hyperchromia \((two \text{ patients} = 6.3\%)\) and atrophy \((one \text{ patient} = 3.1\%)\).

**Conclusions:** 5-FU injections in hypertrophic scars, keloids, and fibroses was found to be a minimally invasive, cost effective, and easily reproducible therapeutic approach with consistent results, which does not invalidate or preclude other techniques.

**Keywords:** cicatrix, hypertrophic; fluorouracil; keloid

RESUMO

**Introdução:** Queloides e cicatrizes hipertróficas fazem parte do desafio cotidiano do dermatologista. Apesar do grande arsenal terapêutico, a eficácia variável, os efeitos colaterais e as recidivas dificultam atingir resultado satisfatório. O 5-fluorouracil (5-FU) isoladamente ou em terapias combinadas tem potencial para ser parte integrante do paradigma do tratamento de cicatrizes hipertróficas e queloides.

**Objetivo:** Avaliar os resultados do uso de 5-FU \((50\text{ mg/ml})\) na proporção de 9:1 com acetato de triamcinolona \((AT – 20\text{ mg/ml})\) em pacientes com queloides e cicatrizes hipertróficas ao longo de 12 anos.

**Métodos:** Estudo retrospectivo de 32 pacientes portadores de queloides, cicatrizes hipertróficas e fibrose cicatricial submetidos de uma a 17 sessões de infiltração com intervalo quinzenal, utilizando-se a combinação de 5-FU com AT. Empregou-se escala analógica visual \((EAV)\) para avaliação de dor/disconforto da lesão, assim como para a percepção pelo paciente da cicatriz ao visualizá-la no espelho.

**Resultados:** Na comparação das escalas analógicas visuais \((EAV)\) após o tratamento, houve redução significativa do nível de dor/disconforto \((EAV \text{ dor}) \((p = 0.001)\) e na análise da estética da cicatriz ao espelho \((EAV \text{ espelho}) \((p <0.001)\). Três pacientes apresentaram complicações \((9.4\%)\): hipercromia \((\text{dois pacientes} = 6.3\%)\) e atrofia \((\text{um} = 3.1\%)\).

**Conclusões:** A infiltração de 5-FU em cicatrizes hipertróficas, queloides e fibroses mostrou-se abordagem terapêutica minimamente invasiva, de baixo custo, de fácil reproduibilidade, com resultados consistentes e que não invalida ou impede outras abordagens.

**Palavras-chave:** cicatriz hipertrófica; fluorouracila; quelode
INTRODUCTION

Scars are the result of a natural physiological process of skin repair after injury. When an imbalance occurs at some stage of this process, keloids or hypertrophic scarring may occur which, in addition to being unsightly, often cause pruritus, pain, and contractures. Therefore, excessive scarring can dramatically affect an individual’s quality of life, both physically and psychologically, stimulating the search for a treatment. 1, 2

There are marked clinical and histological differences between keloids and hypertrophic scars. A keloid is characterized by an excessive growth of the dense fibrous tissue extending beyond the original borders of the wound, which does not regress spontaneously; tends to recur after excision, and affects up to 16% of the population having African ancestry. 1 Some authors define keloids as “confused scars that do not know how to stop growing.” 3 On the other hand, hypertrophic scars can occur in up to 70% of surgical scars and are equally uncomfortable, but remain confined to the borders of the lesion and tend to regress spontaneously in a few years. 1

The proliferation and migration of fibroblasts have a major role in cutaneous healing. The main function of fibroblasts is the synthesis of collagen, proteoglycans, and elastin. Keloids and hypertrophic scars remain in the proliferative phase for a longer period, leading to exacerbated extracellular matrix deposition. 4

Evidence suggests that a propensity for the formation of keloids is autosomal dominant, autosomal recessive, or X-linked with a recessive pattern of inheritance. Nevertheless, the exact incidence and its genesis remain uncertain. 5

Hypertrophic scars and keloids can result from almost any cutaneous trauma, such as acne, burns, minor cuts from shaving, ear or body piercings, or surgical scars. Treatment of keloids can be quite frustrating to both the dermatologist and the patient, for they have a high recurrence rate, as a result of the fact that the new wound will be prone to the same genetic, immunological, biochemical and mechanical mechanisms as the initial wound. 6-8

Literature reports indicate a recurrence rate ranging from 45–100% when the simple excision of keloids is performed. When associated with intralesional injections of corticosteroids, total recurrence falls to a level between 37–50%. The association of radiotherapy minimizes this level to 10% in the first 48 hours of the post-operative period. 9-10 One study showed that electron beam irradiation is superior to betatherapy for the treatment of operated keloids, due to better distribution in the tissue. 11

Cryosurgery uses repeated cooling and heating of the tissue, inflicting vascular damage that leads to anoxia and, ultimately, to cell death. The success rate reported in studies in which as much contact as liquid nitrogen spray were used ranged from 32– 74% after two or more sessions, with better responses in hypertrophic scars when compared to keloids. Its use, however, is limited to small scars. The main adverse effects are hypo- or hyperpigmentation, blistering, and post-operative pain. 12-14 More recently, an intralesional needle adapted to the cryosurgery device showed increased efficacy when compared to the contact/spray treatment, providing a shorter reepithelialization period. 15

Several studies have investigated antineoplastic agents and there seems to be a marked improvement in recurrence rates, patient satisfaction, and overall quality of scars when these agents are used. Intraloesional injection and/or irrigation with interferon α2b, interferon-γ, mitomycin-C, bleomycin or 5-FU seems to have a positive effect in the reduction of pathological scars. There is plenty of evidence that these drugs used in isolation or in combination therapies have the potential to be an integral part of the paradigm for the treatment of hypertrophic scars and keloids. 16

Mitomycin has been highly effective for topical use after the shaving of keloids. 17

Some authors suggest that novel therapies do not hit the target when it comes to the treatment of pathological scarring, leading to worse than expected results. They propose that mTOR (mammalian target of rapamycin) be used as the new target for blocking fibroproliferation. In a study containing the analysis of the fibroblasts’ genome, hypertrophic scars and keloids showed an exacerbated expression of collagen type I and II, which was effectively neutralized by the use of rapamycin. 18

Bleomycin sulfate is an antineoplastic agent that directly inhibits collagen synthesis by decreasing the stimulus via TGF-β1. It was first studied in 1990 as a scar reducing agent. After three to five intraloesional bleomycin injection sessions during one month, the authors observed a keloid reduction rate of 69.4%. Subsequent studies revealed similar results, with a significant improvement in the height and flexibility of keloids and hypertrophic scars, as well as a reduction of erythema, pruritus, and pain. Occasionally there was hyperpigmentation and dermal atrophy. Due to its toxicity, it is necessary to be on the lookout for side effects, although they are typically uncommon. Clinical studies on its effectiveness and additional investigations are needed before it can be included in treatment protocols. 19

Corticosteroids inhibit the healing process in three ways: i) by suppressing local inflammation through the inhibition of the migration of leukocytes and monocytes, and phagocytes; ii) because they are potent vasoconstrictors that reduce local oxygenation; iii) because their antimitotic effect inhibits keratinocytes and fibroblasts, thereby reducing re-epithelialization and new collagen formation. For these reasons, the intraloesional injection of corticosteroids is often related to the atrophy of the scar and surrounding tissues, telangiectasia formation, and a high rate of recurrence. 19

One antineoplastic drug of the pyrimidine analogs class is 5-fluorouracil (5-FU), which is capable of inhibiting the biosynthesis of pyrimidine nucleotides or mimic natural metabolites, thereby interfering with the synthesis of nucleic acids. It effectively inhibits both the thymidylate synthesis (which is an essential precursor of DNA synthesis for cell division) and the processing of RNA and protein synthesis. 20 These characteristics lend it an important role in the treatment of malignant tumors of epithelial origin, such as the colorectal tumor, 4 and in the topical treatment of premalignant skin lesions, such as actinic keratosis. 7 For characteristically inhibiting the proliferation of

fibroblasts, having a wide therapeutic window, and being easy
to handle, it has been used since 1990 in surgeries for glaucoma
filtering (in which exacerbated healing can compromise the sur-
gical outcome) \(^{21-22}\) and in the repair of the flexor tendons of the
hand (since excessive scarring often causes adhesions and limits
functional results). \(^{21-25}\)

In 1999, Richard Fitzpatrick published a review article in the journal
Dermatologic Surgery with a description of his nine
years of experience using 5-FU in more than a thousand pa-
tients with sequelae of hypertrophic scars and keloids resulting
from surgery, acne, and burns. His observation was subjective,
however the incidence of positive results and patient satisfaction
were noteworthy and have yielded 258 citations of his article
to date. Fitzpatrick noted that not all injection sessions resulted
in an obvious clinical improvement, however it was rare that
scars did not respond favorably. In general, the more inflamed,
more symptomatic, more firmly hardened and red scars respond-
ed better. Scars that were several years old and still very firmly
hardened, although not inflamed or symptomatic, responded signif-
icantly less well. With repetitive injections, scars became softer
and more flattened. \(^{26}\)

OBJECTIVE
A retrospective study was carried out to evaluate 5-FU’s
clinical results and complications when used for treating keloids,
hypertrophic scars, and scarring fibrosis, by surveying records
Corresponding to a period of 12 years. The parameters used
were: 1) photographic comparison, 2) visual analog scale (VAS)
to assess the intensity of pain and/or spontaneous discomfort, 3)
patients’ self-assessment of the aesthetic impression of their le-
sions, also through VAS.

METHODS
A survey of the records of 44 patients was carried out
at the Plastic and Reconstructive Hand Surgery of the 11º
Enfermaria da Santa Casa da Misericórdia do Rio de Janeiro
(2003-2004) and at one of the author’s private practice (LDM
2003-2014). The patients had undergone treatment for keloids,
hypertrophic scars, and scarring fibrosis, with intralesional injec-
tions of 5-FU. Of the 44 patients treated, one was excluded due
to complaint of severe pain during the procedure, and a further
11 due to non-participation after the 1st session. The develop-
ment of the lesions ranged from one month to 10 years.

The sample consisted of 32 patients aged from 11 to 73
years (mean age = 39 ± 13.9 years). There was a predominance of
female (71.9%) and Caucasian (78.1%) patients, and hypertro-
phic scars (68.8%), as shown in Table 1.

The four most common body sites were the abdomen (21.9%), breast (15.6%), arm (12.5%) and ear (12.5%), as can be
seen in Graph 1.

The lesions were photographed before, during, and after
the treatment. The analog visual scale (VAS) was used due to the
fact that the authors deemed it easy to understand and use. It was
employed to assess the intensity of pain and/or spontaneous dis-
comfort, and in the self-evaluation of the aesthetic impression of
a patient’s own lesion when visualized in the mirror (VAS pain/
discomfort and VAS “at the mirror”) (Figures 1 and 2).

Another widely used scale that is related to the lesions’
clinical characteristics is the Vancouver scale (Vancouver Scar
Scale – VSS), also known as the Burn Scar Index, which requires
precision equipment for the determination of some measures. \(^{27}\)

The drug was prepared with a mixture of triamcinolone
acetonide and 5-FU in the ratio of 1:9 (0.1-ml of 20-mg/ml tri-
amcinolone for each 0.9 ml of 50-mg/ml 5-FU). The injections

<table>
<thead>
<tr>
<th>Variables</th>
<th>n = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) – mean ± SD</td>
<td>39,0 ± 13,9</td>
</tr>
<tr>
<td>Gender – n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (28,1)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (71,9)</td>
</tr>
<tr>
<td>Race – n (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian/Fair-skinned</td>
<td>25 (78,1)</td>
</tr>
<tr>
<td>African descent/Dark-skinned</td>
<td>4 (12,5)</td>
</tr>
<tr>
<td>Mulatto</td>
<td>3 (9,4)</td>
</tr>
<tr>
<td>Scar type – n (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>22 (68,8)</td>
</tr>
<tr>
<td>Keloid</td>
<td>7 (21,9)</td>
</tr>
<tr>
<td>Retraction fibrosis</td>
<td>3 (9,4)</td>
</tr>
<tr>
<td>Number of sessions – median (P25-P75)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>Injected volume (ml) – median (P25-P75)</td>
<td>1 (1-1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdomen</td>
<td>21,9</td>
</tr>
<tr>
<td>Breast</td>
<td>15,6</td>
</tr>
<tr>
<td>Arm</td>
<td>12,5</td>
</tr>
<tr>
<td>Elle</td>
<td>12,5</td>
</tr>
<tr>
<td>Inguinal region</td>
<td>9,4</td>
</tr>
<tr>
<td>Face</td>
<td>6,3</td>
</tr>
<tr>
<td>Ankle</td>
<td>3,1</td>
</tr>
<tr>
<td>Jaw</td>
<td>3,1</td>
</tr>
<tr>
<td>Nose</td>
<td>3,1</td>
</tr>
<tr>
<td>Other</td>
<td>12,5</td>
</tr>
</tbody>
</table>

**Tabela 1**: Characteristics of the sample

**Graph 1**: Sample distribution regarding body site

**Figure 1**: VAS – front

**Figure 2**: VAS – back

were performed with 13 mm long needles and 30G internal diameter, and syringes with a 1 ml or 3 ml body, depending on the volume needed for the lesion’s size, in fortnightly intervals up until a clinical and aesthetic satisfaction were achieved or there was an interruption due to mutual decision between patient and physician in a case where the treatment was not considered effective. The median values for the number of sessions and injected volumes was 3 (percentiles 25-75:2-5) and 1 ml (percentiles 25-75:1-1), respectively. The follow-up period ranged from 1 to 8.5 months.

The solution was injected into the tissular mass of hypertrophic scars and keloids and in areas of fibrosis (hardened tissue) up until whitening was achieved with an average volume of 0.05 ml per injection point in the hardened area of the scar. Depending on the lesion’s size, multiple injection points may be necessary. In such cases it is important to attempt to distribute the points with a distance of about 1 cm between them.

Statistical analysis
Quantitative variables were expressed as mean values and standard deviations or medians and interquartile range. The normality was assessed using the Shapiro–Wilk test.

The Wilcoxon test was used to compare pre- and post-treatment results. The correlation between the continuous variables was assessed using the Spearman’s rank correlation coefficient. In the comparison between groups, the Mann–Whitney U test and Kruskal–Wallis tests were applied.

The significance level was 5% (p ≤ 0.05), and analyses were performed using the SPSS version 21.0 software.

RESULTS
In the visual analogue scales (VAS) comparison after treatment, there was a significant reduction in spontaneous pain levels associated with lesions (VAS pain) (p = 0.001) as well as in the scar’s aesthetic analysis when evaluated in the mirror (VAS mirror) (p <0.001), as presented in Table 2.

The changes in the VAS scales after the treatment, according to the type of scar are shown in Table 3 showed no significant difference between the diverse types of scarring (p>0.20).

There was no statistically significant correlation between age, gender, scar type, location, and number of sessions and injected volume, with the decrease in the levels of both pain and mirror-based evaluation (p> 0.10).

The seven patients with keloids had both clinical and aesthetic improvements. (Figure 3) Of these, one returned after six years presenting recurrence. The two patients who had serious sequelae from burns and presented fibrotic scar retraction in the neck, hands, and armpit areas that caused a restriction of motion amplitude, had an important improvement in the range of motion and functionality for everyday activities, and a decrease in discomfort/pain (Figure 4).

Of the 22 Caucasian patients with varied hypertrophic scars (Figures 5 and 6), only one did not show satisfactory clinical or aesthetic improvement. The three who had cicatricial fibrosis had improvement (Figure 7).

Complications or adverse events
All patients improved spontaneously in six months to one year.

Three patients had complications (9.4%): two had hyperchromia (6.3%), and one atrophy (3.1%) (Graph 2). Pain, burning, or burning sensation was constant in 100% of cases during application, but with different intensities. However there were no reports of persistence of these symptoms in the hours or days that followed the infiltration. Regional erythema was frequent, but also receded spontaneously after a few hours.

DISCUSSION
Despite the variety of treatment options, such as retinoids, irradiation, intralesional corticosteroids, cryosurgery, silicone gel, pressure, surgery and new modalities like pulsed dye laser, interferon α2b and other antineoplastic agents, there is great difficulty in treating cicatricial lesions. The effectiveness, as well as side effects of these treatments, is variable. 28

---

**Table 2: Pre-/ post-comparison**

<table>
<thead>
<tr>
<th>VAS</th>
<th>Pre Median (P25 to P75)</th>
<th>Post Median (P25 to P75)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>0 (0 to 4)</td>
<td>0 (0 to 0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mirror</td>
<td>7 (6 to 8)</td>
<td>2 (0 to 4)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*p* Wilcoxon test

**Table 3: Assessment of change in VAS levels following treatment, by scar type**

<table>
<thead>
<tr>
<th>VAS</th>
<th>Hypertrophic Median (P25 to P75)</th>
<th>Keloid Median (P25 to P75)</th>
<th>Fibrosis Median (P25 to P75)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>-4,5 (-6 to -3)</td>
<td>-2 (-2 to 0)</td>
<td>0 (-4 to 0)</td>
<td>0.948</td>
</tr>
<tr>
<td>Mirror</td>
<td>-4,5 (-6 to -3)</td>
<td>-4 (-5 to -3)</td>
<td>-7,5 (-8 to -4)</td>
<td>0.291</td>
</tr>
</tbody>
</table>

*p* Kruskal-Wallis test

---

_Figures_ A. Retroauricular keloid before the treatment; B. Retroauricular keloid after the treatment.

---

Figure 4:
A. Decreased amplitude of motion due to keloid in the right axilla; before the treatment; B. Improved amplitude of motion after the treatment

Figure 5:
A. Hypertrophic facial scars after deep peeling, frontal view, before the treatment; B. Hypertrophic facial scars after deep peeling, right hand side view, before the treatment; C. Hypertrophic facial scars after deep peeling, frontal view, after the treatment; D. Hypertrophic facial scars after deep peeling, right hand side view, after the treatment

Figure 6:
A. Hypertrophic scarring following facial lift, before the treatment; B. Hypertrophic scarring following facial lift, after the treatment

Most literature reports on the use of 5-FU injections involve cases that were carried out in keloids. There were no descriptions of its use in patients with cicatricial fibrosis, therefore the three cases described in the present study were the first to be published. In the two patients with keloid and retraction due to burn sequel, the greatest benefit was the increase in the amplitude of motion and improved joint function. Normally, these results would only be obtained with extensive surgery and rotation flaps or skin grafts.

The cases with the greatest satisfaction index were those involving hypertrophic scars with few local symptoms, since there was an improvement of the erythema and a flattening of the scar, which compares to Fitzpatrick’s findings. Nevertheless, these outcomes were not statistically significant in the present study. This may have been due to the fact that most patients present with hypertrophic scars.

Patients with fibrosis also noticed that the tissue became looser and that the fibrosis’ retraction decreased considerably. In these cases, one very rewarding outcome was that of a patient whose nipple had retracted after surgical placement of breast implants. Another was that of a significant retraction of a scar following an appendectomy. However the most interesting case was that of a patient who developed a considerably hard fibrosis in the mesogastrium (7 cm x 6 cm), after an abdominal liposuction. As the series of sessions progressed, all lesions invariably softened and were easier to inject, while at the same time the pain of the procedure minimized. All three cases had 100% improvement.

The first signs of response were decreased pain and pruritus, followed by the softening of the scar, flattening, and decreased erythema. For Fitzpatrick, a few scars seemed not to respond when injected once every two to four weeks, nevertheless they dramatically responded to the twice or three times a week treatment. The authors made a decision to proceed with a fortnightly frequency in their patients.

The authors noticed that the hypertrophic scars responded better than the keloids and that the sooner the treatment began the better the scar’s involution, confirming some authors’ findings. There was no emergence of telangiectasia.

Excessive pain may have been the reason that some patients dropped out of the treatment after only one application, however it should be taken into consideration that several cases that were followed up with had a satisfactory improvement after just one application. Several authors have reported pain during infiltration in virtually all patients, except for Apikian, and Goodman, and Sadeghina, who performed local anesthetic blocks before the injection. Fitzpatrick attempted to add 2% lidocaine to 5-FU, hoping to thereby lessen the discomfort, however, as the most significant pain is linked to the acute expansion of a hardened tissue, he deemed it inefficient. He then began testing blends containing 10-mg/ml triamcinolone acetonide, up to a ratio of 1:9, which he considered ideal, with less pain and greater effectiveness. The authors of the present study observed something similar, nevertheless they concluded that the less uncomfortable manner to carry out the infiltration is by skillfully performing a puncture in the chosen point and pushing the syringe’s plunger very slowly so that the tissues distends slowly. Therefore, the smaller the barrel of the syringe, the greater the control that the applicator has over the pressure of the fluid being injected in the skin. Another variable consistent with the drop out rate is that some patients are originally from very disadvantaged communities and may have had difficulty following the treatment plan due to the travel distance or work restrictions.

Apikian and Goodman used 3 mg betamethasone acetate in suspension and 3.9 mg betamethasone sodium phosphate solution at a ratio of 1:4 to 5-FU in both cases. Other authors have used triamcinolone acetate (TA). Gupta, Nanda and Reddy, and Sadeghina used 5-FU without corticosteroids. In
2007, a double-blind study compared patients using only TA and another twenty using TA + 5-FU, demonstrating that the combination was more effective in the treatment of keloids and hypertrophic scars, in a 12-week follow up. 33

The maximum daily dose of 5-FU recommended for rapid infusion in chemotherapy varies from 800 mg 20 to 1.500 mg, 26 according to the opinions of different authors. Assuming that each syringe with a 1 ml barrel and with a proportional dilution of 1:9 contains 45 mg of 5-FU, 18 to 33 syringe-doses would be necessary to achieve the maximal dose. With the exception of extensive lesions due to burns, a dose of 20 mg to 45 mg per session is in general sufficient for the treatment of scars, therefore with a very wide and safe therapeutic window. This fact is also reflected in a significant way by the cost of the treatment. Currently, a 10 ml vial costs about R$ 18.00 (roughly US $6.05, at the time this paper was published), therefore each syringe-dose containing 0.9 ml 5-FU costs R$ 1.62 (roughly US $0.54, idem). The most limiting factor to its use is perhaps having access to the drug. It is usually only available through large distributors of hospital drugs, which make their supply available only for official institutions or wholesale purchase. Alternatively, the drug can be requested at oncology centers.

In 2011, Sadeghina31 used a technique called 5-FU “tattooing”, employing micropunctures, and reported no adverse effects.

The present study’s results are very positive if compared to those previously reported with 5-FU and other isolated ones, such as intralesional corticosteroids injections (50-100%), cryosurgery (60-75%), radiation (72-92%), 585nm pulsed dye laser (57-83%). 39

There were no cases of ulceration in up to 21% of cases, as already reported by the authors. 28

As suggested by Fitzpatrick 26 and Alster, and Handrick, 34 intralesional injections of 5-FU also have the advantage that they can be combined with other treatments, such as intralesional corticosteroids, laser, and cryosurgery, for the optimization of results. This may also reduce the duration of the treatment as well as the side effects related to a prolonged treatment employing just a single therapy.

CONCLUSION

Intralesional injection of 5-FU remain as a safe and effective alternative for the treatment of hypertrophic, fibrous, painful, and unsightly scars or those causing a functional limitation. This is a minimally invasive, cost effective, and easy to reproduce therapeutic approach that has consistent results and does not invalidate or preclude other approaches in case of failure.

ACKNOWLEDGEMENTS:

The authors of the present study would like to thank Dr. Joseph Gervais (Head of Plastic and Reconstructive Hand Surgery of the 11ª Enfermaria da Santa Casa da Misericórdia do Rio de Janeiro), and Dr. Bogdana Victoria Kadunc (S&CD’s Chief/Head Editor) for all the encouragement and support for the publication of this study.
REFERENCES


Efficacy and safety of a topical formulation in patients with Brittle Nail Syndrome: a randomized, single-blind, crossover, controlled study

Eficácia e segurança de uma formulação tópica em pacientes com síndrome das unhas frágeis. Estudo randomizado, cego simples, cruzado e controlado

ABSTRACT

Introduction: A topical cosmetic formulation is currently commercially available for the treatment of Brittle Nail Syndrome, a formulation made up of Equisetum arvense, Methylsulfonyl methane and Hydroxypropyl chitosan. However, the habit of applying nail polish hinders the adherence to treatments that preclude their use.

Objective: To propose a scheme that alternates the use of the formulation five times a week, with nail polish.

Methods: A clinical, single-blind, crossover controlled intraindividual trial was carried out with 38 female patients. The patients’ hands were randomized into two groups (A and B).

Results: From weeks 1 to 8, and from Sunday to Thursday, Group A applied the formulation A while Group B did not undergo treatment. In weeks 9 to 16, Group A suspended the application of the formulation, while Group B began treatment. From Thursday to Sunday Groups A and B had their nails painted. A common nail polish was standardized for both groups. A quantitative score was used to evaluate outcomes and observe the percentage of patients who had improvements greater than 50% and 75%.

Conclusions: The formulation was more effective in controlling the signs of the syndrome when the nail polish was used in the intervals of the applications. The present study allowed the authors to propose a treatment regimen using the formulation 5 times a week, alternating with the practice of painting the nails.

Keywords: nail diseases; nails; products for nails and cuticles

RESUMO

Introdução: Existe no mercado formulação cosmética tópica de Equisetum arvense, Metil sulfonil metano e Hidroxipropil chitosan para tratar a síndrome das unhas frágeis. O hábito de aplicar esmalte cosmético, porém, dificulta a adesão a tratamentos que impeçam seu uso.

Objetivo: Propor esquema alternando o uso da formulação cinco vezes por semana com esmalte cosmético.

Métodos: Estudo clínico, cego simples, cruzado e controlado intraindividual. Participaram 38 pacientes do sexo feminino. As mãos das pacientes foram distribuídas aleatoriamente em dois grupos: A e B.

Resultados: Nas semanas de um a oito, de domingo a quinta-feira, o grupo A aplicou a formulação, e o B não tratou. Nas semanas de nove a 16, o grupo A suspendeu a formulação, e o B iniciou o tratamento. De quinta a domingo A e B pintaram as unhas. O esmalte cosmético comum foi padronizado para os dois grupos. Para avaliar os resultados e observar a porcentagem de pacientes com melhora superior a 50% e 75% usou-se escore quantitativo.

Conclusões: A formulação foi mais eficaz para controlar os sinais da síndrome do que deixar intervalo sem uso de esmalte cosmético. Este estudo permitiu propor um esquema de tratamento usando a formulação cinco vezes por semana, alternando com o hábito de pintar as unhas.

Palavras-chave: doenças da unha; produtos para unhas e cutículas; unhas
INTRODUCTION

Brittle nail syndrome (BNS) is a common complaint. It affects 20% of the general population, and is twice as prevalent in females.1-2 It is characterized by decreased elasticity and increased fragility of the nails. The most common signs are onychoschizia (lamellar desquamation of the free ungual border), roughness (presence of longitudinal ridges, which can be more or less deep), and onychorexis (longitudinal clefts or fragmentation of the nail plate and/or triangular fragmentation of the free ungual border).1,3

Two origins are cited for BNS: idiopathic, or secondary to other skin or systemic diseases.

In idiopathic BNS, when examined under electron microscopy, it is possible to observe an intrinsic or acquired defect in the intercellular adhesion of keratinocytes, as well as a disorganized structure of proteins, lipids, and keratin fibrils in the nail plate.2,3

The nail’s flexibility is determined by its water content (18%) and when this amount is less than 16%, brittleness increases. The lipids present in the nail assist in retaining water. A decrease in the amount of these lipids can promote the manifestation of the syndrome, as occurs after menopause and with exposure to any external agent which leads to water loss. Intercellular junctions between corneocytes seem to be weaker in females. This fragility increases with age, thereby facilitating BNS.2,8

Secondary BNS is associated with several dermatological or systemic diseases, nutritional deficiencies, drug treatments that affect the ungual matrix or nail plate, and occupational factors.2

The treatment takes into consideration several aspects:2,3

• General measures: avoid trauma, contact with irritants, and dryness. The use of glove is recommended in wet environments or when handling aggravating chemicals.
• The research and treatment of systemic or dermatological diseases, as well as nutritional deficiencies in cases of onychorexis.
• The use of emollients containing phospholipids.

In the literature, there are reports of cases of systemic treatment with biotin and topical treatment with tazarotene, however these studies offer a low level of evidence.6-9

Currently there is a commercially available cosmetic formulation (CF) composed of Equisetum arvense, Methyl sulfonyl methane and Hydroxypropyl chitosan. Equisetum arvense (extracted from a plant) is a source of organic silicon. Nails contain 16 mg of silicon dioxide per 100 g, which seems to contribute to their strength and hardness while maintaining stability among keratin fibrils.10 Methyl sulfonyl methane is a natural and bioavailable source of sulfur, which seems to improve the quality and growth of the nail plate.10 Finally, Hydroxypropyl chitosan is a water-soluble film-forming agent and an active principle carrier that promotes the long-lasting adhesion of the nail’s surface, with penetration into the ridges, improving the hydration of the nail plate.10,11

Studies carried out with the daily application of the topical CF for four weeks to treat nail plate alterations of diverse etiologies suggest an improvement of 70-85% in the patients’ onychoschizia, as well as in the ungual fragility (90%) and a 20% reduction in the longitudinal ridges.11 The currently recommended regimen is a daily topical application (in the evening) for at least three months, with the complete suspension of cosmetic nail polish use during that period.

For most patients, BNS is an aesthetic problem. Some, however, have reported changes in their quality of life. In Brazil, due to the cultural trend of frequent use of nail polish, which is associated with femininity, hygiene, and personal care, it is most likely that patients will find it difficult to adhere to the daily use of the CF or to maintenance schemes that prevent the application of conventional nail polishes.

For this reason, even though following the daily application scheme of the CF for the treatment of BNS is the ideal approach, the present study was aimed at proposing an alternate safe and effective application scheme that would reconcile the habit of use of the CF with that of having the nails painted with nail polish.

MATERIALS AND METHODS

• Methodology
A simple blind, crossover clinical trial was carried out with intra-individual control, with a blinded clinical evaluator and histopathologist physician. The study was approved by the Research Ethics Committee of the Hospital do Servidor Público Municipal de São Paulo, in the State of São Paulo, Brazil.

Women bearing idiopathic BNS, between 18 and 65 years old, who signed the free and informed term of consent, were included. Patients were required to have at least two affected nails on each hand. Blood count, ferritin, serum iron, thyroid profile, glucose, and folic acid were requested for all candidates. Patients with any other disease affecting the nails, secondary brittle nail syndrome, hypothyroidism, anemia, polycythemia vera, scleroderma, Darier disease, hypopituitarism, diabetes, neuropathy, peripheral arterial disease, gout, Raynaud’s syndrome, sarcoidosis, psoriasis, alterations in the keratinization, cachexia, and iron deficiency were excluded. Patients who were using antimetabolites, gold, penicillamine, antiretrovirals or systemic retinoids were not included. The use of vitamin supplements, amino acids or any topical product for strengthening nails was suspended four weeks before the beginning of the study.

• Phases and study groups
The hands of each patient were randomly assigned to two groups: one to Group A, and the other to Group B, implying that the patient was her own control.

- Group A
From Week 1 to Week 8: the fingernails of patients in Group A received an application of the CF in the evening, from Sunday to Wednesday. On Thursday, regardless of the time of the day, the patient applied the CF on all nails. Once it dried, the patient applied a coat of nail polish, which remained until Sunday evening.

From Week 9 to Week 16: the treatment with CF was suspended and the isolated use of the nail polish was maintained from Thursday to Sunday.

- Group B
  From Week 1 to Week 8: no applications were carried out from Sunday to Wednesday. The patient applied nail polish on Thursday, removing it on Sunday.
  From Week 9 to Week 16: the fingernails of patients in Group B began receiving the CF, as described for Group A.
  The nail polish, as well as nail polish remover, were standardized for all patients and did not contain formaldehyde or acetone.

The objective of Phase 1 of the study (Week 1 to Week 8) was to assess the CF's efficacy. The objective of Phase 2 (Week 9 to Week 16) was to evaluate the maintenance of the results after the CF had been suspended for Group A. Due to an ethical issue, Group B received the CF between Week 9 and Week 16, in order that both hands were equally treated.

Quantitative score for the clinical evaluation of brittle nail
A quantitative score was created based on Van de Kerkhof et al. proposal. This scale was used at each evaluation visit starting on the day of the patient's inclusion in the study.

The score assessed the onychoschizia, the onychorexis, and roughness for each of the nails and the hands in light of the main signs of BNS. Each nail received an individual score for these three parameters. The sum of the scores for the five fingers for each symptom resulted in three scores: onychoschizia (SDL), onychorexis (SO), and roughness (SR). The total score (TS) of the brittle nail for each hand was calculated as the sum of the three ratings for the symptoms (TS = SDL + SO + SR).

- Scores assigned to each nail
  a. Onychoschizia
     0 = absence of lamellar desquamation
     1 = mild: lamellar desquamation that does not affect the entire free border of the nail
     2 = moderate: lamellar desquamation affecting the entire free border of the nail plate
     3 = severe: total compromise of the free border and up until one third of the nail plate
  b. Onychorexis
     0 = absence of signs of longitudinal ridges
     1 = mild: one longitudinal ridge
     2 = moderate: at least one deep longitudinal ridge
     3 = severe: multiple superficial and deep longitudinal ridges
  c. Roughness of the nail plate
     0 = imperceptible elevations and longitudinal ridges
     1 = mild: some flattened elevations and longitudinal ridges
     2 = moderate: some prominent elevations and longitudinal ridges
     3 = severe: more than 70% of the nail plate with protruding elevations and deep grooves

In order to assess the effectiveness of the treatment scheme, the percentage of patients with an improvement of at least 50% and 75% in the total clinical score (TS) for brittle nail and in the individual scores for each symptom (SDL, SO, SR) were analysed. Phase 2's main objective was to evaluate the maintenance of efficacy eight weeks after the completion of the use of the product, i.e., to compare the outcomes between Week 8 and Week 16 in Group A.

- Histology
  In the enrollment visit, the most affected nail (object-nail) of each hand was selected, and a cross-sectional sample of the free border was collected with the assistance of a nail plier. The same procedure was carried out in Week 8 and Week 16 with the same nail that was selected in the enrollment visit for each hand.
  The samples were analyzed by conventional microscopy. The nail samples were cut with a razor along the longer axis in order for the cut surfaces to be rectified, and were subsequently included as fresh tissue in paraffin blocks. Samples with a 4μm were carried out and stained with hematoxylin-eosin. Histology was not used as a parameter to evaluate the effectiveness of the treatment, but to observe the main findings of the syndrome in the patients.

- Statistical analysis
  In Phase 1 of the study, the treatments were compared using ANOVA models (sources of variation: Group, week, patient, and interaction week versus patient). The residues' normality and homocedasticity were assessed using the Shapiro-Wilk test and a graph plot of predicted and residual values, respectively. Wilcoxon signed-rank nonparametric tests were performed for each week in the case of violations of the model's assumptions. Then, the proportion of patients with improvement in the score of at least 50% and 75% was compared between Weeks 8 and Week 16, for each week in the case of violations of the model's assumptions. The comparison was performed using the McNemar test.

  In Phase 2, in order to assess the continuing efficacy of the treatment, the results of Week 0, Week 8, and Week 16 were compared by ANOVA models or the Friedman test, in the case of violations of the normality of the model's residues. In a second step, the percentage of patients with improvement of at least 50% and 75% was compared between Weeks 8 and Week 16, using the McNemar test. Phase 2's analyses were carried out only for Group A.

  Exploratory data analysis via frequencies, percentages, mean values and standard deviations were performed in order to evaluate the histological data, with graphs having been built for better visualization of the results.

  The confidence level used in the analysis was 95%, and the software employed was the XLSTAT 2013.

RESULT
The study included 38 female patients, whose hands were randomly distributed into Group A and Group B (38 hands each per group). Three patients did not complete the study, hav-
ing denied the occurrence of adverse events when asked about their motives for leaving the follow up course. The mean age of the patients was 49 years (min = 33 years old, max = 63 years old). The results were analyzed according to the improvement achieved in each of the individual parameters (onychoschizia, onychorexis, and roughness) and the brittle nail total score.

**Ongchoschizia**

During Phase 1 of the study (Week 0 to Week 8), Group A had a mean value for onychoschizia that was significantly lower than that of the Group B (ANOVA, p = 0.004) (Table 1). The interaction between week and Group was not significant (p = 0.191), therefore, it was not necessary to compare the groups separately in each week.

During this phase, the proportion of patients with an improvement of at least 50% did not significantly differ between Groups A and B (McNemar’s test, p-value W2 = 0.219, p-value W4 = 0.581 and p-value W8 = 0.180).

Although this difference was not statistically significant, it was possible to notice that the improvement for Group A was greater in all weeks evaluated. At Week 8, 80% (n = 28) of Group A’s hands had clinical improvement greater than 50% for desquamation, as compared to 62.9% (n = 22) in Group B (Graph 1).

Significant differences were found between Week 0, Week 8, and Week 16 for Group A (ANOVA: p-value <0.001). During Phase 2 of the study (Week 9 to Week 16), Group A did not show a significantly different mean value for desquamation at Week 16 as compared to Week 8, while Week 8 and Week 16 had lower mean values than those of Week 0 (Table 1). These results evidenced the maintenance of the treatment’s efficacy throughout the 16 weeks of the study.

The proportion of patients with improvement of at least 50% did not differ significantly between Week 8 and Week 16 (McNemar test, p = 0.688).

**Onychorexis**

There were no significant differences between Groups A and B at Weeks 2, 4, and 8 (Wilcoxon signed-rank; pW2 > 0.999, pW4 = 0.197, pW8 = 0.729).

As this symptom was virtually absent in the sample throughout the study, the percentage of patients with improvement of at least 50% or 75% as compared to Week zero was not calculated. Nevertheless, the percentage of patients with onychorexis did not increase during the study. The Phase 2 analyses were performed only for Group A. No significant differences were found between Week 0, Week 8 and Week 16 (Friedman; p-value = 0.607).

**Roughness**

There were no significant differences between Groups A and B at Weeks 2, 4, and 8 (Wilcoxon signed-rank; p-value W2 > 0.999, p-value W4 = 0.856, p-value S4 = 0.309).

Fifteen hands (39.5%) had a score equal to zero from Week zero for Group A, and 16 hands (42.1%) for Group B.

### Table 1: Scores for onychoschizia. Mean value

<table>
<thead>
<tr>
<th>Group A</th>
<th>Statistic</th>
<th>W0</th>
<th>W8</th>
<th>W12</th>
<th>W16</th>
<th>Δ(W16-W0)</th>
<th>Δ(W16-W8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td>3,7</td>
<td>1,3</td>
<td>1,2</td>
<td>1,3</td>
<td>-2,5</td>
<td>-</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td></td>
<td>2,1</td>
<td>2</td>
<td>2,1</td>
<td>1,8</td>
<td>1,4</td>
<td>1,8</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>3</td>
<td>0,5</td>
<td>-</td>
<td>-</td>
<td>-2</td>
<td>-</td>
</tr>
<tr>
<td>Min</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-5</td>
<td>-4</td>
</tr>
<tr>
<td>Max</td>
<td></td>
<td>10</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>-</td>
<td>-5</td>
</tr>
<tr>
<td>Standard Error</td>
<td></td>
<td>0,34</td>
<td>0,33</td>
<td>0,36</td>
<td>0,30</td>
<td>0,24</td>
<td>0,31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group B</th>
<th>Statistic</th>
<th>W0</th>
<th>W8</th>
<th>W12</th>
<th>W16</th>
<th>Δ(W16-W0)</th>
<th>Δ(W16-W8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td>3,6</td>
<td>1,8</td>
<td>1,1</td>
<td>1</td>
<td>-2,6</td>
<td>0,7</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td></td>
<td>2,2</td>
<td>2</td>
<td>2</td>
<td>1,8</td>
<td>1,8</td>
<td>1,9</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-2</td>
<td>-</td>
</tr>
<tr>
<td>Min</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-7</td>
<td>-4</td>
</tr>
<tr>
<td>Max</td>
<td></td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Standard Error</td>
<td></td>
<td>0,36</td>
<td>0,34</td>
<td>0,35</td>
<td>0,31</td>
<td>0,30</td>
<td>0,34</td>
</tr>
</tbody>
</table>

**GRAPH 1:** Onychoschizia. Percentages of patients with an improvement of at least 50% as compared to W0, per group

**GRAPH 2:** Onychoschizia. Percentages of patients with an improvement of at least 75% as compared to W0, per group

meaning that it was not possible to assess the improvement over time in such cases. For the remaining hands that had some degree of roughness, only 19 could be evaluated both to Group A and Group B, for Week 2 and Week 4; and only 18 for Week 8. The proportion of patients with an improvement of at least 50% did not differ significantly between groups (McNemar test, p-value W2 = 1.000, p-value W4 = 1.000 and p-value W8 = 1.000).

The proportion of patients with an improvement of at least 75% also did not differ significantly between groups (McNemar test, p-value W2 = 1.000, p-value W4 = 1.000 and p-value W8 = 1.000).

Significant differences were found between Week 0, Week 8, and Week 16 for Group A (ANOVA; p-value > 0.001). A significant improvement in the score’s mean value for roughness in Group A at Week 16 was found as compared to Week 0 and Week 8 (Table 2).

The proportion of patients with improvement of at least 50% did not differ significantly between Week 8 and Week 16 (z test for two proportions; p-value = 1.000). The total number of patients with evaluations for both groups in these weeks was 15.

Total score

In the total score, Group A presented a mean value that was significantly lower than that of Group B over the eight weeks (ANOVA, p = 0.008) (Table 3). The proportion of patients with an improvement of at least 50% was significantly higher in Group A than in Group B at Week 4 (McNemar test, p-value W2 = 0.125; p-value W4 = 0.039 and p-value W8 = 0.167) (Graph 3). It is important to note that in Week 8 roughly 66% (23) of the patients showed a clinical improvement greater than 50% in the total score for Group A and 45.7% (16) for Group B.

The proportion of patients with an improvement of at least 75% was a majority in Group A as compared to Group B only at Week 8 (McNemar test, p-value W2 = 1.000; p-value W8 = 0.219 and p-value W16 = 0.77). Significant differences were found between Week 0, Week 8, and Week 16 for Group A (ANOVA; p-value > 0.001). The mean value for the total score in Group A was significantly lower at Week 16 when compared to Week 8 and Week 0. These results evidenced an even greater efficacy of the treatment over the 16 weeks of the study. The factor that contributed to the continued improvement from Week 8 was the improvement in roughness for both groups between Week 0 and Week 16.

The proportion of patients with an improvement of at least 50% did not differ significantly between Weeks 8 and Week 16 (McNemar test, p-value = 1.000). The total number of patients with evaluations for both groups in these weeks was 26.

Histological analyses

Histological evaluations were performed for the hand’s object-nail (most affected) in both groups. The most examined nail was that of the first finger, followed by the fourth and second finger, respectively. The third and the fifth nails presented low percentages for both groups. All 38 participants were assessed for the subject-nail.

It was possible to observe that 81% and 90% of the ob-

<table>
<thead>
<tr>
<th>Group A</th>
<th>Tabela 2: Scores for roughness. Mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>W0</td>
<td>W8</td>
</tr>
<tr>
<td>Mean</td>
<td>2.4</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>2.8</td>
</tr>
<tr>
<td>Median</td>
<td>1.1</td>
</tr>
<tr>
<td>Min</td>
<td>-1.0</td>
</tr>
<tr>
<td>Max</td>
<td>11.0</td>
</tr>
<tr>
<td>Standard Error</td>
<td>0.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group B</th>
<th>Tabela 3: Total score. Mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>W0</td>
<td>W8</td>
</tr>
<tr>
<td>Mean</td>
<td>2.4</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>2.94</td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
</tr>
<tr>
<td>Min</td>
<td>-1.0</td>
</tr>
<tr>
<td>Max</td>
<td>10.0</td>
</tr>
<tr>
<td>Standard Error</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Graph 3: Total score. Percentages of patients with an improvement of at least 50% as compared to W0, per group

surgical 07 ntingles.indd 30  30
surgical 07 ntingles.indd 30
22/06/15 10:33
ject-nails in Group A and Group B, respectively, showed fragmentation of the nail plate. This finding varied very little in Week 8 and Week 16 for both groups.

**Adverse Events**

No adverse events were reported related to the product under investigation during the clinical study.

**DISCUSSION**

In the present study it was possible to observe that the most frequent symptom was the onychoschizia, found in all patients, followed by roughness, present in 60% of the sample. The presence of onychorexis was rare in this sample of patients, which is why the results were not conclusive in evaluating the product’s effectiveness with this particular symptom. However, none of the patients with this event worsened during the study, while the prevalence of onychoschizia in the sample remained stable. The most affected nail was that of the first finger, followed by the nails of the fourth and second fingers.

At present, the evaluation of BNS is clinical. Microscopic alterations described in the literature were observed by electron microscopy. However, this method is expensive and impractical. For this reason the authors decided to observe and describe the findings of conventional microscopy in the studied sample. Before the beginning of the treatment, nail fragmentation was observed in all samples through hematoxylin–eosin staining. The authors initially considered that this could clinically correspond to onychoschizia. However, despite the clinical improvement of onychoschizia, histological nail fragmentation did not change. One hypothesis is that this fragmentation could be caused by a technical device in the cutting of the blocks.

During the first eight weeks, there was significant improvement in onychoschizia and ungual roughness for both groups, for which the proportion of patients with improvement higher than 50% was similar. It is worth noting that before starting the study all patients used nail polish consistently and without interruption, but that during the study protocol nail polish was only applied from Thursday to Sunday. Thus, due to the fact that contact of the nail plate with aggravating agents such as acetone, formaldehyde and nail polish decreased, this had led to an improvement in the group that did not initially receive the CF. However, the reduction in the mean onychoschizia score and improvement in onychoschizia and ungual roughness for both groups, for which the proportion of patients with improvement of at least 75% was statistically higher for Group A, showing thus the CF’s rapid onset of action. At Week 8 the proportion of patients with improvement of at least 75% was statistically superior to that of the group using CF when compared to the group that did not use the product. Between Week 8 and Week 16, the improvement in the total score for Group A continued even after the cessation of treatment. These results confirmed the CF’s efficacy for the idiopathic BNS’ symptoms, even when the frequency of application decreased to five days per week. The maintenance of benefits after cessation of use could be linked to the prolonged action of the product, as well as to the control exerted over aggravating agents (not using nail polish for some time, nail polish without formaldehyde, and nail polish remover without acetone).

Despite the fact that the ideal treatment for BNS with CF is a daily application for three months, the authors believe that the scheme proposed in this study may be an alternative posology for patients who do not want to stop using conventional cosmetic nail polishes. The maintenance of the benefits after the suspension of the CF observed in the present study suggests that the guidelines for the treatment should go along with those of pulse therapy, alternating treatment intervals of at least two months with a pause in treatment. Nevertheless, further studies are necessary in order to confirm what would be the ideal treatment period.

**Figures 1 and 2** show the development of two patients during Phase 1 of the study.

**CONCLUSION**

In the group of patients involved in this study, the most common symptoms of BNS were onychoschizia and the ungual...
roughness. Changes in the nail care habits, the temporary suspension of the habit of applying nail polish, and the use of fewer aggravating products, without acetone and formaldehyde, led to the improvement of these symptoms. The alternative scheme of five CF applications per week was more effective for the control of BNS symptoms than just reducing the aggravating factors. It was not possible to evaluate the product’s affect on onychorexis in the study’s sample, due to the fact that that symptom was virtually absent.

The present study, therefore, allows for the proposal of an alternative scheme of CF use (five times a week) to reconcile the management of BNS with the habit of applying nail polishes.

REFERENCES

Resurfacing com laser fracionado para cicatrizes atróficas de acne: avaliação na população brasileira

Fractional Laser resurfacing for atrophic acne scars: evaluation in the Brazilian population

ABSTRACT

Introduction: With several treatment options available – including laser – atrophic acne scars are nonetheless difficult to treat. The use of fractional technology results in dermal–epidermal ablation columns, interspersed with intact skin islands, allowing selective thermal damage, effective treatment and faster recovery. The objective of the present study is to demonstrate the efficacy and safety of fractional laser use in the treatment of atrophic acne scars among the Brazilian population.

Methods: An open, prospective, interventional study was carried out with patients with acne scars, without restriction regarding the gender and skin phenotype. Exclusion criteria were: pregnancy, breast-feeding, presence of infections or blood dyscrasias and the use of anticoagulants. The evaluation was performed by comparing texture, appearance, and relief as observed in digital photographs.

Results: Of the 30 selected patients, 24 were included in the study. An improvement was noted in the parameters evaluated in the cases that underwent fractional laser (CO2, Erbium-Glass or both). Individuals who underwent multiple treatments showed better results. All those treated with 4 sessions had improvements greater than 50%. Post-inflammatory hyperpigmentation was detected in 7 of the 24 treated patients.

Conclusion: The present study showed that, when using appropriate parameters and adequate care, fractional laser-assisted resurfacing is an effective and safe method for treating atrophic acne scars in the Brazilian population.

Keywords: acne vulgaris; cicatrix; lasers; chemexfoliation

RESUMO

Introdução: As cicatrizes atróficas de acne são de difícil tratamento, com várias opções terapêuticas descritas, entre elas o laser. A tecnologia fracionada resulta em colunas de ablação dermoepidérmica, entremeadas por ilhas de pele íntegra, permitindo tratamento eficaz, danos térmicos seletivos e recuperação mais rápida. O objetivo deste estudo foi demonstrar em população brasileira a eficácia e segurança dos lasers fracionados na terapia de cicatrizes atróficas de acne.

Métodos: Estudo aberto, prospectivo, intervencionista em pacientes com cicatrizes de acne, sem restrição quanto a sexo e fototipo. Foram excluídos: gestantes, lactantes, portadores de infecções ou discrasias sanguíneas e usuários de anticoagulantes. A avaliação foi realizada por fotografia digital comparando textura, aparência e relevo.

Resultados: De 30 pacientes selecionados, 24 foram incluídos no estudo. Houve melhora dos parâmetros avaliados nos casos submetidos aos laser fracionados: CO2, Erbium-Glass ou ambos. Os indivíduos submetidos a múltiplos tratamentos apresentaram melhores resultados. Todos aqueles tratados com quatro sessões obtiveram melhora superior a 50%.

Conclusão: Utilizando parâmetros e cuidados adequados, nosso estudo demonstrou que o resurfacing com laser fracionado constitui método eficaz e seguro para o tratamento de cicatrizes atróficas de acne na população brasileira.

Palavras-chave: acne vulgar; cicatrix; laser; chemexfoliation
INTRODUCTION

Acne is a common problem among teenagers and affects up to 5% of adults. The scars associated with acne result from the loss of collagen and elastic fibers, whose normal production is impaired during the healing period, due to increased inflammatory activity. Atrophic sequelae are difficult to treat and are classified into distensible and non-distensible scars. The latter can be further sub-classified into superficial, medium, and deep (“ice picks” and “tunnels”). Treatment should be individualized according to each scar type. Some of the described treatment options are: chemical peels, surgical excision, dermabrasion, elevation and/or grafting with punches, dermal filling, and laser resurfacing.

Traditional ablative laser removes all of the epidermis and most of the dermis with excellent outcomes, however with long recovery periods. Fractional technology produces total dermal-epidermal ablation columns, interspersed with islands of intact skin, allowing effective treatment, more selective thermal damage and faster recovery, which occurs from the islands of untouched skin.

The objective of the present study is to demonstrate the efficacy and safety of using fractionated lasers in the treatment of atrophic acne scars in the Brazilian population.

METHODS

An open, prospective, interventional study was carried out at the Hospital do Servidor Público Municipal de São Paulo (HSPM), in 2011. Patients bearing atrophic acne scars, older than 18, without restriction regarding gender and skin phototype, and being treated at the HSPM’s Dermatology ambulatory, were selected for the analysis. Exclusion criteria were: pregnancy, breast-feeding, blood dyscrasias or infection, use of anticoagulant medications or isotretinoin, and a tendency towards keloid formation. Patients who had a history of herpes infection were prophylactically treated with 200 mg acyclovir five times per day for five days. Treatment: 30 minutes before the procedure, cleansing and disinfection with aqueous chlorhexidine solution and topical anesthesia with 4% lidocaine (Dermomax®, Laboratório Aché, São Paulo, Brazil) were performed. The technique consisted of a pass of fractional CO2 laser (Sellas, LGM lasers, São Paulo, Brazil) or Erbium-Glass laser (Sellas Evo LGM lasers, São Paulo, Brazil) per session, in the affected areas, with a minimum overlap of 10%. An immediate post-operative example can be seen in Figure 1, showing the micro thermal zones (MTZ), erythema, edema, and slight exudation in the treated areas. Each session was carried out with an average interval of 60 days. In the post-operative period, the following substances were used: mild soap associated with moisturizing cream for two or three days, sunscreen after the fourth day and whitening cream containing 0.05% tretinoin, 4% hydroquinone, and 0.01% fluocinolone acetoneide from the tenth day.

The clinical response was documented with digital photographs from before and after the procedures. The parameters analyzed were: texture, appearance, and relief. A rating method described in the literature was employed – values from 0 to 3, according to the degree of improvement: 0) less than 25%, 1) 25-50%, 2) 51-75%, and 3) greater than 75%.

RESULTS

Table 1 presents data from all the patients, the parameters used, the number of sessions and the degree of improvement. Of the 30 selected individuals, 24 were included (21 women and 3 men). The mean age was 44.5 years (29 to 60

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age</th>
<th>phototype</th>
<th>Session 1</th>
<th>Session 2</th>
<th>Session 3</th>
<th>Session 4</th>
<th>AE</th>
<th>DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>IV</td>
<td>144/80</td>
<td>144/60</td>
<td>144/60</td>
<td>169/60 E</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>III</td>
<td>144/60</td>
<td>144/60</td>
<td>144/60</td>
<td></td>
<td>Ert</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>IV</td>
<td>169/55 E</td>
<td>169/55 E</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>IV</td>
<td>144/60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>V</td>
<td>144/80</td>
<td>144/40</td>
<td>144/35</td>
<td>PIHP</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>IV</td>
<td>144/60</td>
<td>144/60</td>
<td>144/40</td>
<td>169/60 E</td>
<td>PIP</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>33</td>
<td>III</td>
<td>144/25</td>
<td>169/60 E</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>III</td>
<td>144/80</td>
<td>144/40</td>
<td>169/60 E</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>IV</td>
<td>144/80</td>
<td>144/65</td>
<td></td>
<td>PIPH</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>III</td>
<td>144/85</td>
<td>144/40</td>
<td>144/35</td>
<td>169/60 E</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>34</td>
<td>IV</td>
<td>144/35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>37</td>
<td>IV</td>
<td>144/80</td>
<td>144/60</td>
<td>169/55 E</td>
<td>PIPH</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>47</td>
<td>V</td>
<td>144/80</td>
<td>144/65</td>
<td></td>
<td>PIPH</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>34</td>
<td>II</td>
<td>169/55 E</td>
<td>144/35</td>
<td>169/65 E</td>
<td>PIPH</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>52</td>
<td>II</td>
<td>144/80</td>
<td>144/60</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>30</td>
<td>III</td>
<td>144/60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ert</td>
</tr>
<tr>
<td>17</td>
<td>40</td>
<td>V</td>
<td>144/60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>18</td>
<td>32</td>
<td>V</td>
<td>144/80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>19</td>
<td>34</td>
<td>IV</td>
<td>144/80</td>
<td>144/35</td>
<td>169/55 E</td>
<td>Ert</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>39</td>
<td>III</td>
<td>169/55 E</td>
<td></td>
<td></td>
<td>Ert</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>60</td>
<td>V</td>
<td>169/80 E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>22</td>
<td>40</td>
<td>III</td>
<td>144/80</td>
<td>144/60</td>
<td>144/40</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>30</td>
<td>III</td>
<td>144/80</td>
<td>144/60</td>
<td>144/40</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>29</td>
<td>IV</td>
<td>144/60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PIP</td>
</tr>
</tbody>
</table>

The parameters analyzed were: texture, appearance, and relief. A rating method described in the literature was employed – values from 0 to 3, according to the degree of improvement: 0) less than 25%, 1) 25-50%, 2) 51-75%, and 3) greater than 75%.
years old), and there was a prevalence of skin phototypes III and IV (17 of the 24 cases, corresponding to 70.8%). Eight patients (33.3%) underwent one session, 5 (20.8%) underwent two sessions, 7 (29.2%) underwent three sessions, and 4 (16.7%) completed all four applications. The average number of sessions was 2 sessions per patient. The mean interval between sessions was 2 months. Most cases (13 cases, 54.2%) were treated with CO2 laser, 3 cases (12.5%) were treated only with Erbium laser, and 8 cases (33.3%) were treated with both devices at different times, with an average interval of 60 days.

The used densities (number of micro thermal zones - MTZ) varied according to the device (CO2 laser: 144MTZ, Erbium-Glass laser: 169MTZ), while fluences ranged from 25mJ to 85mJ for CO2 lasers and from 55mJ to 80mJ for Erbium-Glass Lasers), depending on the severity and depth of the scars.

Using the parameters above, the authors obtained improvement of the skin’s relief, texture, and appearance in individuals subjected to CO2, Erbium-Glass, or both lasers. (Figures 2 to 5).

Post-inflammatory hyperpigmentation (PIHP) occurred in 29.2% of cases. No infection, herpes, hypopigmentation or hypertrophic scars were observed. As expected, all patients had mild erythema and edema after the procedure that resolved within three to five days.

DISCUSSION
The present study demonstrated the effectiveness and safety of fractional resurfacing (CO2 and Erbium-Glass lasers) in the correction of atrophic acne scars. The objective was not to evaluate the difference in response between the devices, but the improvement and safety of fractional technology for the correction of scars in Brazilian patients.

Outcomes were better in patients who received multiple treatments. All patients who underwent four sessions showed improvement in excess of 50%, both in texture, appearance, and skin relief. In some cases there was perceptible skin tightening, leading to the improvement of the sagging and fine wrinkles, though the study was not aimed at assessing this outcome. The superior improvement after multiple sessions is also described in the literature.6,7 The recovery was fast and ranged from five to seven days with both lasers, however no comparative data between them have been evaluated. Complications such as infections, hypertrophic scars or hypochromia did not occur. Post-inflammatory hyperpigmentation is a continual concern when procedures are performed in patients with pigmented skin, as is the case for most of the Brazilian population. Despite the fact that most patients in the present study had skin phototypes III and IV, that occurrence was observed in only seven (29.2%) of the 24 patients treated. This response resulted from the careful application of the technique and the decision to perform only one pass per session, which reduced the inflammatory response during the re-epithelization period – an outcome already described by Alster et al.7 The use of a whitening agent during the intervals between sessions also contributes to this result.

CONCLUSION
Using appropriate parameters and application techniques, the present study has demonstrated that fractional resurfacing is an effective and safe method for the treatment of atrophic acne scars in the Brazilian population.

REFERENCES

In vivo and in vitro evaluation of the cutaneous anti-aging efficacy of a product containing vitamin C, fragmented hyaluronic acid, and mannose

Avaliação in vivo e in vitro da eficácia de um produto com associação de vitamina C, ácido hialurônico fragmentado e manose na prevenção do envelhecimento cutâneo

ABSTRACT

Introduction: Skin aging is a complex biological process that is characterized not only by clinical but also cellular alterations. The use of effective topical formulations for reducing and preventing oxidative stress is of utmost importance to delay cellular senescence.

Objective: To evaluate the in vitro and in vivo efficacy of a formulation containing vitamin C, fragmented hyaluronic acid and mannose, in the prevention of skin aging.

Methods: Clinical, subjective, and instrumental evaluations were carried out in 37 women (mean age: 46 years) and in vitro comparative evaluations of a dermal equivalent model contraction.

Results: Statistical improvement was observed in the clinical parameters of hydration, sagginess, brightness, uniformity of skin color and amount of wrinkles after 3 months of treatment. A reduction by 12.6% in the volume of wrinkles 30 minutes after application and by 17.8% after three months of use was also evidenced by instrumental evaluation. There was greater contraction of the dermal equivalent model when compared to a commercial product for wrinkle reduction containing the same active principle.

Conclusions: The product was proven effective in skin rejuvenation, by significantly reducing the amount of wrinkles. The in vitro study showed an increase in collagen synthesis, suggested by the greater activation of fibroblasts in the dermal equivalent model.

Keywords: skin aging; ascorbic acid; hyaluronic acid; mannose

RESUMO

Introdução: O envelhecimento cutâneo é processo biológico complexo que se caracteriza por alterações não somente clínicas como também celulares. O uso de formulações tópicas eficazes no combate e prevenção do estresse oxidativo é de extrema importância para retardar a senescência celular.

Objetivo: Avaliar a eficácia in vitro e in vivo de formulação contendo vitamina C, ácido hialurônico fragmentado e manose na prevenção do envelhecimento cutâneo.

Métodos: Avaliações clínica, subjetiva e instrumental em 37 mulheres (média de idade: 46 anos) e avaliações comparativas in vitro da contração do equivalente dérmico.

Resultados: Melhora estatística nos parâmetros clínicos de hidratação, flacidez, luminosidade, uniformidade do tom e quantidade de rugas após três meses de tratamento. Redução de 12,6% no volume das rugas 30 minutos após a aplicação e de 17,8% após três meses de uso, por avaliação instrumental. Maior contração do equivalente dérmico, quando comparado a produto comercializado para redução de rugas contendo o ativo.

Conclusões: O produto em teste mostrou-se eficaz no rejuvenecimento cutâneo, nas avaliações in vivo. Nos testes in vitro, observou-se aumento da produção de colágeno pela maior ativação de fibroblastos no equivalente dérmico.

Palavras-chave: envelhecimento da pele; ácido ascórbico; ácido hialurônico; manose
INTRODUCTION

According to the Brazilian Society of Dermatology, aged skin is characterized as “thin, inelastic, presenting wrinkles and a deepening of expression lines.” In addition, it is possible to observe decreased hydration, loss of brightness, increased sagging, and uneven hue. Aging occurs both due to genetics or environmental factors and lifestyle habits, such as smoking, unhealthy diet, and lack of physical exercise. During intrinsic cutaneous aging a change in the genetic material takes place, with a decrease in cellular proliferation, which results in the loss of elasticity and the ability to regulate metabolism, in addition to a loss in the replication efficiency of the tissues. Chemical and enzymatic oxidations involving the formation of free radicals accelerate this phenomenon, generating oxidative stress, an effect having as its greatest damage the peroxidation of fatty acids in the cell membrane’s double lipid layer, leading to apoptosis. The skin has its own defense mechanism aimed at avoiding this process. Nevertheless, this mechanism’s protective ability decreases with aging, and exogenous compounds can enhance the natural protection. Anti-aging products are employed in an attempt to minimize these characteristics of aging skin.

Many antioxidants are currently available in cosmetic formulations and medications. The most common are: vitamins C and E, retinoids, resveratrol, coenzyme Q-10, idebenone, lipoic acid and flavonoids, among others. Pure vitamin C, also known as L-ascorbic acid (AA), is vital for the formation of collagen and elastin, increasing the skin’s firmness, and is considered to be highly tolerable. AA is able to stimulate cell proliferation and collagen synthesis by dermal fibroblasts, regardless of patient age. Data indicate that topical application of vitamin C partially restores the anatomical structure of the dermal-epidermal junction in young skin and increases the number of nutritional capillary loops in the papillary dermis (near the epidermal tissue) in the skin of post-menopausal women. Haftek et al. have found significant clinical improvement in the clinical rating of superficial and deep wrinkles, sagging, firmness, uneven texture, and moisture levels in the skin of 20 women after six months of treatment with a dermocosmetic containing AA combined with madecassoside (0.1% stabilized vitamin C and 0.1% madecassoside-Redermic, La Roche-Posay Laboratoire Pharmaceutique, La Roche-Posay, France). These results were obtained by instrumental evaluations of the skin’s elasticity and semiquantitative histological evaluations of the elastic fiber network of the papillary dermis.

Monosaccharides are ingredients widely used in anti-aging products as well. Among them is mannose, a monosaccharide of vegetal origin with a high water retention capacity, which is responsible for the synthesis of glycoproteins. It is able to alter the skin’s light reflection properties, causing an optical smoothing effect. Another active principle that acts on skin rejuvenation is fragmented hyaluronic acid (HA). It is a polysaccharide produced by fibroblasts and keratinocytes, consisting of glucuronic acid and N-acetylglucosamine. It is one of the main substances in the extracellular matrix, in which collagen and elastin fibers are immersed. It has a high hygroscopicity, and is responsible for maintaining the extracellular space and tissue hydration.

Farwick et al. performed tests with HA of different molecular weights (between 800kda and 20kda), having found that 50 kda is ideal for topical use, given that fragmented HA permeates the skin at three times the rate of non-fragmented HA. Due to fragmentation, this active principle is able to act on the skin’s rejuvenation, as well as to provide greater skin hydration, reducing the unwanted effects mediated by Toll-like receptors (TLR), which activate proinflammatory mediators. Thus, it is clear that the topical application of fragmented HA can improve the skin’s hydration and rejuvenation functions due to its ability to penetrate, which is achieved with the decreased size of its molecules.

The active principles vitamin C, mannose and fragmented HA have a proven efficacy in reducing skin wrinkles, homogenization, and hydration. The present study is aimed at investigating whether the association of these active principles can provide an improvement in outcomes and an increase in a product’s anti-aging benefits for patients.

The study evaluated – in vivo and in vitro – the effects of a product containing the combination of these three active principles (5% pure vitamin C, 5% mannose, and fragmented HA) for the reduction of wrinkles and fine lines, in the immediate impression of skin uniformity, in the improvement of skin’s firmness and hydration, and its comparative effectiveness in the contraction of dermal equivalents.

METHODS

In vivo evaluation

A monocentric, blind study was carried out via clinical, subjective, and instrumental evaluations at the Allergia Pesquisa Dermato-cosmética Ltda’s research center, in Campinas (SP), Brazil, from February 14, 2013 to May 22, 2013. It was conducted in accordance with the Declaration of Helsinki’s principles. Having been approved by the Research Ethics Committee of the Irmandade de Misericórdia de Campinas – Hospital Irmãos Penteado, 45 Brazilian women aged 40 to 50 years (mean = 46 years +/- 4.6) were recruited to take part in the evaluation. The volunteers were healthy and did not have active dermatoses in the facial area. They had mild or moderate signs of facial aging, and fell into Groups 2 and 3 according to the Glogau aging scale. They had fine lines, wrinkles, and signs of facial hyperpigmentation corresponding to Fitzpatrick skin phototypes I and III. All volunteers expressed their willingness to participate in the study by signing the Term of Free and Informed Consent (FICT) prior to undergoing any procedures provided by the protocol.

The volunteers used the test product during the study, applying it twice daily to the face for 12 weeks. In order to ensure that the product was being used appropriately, the product containers were weighed at each experimental visit. In addition, daily applications of sunscreen were carried out.

The test product contained 5% pure vitamin C, 5% mannose, and fragmented HA (Redermic Hyalu C, La Roche-Posay Laboratoire Dermatologue, La Roche Posay, France). The as-
Topical vitamin C, hyaluronic acid, and mannose in skin aging

sociated sunscreen was Anthelios AC Cream Gel Dry Touch SPF 30 E PPD 15 (La Roche-Posay Laboratoire Dermatologique, La Roche-Posay, France).

Visits to the research center took place at baseline (T0) and after 28 (T28), 56 (T56) and 84 (T84) days of product use by the volunteers, when clinical assessments were performed by a dermatologist in addition to perceived efficacy and instrumental tests.

The clinical characteristics analyzed with a standardized visual scale (VAS - Visual Analog Scale) were: wrinkles, hydration, texture, sagging, brightness, and hue homogeneity. The perceived efficacy criteria were determined using a standardized questionnaire with categories for: tonicity, comfort, softness, and dryness. The devices used in the instrumental data were: Optical 3D Skin Measuring Device PRIMOS Compact 5.075 (GFMeßtechnik GmbH, Teltow, Germany) and Visia CR (Canfield Imaging Systems, Farfield, United States). They were used for evaluating wrinkles and fine lines in the frontal and lateral region, and for taking standardized photographs, respectively.

Exploratory data analysis was performed (summary tables, graphs, frequencies and percentages). Results from experimental visits were compared using the paired Student’s t-test, with unilateral hypothesis for the instrumental data and via ordinal logistic regression for the efficacy data. The confidence level considered in the comparative analysis was 95%. Software: XLSTAT 2013, STATA 10 and MINITAB 14.

In vitro evaluation

Evaluation of contraction of the dermal equivalents

The in vitro evaluation of the contraction of the dermal equivalents was carried out following the application of the test product, in addition to another commercial product for wrinkle reduction purposes also containing fragmented HA, and the control product.

The method used followed the ISO 10.993-518 international standards, based on the reduction of cellular growth caused by the exposure to a cytotoxic agent, reflected in the number of cells. The degree of growth inhibition, related to the contraction of the test sample, provided an indication of toxicity. The cells were kept in a culture, having been exposed to various concentrations of the test substance. The cultures were visually examined 24 hours after, with the highest tolerated dose (HTD) being estimated and the number of viable cells and/or total cell content determined. The number of cells present in the test substance was compared to that observed in the control, and the percentage of growth inhibition calculated. The concentration of the test sample, which showed a 50% inhibition of cell growth (IC50), was determined and expressed in mg/ml. This value allowed the comparison of the analyzed compound’s relative cytotoxicity. 18

In order to assess the contraction of the dermal equivalent, the following methodologies were also implemented:

- preparation of the dermal equivalent without the presence of glycosaminoglycans (GAGs);
- preparation of the dermal equivalent in the presence of GAGs.

The cell viability calculation – expressed in NRU (Neutral Red Uptake – the measure of the viability of cells in culture) – was performed for each concentration of the test substance by using the average NRU computed from the values of six replicates per test concentration. This value was compared with the average NRU of all the values of the negative control (NC). The relative cell viability was then expressed as a percentage of the untreated control. 19

RESULTS

In vivo evaluation

The results of the clinical trial showed that, according to the evaluation performed by dermatologists, the criteria wrinkle/amount of wrinkles, sagging, texture, hydration, and brightness improved significantly over time (Graphs 1 to 5 and Figures 1 to 3). The comparative results between experimental stages are shown in Table 1.

According to the evaluation of the perceived efficacy, volunteers reported improvement in tonicity, comfort, smoothness, and dryness as can be seen in Table 2.

Based on the instrumental evaluation with the PRIMOS device, it was possible to observe reductions of 12.6% in the volume and 8.3% in the depth of wrinkles 30 minutes after the product’s application. At the T84 measurement (after 84 days of use), there were reductions of 17.8% in the volume of wrinkles and of 10.2% in the epidermis’ undulation (p<0.05) (Figures 4, 5 and 6).

The comparative results between experimental stages are shown in Table 1.

According to the evaluation of the perceived efficacy, volunteers reported improvement in tonicity, comfort, smoothness, and dryness as can be seen in Table 2.

Based on the instrumental evaluation with the PRIMOS device, it was possible to observe reductions of 12.6% in the volume and 8.3% in the depth of wrinkles 30 minutes after the product’s application. At the T84 measurement (after 84 days of use), there were reductions of 17.8% in the volume of wrinkles and of 10.2% in the epidermis’ undulation (p<0.05) (Figures 4, 5 and 6).

The method used followed the ISO 10.993-518 international standards, based on the reduction of cellular growth caused by the exposure to a cytotoxic agent, reflected in the number of cells. The degree of growth inhibition, related to the concentration of the test sample, provided an indication of toxicity. The cells were kept in a culture, having been exposed to various concentrations of the test substance. The cultures were visually examined 24 hours after, with the highest tolerated dose (HTD) being estimated and the number of viable cells and/or total cell content determined. The number of cells present in the test substance was compared to that observed in the control, and the percentage of growth inhibition calculated. The concentration of the test sample, which showed a 50% inhibition of cell growth (IC50), was determined and expressed in mg/ml. This value allowed the comparison of the analyzed compound’s relative cytotoxicity. 18

In order to assess the contraction of the dermal equivalent, the following methodologies were also implemented:

- preparation of the dermal equivalent without the presence of glycosaminoglycans (GAGs);
- preparation of the dermal equivalent in the presence of GAGs.
In vitro evaluation

The in vitro analysis assessed the percentage of retraction (or contraction) of the dermal equivalent that was exposed to the test product and to the HA-containing commercial product for reducing wrinkles. Measurements were taken at 24, 48, and 96 hours of exposure, after an incubation time of four hours (the baseline for the start of the contraction). After 24 hours of exposure, the greatest contraction observed for the dermis treated with 0.01mg/ml test product was that of the control sample. Nevertheless, it was possible to observe 8.36% more contraction.
Table 1: Comparative clinical efficacy results between experimental evaluation visits

<table>
<thead>
<tr>
<th>Attributes</th>
<th>T28 x T0 P-value</th>
<th>T56 x T0 P-value</th>
<th>T84 x T0 P-value</th>
<th>Result</th>
<th>Result</th>
<th>Result</th>
</tr>
</thead>
</table>
| Rugas/Quantidade de rugas | 0,05*            | 0,03*            | 0,03*            | T28<T0< p="">
|                     |                   |                   |                   | T56<T0< p="">
|                     |                   |                   |                   | T84<T0< p="">
| Sagging             | 0,031*           | 0,031*           | 0,030*           | T28<T0< p="">
|                     |                   |                   |                   | T56<T0< p="">
|                     |                   |                   |                   | T84<T0< p="">
| Texture of skin’s relief | 0,009**         | <0,001***        | <0,001***        | T28>T0< p="">
|                     |                   |                   |                   | T56>T0< p="">
|                     |                   |                   |                   | T84>T0< p="">
| Hydration           | 0,001**          | <0,001***        | <0,001***        | T28>T0< p="">
|                     |                   |                   |                   | T56>T0< p="">
|                     |                   |                   |                   | T84>T0< p="">
| Brightness          | <0,001**         | <0,001***        | <0,001***        | T28>T0< p="">
|                     |                   |                   |                   | T56>T0< p="">
|                     |                   |                   |                   | T84>T0< p="">

* 5% level of significance, ** 1% level of significance, *** 0.1% level of significance

Table 2: Percentage of volunteers with improvement in the parameters, according to the perceived effectiveness at experimental evaluation visits

<table>
<thead>
<tr>
<th>EXPERIMENTAL VISIT</th>
<th>T28</th>
<th>T56</th>
<th>T84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonicity</td>
<td>71,1</td>
<td>78,9</td>
<td>83,8</td>
</tr>
<tr>
<td>Softness</td>
<td>94,7</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Comfort</td>
<td>86,8</td>
<td>92,1</td>
<td>92,1</td>
</tr>
<tr>
<td>Dryness</td>
<td>86,8</td>
<td>86,8</td>
<td>92,9</td>
</tr>
</tbody>
</table>

FIGURE 4: Evaluation of the wrinkle volume (Ti) 30 minutes after the first application of the product. Equipment: PRIMOS; Volunteer number 005

FIGURE 5: Evaluation of wrinkle depth (Ti) 30 minutes after the first application of the product. Equipment: PRIMOS; Volunteer number 028

FIGURE 6: Evaluation of the undulation of the epidermis 84 days after the beginning of product use. Equipment: PRIMOS; Volunteer number 036

than in the control for the dermis treated with 0.1 mg/ml. The contraction difference, as compared to the control (untreated dermis), was best seen after 96 hours of exposure. For the dermis treated with 0.01 mg/ml, it was possible to observe a contraction 11.99% greater than that of the control, and the dermis treated with 0.1 mg/ml, a 23.55% greater contraction. These numbers suggest that the test product increased the contraction rate in the treated equivalent dermis as compared to the untreated dermis.

In the dermis treated with the wrinkle-reducing commercial product containing HA, an increase in the contraction rate was observed after 24 hours of exposure. When compared to the untreated control, the dermis treated with 0.01 mg/ml had 3.02% more contraction, while the one treated with 0.1 mg/ml had 7.87% more contraction. On the other hand, less contraction (as compared to the untreated control) could be better observed after 96 hours of incubation. The dermis treated with 0.01 mg/ml had 2.51% less contraction than the control, while the dermis treated with 0.1 mg/ml had 7.77% less contraction. These results suggest that the HA-containing commercial product for wrinkle reduction has a slower contraction rate than that of the control.

Thus, the test product showed greater contraction of the dermis when compared to the control and to the commercial product for wrinkle reduction containing the active principle, which is linked to the increased collagen production (as a result of the increased activation of fibroblasts) (Figure 6 and Figure 7).

DISCUSSION

In vivo evaluation

In the in vivo study, in light of the methodology used to assess the test product’s efficacy, a significant improvement in the hydration, texture of the skin’s relief, and brightness was observed after 28, 56, and 84 days of use. The product promoted the reduction of wrinkles immediately after the application. An increase in the contraction rate was observed after 24 hours of exposure. When compared to the untreated control, the dermis treated with 0.01 mg/ml had 3.02% more contraction, while the one treated with 0.1 mg/ml had 7.87% more contraction.
increase in the skin’s firmness and a reduction of transepidermal water loss were observed after 28, 56, and 84 days of use. The results observed in the present study confirm the already widely proven action of AA in increasing cell proliferation and collagen synthesis by dermal fibroblasts. AA also figures as an essential cofactor in the hydroxylation of proline and lysine, which are necessary for collagen structure and function. The findings on the action of vitamin C in the skin described in the literature corroborate the results obtained in the present study, and can be further supported by the cutaneous effects of fragmented HA and mannose.

Hyaluronic acid is one of the main substances of the extracellular matrix, where the collagen and elastin are soaked. Another HA characteristic is its high binding capacity with the water, contributing to the maintenance of the extracellular space and tissue hydration. These properties make HA a valuable component in anti-aging cosmetic applications. Mannose also has a high hygroscopic capacity due to its molecular structure, preventing transepidermal water loss and, therefore, a mitigating effect on wrinkles and fine lines. In the literature, there is an absence of reports on the associated effect of these three active principles, however the present study’s findings give evidence to their synergistic action on the signs of skin aging.

In vitro evaluation

The first skin equivalent model described in the literature used collagen gel and was proposed by Karasek and Charlton in 1971, and was been developed by Bell et al. in 1979. The resistance of the collagen and its insolubility are obtained through the retraction of the gel, which is obtained by fibroblasts. This process initiates the formation of a living equivalent of the dermis, with a final size that is directly proportional to the number of cells and inversely proportional to the concentration of collagen, meaning that the greater the number of cells, the smaller the area of the dermis.

A significant increase in collagen production was observed in the test product as compared to the control, due to the increased activation of fibroblasts (decrease/contraction of the equivalent dermis). On the other hand, the HA-containing commercial product for wrinkle reduction significantly reduced the contraction of the equivalent dermis when compared to the control. The dermis treated with the test product had greater contraction when compared to the dermis treated with the commercial product for wrinkle reduction containing HA.

The use of skin models reconstructed in vitro, which has the expression of fibroblast as an activity marker, is widely described in literature. The increased activation of fibroblasts and collagen production by the test product is supported by the already described actions of AA and AH in increasing cell proliferation and collagen synthesis, provided by dermal fibroblasts.

CONCLUSION

The active principles vitamin C, mannose, and fragmented HA have proven effective in reducing wrinkles, and in homogenizing and hydrating the skin, however their associated action had not been previously described in the literature. The present study has demonstrated the effectiveness of an anti-aging product containing the three active principles in reducing wrinkles, decreasing the degree of sagging, and improving the hydration, brightness, and hue uniformity of the skin. The results were obtained both in vivo (from clinical evaluations carried out by dermatologist physicians) and in vitro (via the analysis of the degree of contraction of the equivalent dermis). The test product significantly increased the contraction of the equivalent dermis as compared to the control. On the other hand, the HA-containing commercial product for wrinkle reduction significantly reduced the contraction of the equivalent dermis when compared to the control. These findings demonstrate the synergic benefits of active principles in skin rejuvenation.
REFERENCES


The use of 1,340nm ND:YAP laser to treat hidradenitis

Tratamento de hidrosadenite com laser ND:YAP 1340 NM

ABSTRACT

Introduction: Hidradenitis is a chronic inflammatory disease that has a negative impact on the patient’s quality of life but which has few effective therapeutic options. Currently, the use of laser technology has been standing out as a treatment.

Objective: To evaluate the use of 1,340nm ND:YAP laser (Neodimium:Ytrium Aluminum Perovskite) to treat hidradenitis.

Methods: Performing 4 1,340nm ND:YAP laser sessions in 3 patients bearing hidradenitis.

Results: All patients had a clinically and histologically evidenced reduction of inflammatory lesions.

Conclusions: In the present study, the 1,340nm ND:YAP laser was effective in the treatment of hidradenitis, and can potentially become a new therapeutic option.

Keywords: hidradenitis; lasers; laser therapy

RESUMO

Introdução: A hidrosadenite é doença inflamatória crônica que tem impacto negativo na qualidade de vida dos pacientes e poucas opções terapêuticas eficazes. Atualmente, o uso de tecnologias a laser tem-se destacado para seu tratamento.


Métodos: Realização de quatro sessões de laser ND:YAP 1340nm em três pacientes portadoras de hidrosadenite.

Resultados: Todas as pacientes apresentaram redução das lesões inflamatórias evidenciadas clinicamente e histopatologicamente.

Conclusões: O laser ND-YAP 1340nm mostrou-se eficaz no tratamento de hidrosadenite neste trabalho, podendo representar nova opção terapêutica à hidrosadenite.

Palavras-chave: hidradenite; lasers; terapia a laser
INTRODUCTION

Hidradenitis is a chronic and recurrent inflammatory disease that affects flexural areas of the skin, such as the armpits, and the inframammary and groin regions. It is a painful and often disfiguring condition, which manifests after puberty and is characterized by deep inflammatory lesions in the region of the apocrine glands. The prevalence of hidradenitis in the general population is about 1%, affecting more women than men (4:1), and is associated with genetic and hormonal predisposition (androgen excess).2,3,4

Hidradenitis initially emerges as an inflammation around the hair follicle, followed by a series of damaging events that lead to a rupture of the follicular infundibulum, forming deep painful nodules and abscesses that generate fistulas and scarring. This sequence of events tends to be recurrent in most patients.3,5 Thus, hidradenitis may arise in the form of abscesses, folliculitis, pyogenic granuloma, comedones, fistulas, scars, and keloids.6

Given the variety of possible manifestations of this disease, the Hurley’s staging system is used to classify the picture into three stages. During Stage I there are one or more separate abscesses, but an absence of fistulas or scars; in Stage II there are one or more separate abscesses, and scarring and fistula formation; and in Stage III there is a confluence of the lesions with interconnected fistulas and abscesses.1,3 The lesions’ pathophysiology involves both follicular innate immunity defect and hyper-reactivity to coagulase-negative staphylococci.6

Hidradenitis can have significant clinical consequences, but most of all it can negatively affect a patient’s quality of life.1,7 The pain picture, the unpleasant odor, and the scars are all factors that have an impact on patients.4 Despite the importance of a treatment to resolve this condition, the current options are limited, and there is a lack of studies involving safe and effective therapies.2

Pharmacological treatments include topical and oral antibiotics, intralesional corticosteroids, hormone therapy, retinoids, immunosuppressants and biological agents. Surgical treatments vary from drainage and incision procedures to debridement and a wide surgical excision of fistulas and abscesses. Most recently, there have been reports of the use of technologies such as diode laser, CO2 laser, Nd:YAG (Neodinium:Yttrium Aluminum Garnet) and photodynamic therapy with good results in the treatment of hidradenitis.1,3,6,9

Due to the success of some laser types in hidradenitis, the authors sought to evaluate the use of a new technology, the 1,340nm Nd:YAP (Neodinium:Yttrium Aluminum Perovskite). This laser was effective in the treatment of inflammatory acne through the organization of the collagen fibers and reduced inflammatory infiltrate.10 Thus, since it is also a chronic inflammatory disease, the authors sought to obtain positive results in the treatment of hidradenitis with 1,340nm ND:YAP.

METHODS

Three female patients, all bearers of hidradenitis at Hurley’s Stages I or II, who were being treated at the Dermatology Ambulatory of the Faculdade de Medicina de São Jose do Rio Preto (FAMERP), were selected. The patients had already undergone drug treatments without success. They did not use systemic or topical therapy for three weeks and had not undergone previous surgical treatment. The diagnosis of pregnancy was excluded for the three patients. The study was approved by the Research Ethics Committee of FAMERP.

In a prospective study, the patients underwent four 1,340nm ND:YAP laser sessions (Etherea®, Industra Tecnologies Industria e Comércio Ltda., São Carlos, São Paulo, Brazil), with the following parameters: 100mJ, 100mtz and 8mm tip. The interval between sessions was one month. The response to the treatment was assessed through a comparison of photographs taken prior to and one month after the fourth laser therapy session. Two dermatologists unrelated to the study compared the photographs and classified them as follows: 0 – worsening, 1 – lack of improvement, 2 – moderate improvement, and 3 – significant improvement. Each patient’s degree of satisfaction was evaluated based on a rating scale of: 0 – unsatisfied; 1 – somewhat satisfied; 2 – satisfied; and 3 – very satisfied.

RESULTS

The objective analysis of the photographs carried out by dermatologists unrelated to the study was rated with “significant improvement” of the inflammation in all cases (Figures 1 and 2). The three patients were very satisfied with the outcome and showed only mild erythema and pain as adverse effects to the treatment. During the six months following the treatment, none of the patients had a recurrence.

A chronic inflammatory process with significant lymphocytic inflammatory infiltrate and disorganization of collagen fibers was observed in a histological examination performed prior to the treatment (Figures 3 and 4). After the treatment, however, a significant reduction of the inflammatory infiltrate and organization of collagen fibers became apparent (Figures 5 and 6).

DISCUSSION

Hidradenitis is a chronic inflammatory disease that adversely affects a patient’s quality of life and is associated with clinical morbidity. Nevertheless, there is a lack of effective and permanent treatment for this disease, since recurrences are frequent.11 Laser treatment has the advantage of being restricted to the affected body site and not being associated with systemic side effects.3

1,064nm ND:YAG laser (Neodymium:Yttrium Aluminum Garnet) laser has recently shown good results in the treatment of hidradenitis.1,3,12,13 According to Mahnoud et al. 2010, it is likely that the mechanism of action responsible for the therapeutic success is the follicular ablation and destruction of inflammatory lesions through selective photodermolysis.

In the present study, the authors describe the unprecedented success of 1,340nm Nd:YAP laser to treat hidradenitis. This technology has already proven effective in the treatment of inflammatory acne, with possible similar action in fibrous and inflammation, which also characterize the hidradenitis.10 Thus, it was possible to guarantee satisfaction to patients and approval.
from a medical point of view, confirming this therapy’s efficacy in the histological examination.

The action of 1,340nm Nd:YAP in hidradenitis lesions (Stages I and II) was demonstrated to be durable, with no recurrence reported within the six months following the treatment. Side effects were minimal and localized. Therefore, the authors sought a safe and effective therapeutic alternative in the face of a condition having a great impact on the patient.

**CONCLUSION**

Since it is a case of a pathology associated with functional, aesthetic, and psychological damage, hidradenitis calls for effective therapeutic methods. In the present study, the authors conclude that 1,340nm Nd:YAP laser was effective and safe in three patients with hidradenitis, presenting a new therapeutic modality for the condition. Further studies on the different hidradenitis stages and with longer follow up are necessary.\(^1\)
REFERENCES


Tear trough filling with hyaluronic acid – superficial technique

Preenchimento da goteira lacrimal com ácido hialurônico – técnica superficial

RESUMO

Introdução: São frequentes na pálpebra inferior despigmentações e sulcos que conferem a seus portadores um olhar cansado, aprofundado e envelhecido, mesmo em pacientes jovens. Na busca da sua correção, o preenchimento para a restauração do volume local tem sido atualmente indicado, com proposição de vários produtos e técnicas.

Objetivo: Descrição e avaliação da técnica de aplicação superficial com o uso de ácido hialurônico monofásico polidensificado fluído.

Casuística e Método: 60 pacientes atendidas entre 2011 e 2014 foram submetidas à técnica. A avaliação foi feita por comparação fotográfica pelo médico aplicador e através de questionários respondidos pelas pacientes com base na classificação de Hirmand.

Resultados: O médico aplicador considerou o tratamento excelente (35% dos casos), muito bom (50%) ou bom (15%), enquanto para as pacientes os resultados foram excelente (30%), muito bom (50%) ou bom (20%). Não foram registrados efeitos adversos importantes ou de longa duração.

Conclusão: A técnica subdérmica superficial é de fácil execução, com poucos efeitos adversos e bons resultados, apresentando alto grau de satisfação por parte das pacientes.

Palavras-chave: envelhecimento da pele; ácido hialurônico; hiperpigmentação

ABSTRACT

Introduction: Discoloration and grooves are common in the lower eyelid and tend to give the bearer’s appearance – even at a young age – an effect of tiredness, advanced age, and deepening of the eyeballs. Aimed at correcting these visual effects, cutaneous filling for local volume restoration has been currently indicated as a treatment, with the proposition of a number of products and techniques.

Objective: To describe and evaluate the superficial application technique with the use of a fluid monophasic polydensified hyaluronic acid.

Materials and methods: Sixty patients being treated between 2011 and 2014 underwent the technique. The evaluation was carried out by an applicator physician through the comparison of photographs and through questionnaires based on the Hirmand’s classification answered by the patients.

Results: The applicator physician rated the treatment as excellent (35% of cases), very good (50%) or good (15%), whereas for patients the results were excellent (30%), very good (50%) or good (20%). There were no reports of significant or long-term adverse effects.

Conclusion: This superficial subdermal technique is easy to perform, has few adverse effects, and yields good results, leading to a high degree of patient satisfaction.

Keywords: skin aging; hyaluronic acid; hyperpigmentation
INTRODUCTION

The quest for the prevention or correction of signs of aging in the facial area has motivated the development of new surgical techniques and minimally invasive nonsurgical treatments. Special attention has been given to the periocular region, where multifactorial alterations – texture, color and skin firmness, bone resorption, and displacement of soft tissue – lead to the emergence of depigmentation, wrinkles and/or fat pads (Figure 1). According to clinical findings, one therapeutic option alone may not be sufficient.1,2

One of the main complaints related to the lower eyelid is the tear trough’s deformity that, when pronounced, translates into an unsightly depression, lending a tired and aged appearance to one’s gaze – even in young patients.3,4 According to Stutman, one of the most important elements in the aesthetics of the infraorbital region is the smooth transition between preseptal and orbital portions of the orbicularis oculi muscle, in continuity with the malar region, without a marked transition line.2

The first reference to infraorbital depression dates from 1932, having been described by Whitnall. The expression nasojugal groove was introduced later on by Dukes-elder and Wybar, in 1961. The terms lacrimal canal deformity and tear trough deformity were consolidated by Flowers and Loeb in 1969.2

In its upper portion, the tear trough corresponds to a cutaneous groove that runs obliquely and inferolaterally, from the inner canthus up to about the mid-pupillary line, and can continue laterally along the palpebromalar sulcus (Figure 2).3,4,5 It can be a result of both genetic and anatomical variations present in young individuals and the individual body region’s aging process.

The exact anatomical origin of the lacrimal groove remains unclear, with several conflicting reports in the literature.6,7 The references suggest the following as possible causes: (1) the prominence of the orbital border resulting from the downward displacement of the malar fat pad; (2) the orbital septum’s anchorage on the orbit’s marginal arc, at the inferomedial portion level of the arc; (3) the loss of local fat or the postseptal fat pad herniation; (4) the presence of a triangular cleft limited by the orbicularis muscle of the eye, levator labii superiores alaeque nasi and levator labii superiors muscles; (5) the absence of adipose tissue in the central and medial portions underlying the orbicular muscle in the groove’s region.2,3,5,6 Through dissections of cadavers, Haddock et al. correlated the lacrimal groove with the preseptal portion of the orbicularis oculi muscle and the junction of the orbital portions with differences in skin texture and underlying fat. In the deep plane, they found a separation between the tear trough and the palpebromalar junction.4 Wong, Hsieh and Mendelson identified a true osteocutaneous ligament: the tear trough ligament, which they defined as the main etiological factor for the lacrimal groove. This ligament is located...
between the eyelid and the origins of the orbital portions of the orbicularis oculi muscle. It inserts firmly in the region’s skin and originates from the maxillary bone.3

Surgical correction of the lacrimal groove deformity is considered difficult.2 The objective of traditional blepharoplasty is the removal and anchorage of the orbital septum’s tissues. However, recent studies of facial aging have highlighted the correction of the local volume losses and not just the removal of tissues. In this way, the idea of infraorbital groove filling for the restoration of the lost volume has arisen.

The first studies reporting the use of fillers in the naso-jugal groove date back to 2003 and were carried out by Michel Kane, whose team applied hyaluronic acid more superficially.6 In 2004, Robert Alan Goldberg described the hyaluronic acid application technique (Restylane®) with a 30G needle under the orbicularis oculi muscle.7 Many application techniques have been described to date.2,8,9

The objective of the present study is to describe the technique for the superficial filling of the lacrimal groove using fluid polydensified monophasic hyaluronic acid, which is indicated for subepidermal or dermal superficial applications, and to describe its safety and effectiveness.

MATERIALS AND METHODS

The present paper describes a retrospective study of patients treated by the authors at private practices and at the Cosmetic Dermatology Sector of the Dermatology discipline, at FMABC between 2011 and 2014. Sixty patients aged between 18 and 50 years (mean = 27.6 years), with tear troughs Classes 1 and 2 according to the Hirmand’s classification (Figure 3, Table 1) were treated. Fluid polydensified monophasic hyaluronic acid 20 mg/ml Anteis Soft® (Merz Aesthetics, São Paulo, Brazil), indicated to increase the volume of cutaneous tissue with superficial applications, was used. Polydensification provides the product with great integration properties into the dermal tissue, promoting uniform volume increase at the injection site, without the risk of the Tyndall effect.

The employed technique was the superficial subdermal – which allows the visualization of the needle – in retroinjection with a 30G 1/2 (0.3 mm x 13.0 mm) needle, forming “sticks” in the groove line, and subsequent molding of the injected material up until the complete filling of the tear trough. The product amount varied according to the groove’s depth (between 0.3 ml and 0.6 ml on each side). Cold compresses were applied before and after the procedure to prevent edema and hematoma. All patients were photographed and analyzed under standardized conditions before the treatment and 30 days after its completion.

The evaluation was performed by the applicator physician using photographic comparisons and the Hirmand’s classification questionnaire administered to the patients.

RESULTS

The results presented in this study were observed after a single application and were based on the Hirmand’s classification,5 having been rated as excellent by the patients and the
applicator physician when there was a total disappearance of the groove; as very good when the groove transitioned from Class 2 to Class 1; and as good when the groove transitioned from Class 2 to Class 1, but maintained the color difference (Figures 4 and 8). There were no cases with an absence of improvement, or with patient or applicator physician dissatisfaction (Tables 2 and 3).

Adverse effects were minor and transient. There were slight hematomas after the application, which could be camouflaged with corrective makeup and which resolved in a few days; transient edema of short duration (about two hours); and immediate local erythema – more frequently observed in patients with skin phototypes I and II. The use of local cooling before and after the application minimizes these complications. There were no cases of persistent edema among the patients treated, and there were no cases of the Tyndall effect (Table 4). The duration of the corrective effect ranged from 9 months (80% of patients) and 12 months (20% of patients).

DISCUSSION

The skin of the palpebral region is the thinnest on the human body (<1 mm), with the epidermis consisting of a very thin stratified epithelium (0.4 mm) and the dermis also extremely thin, composed of loose connective tissue and virtually absent in the pre-tarsal skin and eyelid’s medial and lateral ligaments, where it adheres to the fibrous underlying tissue.

The tear trough consists of a cutaneous groove, which runs obliquely and inferolaterally from the inner canthus to, approximately, the mid-pupillary line, continuing laterally with the palpebromalar sulcus.

Diverse techniques are described for its treatment. Several studies mention the use of cutaneous filling, with the discussion focusing on which filler would be more appropriate, since the skin is very thin and vascularized in this region. Among the filling substances, hyaluronic acid stands out as the most suitable due to its application straightforwardness, low allergenic potential and homogeneous texture with good esthetic outcomes, as well as a low risk of complications, especially using the superficial application technique.

Like any filler, hyaluronic acid has advantages and disadvantages. The advantages are: minimal degree of invasion, straightforward application, low allergenic potential and absence of a need for prior skin test. Furthermore, because of its viscosity, it adapts better to nasojugal contours and provides better esthetic results and a lower risk of complications due to its homogeneous texture. Among the disadvantages are: impermanent results, effectiveness for about only nine months and the necessity for topical anesthesia before application.

The optimal duration observed in patients in the present study may be linked to the replacement of hyaluronic acid, which entails hydric replacement in the dermis with the subsequent increase in thickness, and improvement in turgor, elasticity, and firmness as a result of new collagen production. Complications include erythema immediately after the application, hematomas, contour irregularities, overcorrection of the groove, persistent malar edema, and color alterations in the periorbital area – all of which occur independently of the filling substance used. The color alterations can be of two types: one that can be observed in patients with prominent dark circles, which after filling procedures in the groove convey the impression of worsening due to the increased exposure of a darkened surface (the patient should be warned about this risk); and another, characterized by the presence of a bluish area due to the superficialization of the filler – known as the Tyndall effect – and which can be observed in people with very fair and thin skin.

Despite being considerably rare, another possible complication described is blindness. In order to avoid the embolization of the ophthalmic artery, some precautions have been described. Among them are: to avoid applying filling substances close to the inner canthus (this region houses the supratrochlear, supraorbital, and dorsal nasal arteries (with the latter being a tributary of the ophthalmic artery); to apply small filler amounts at a time; to inject slowly; to avoid applications in bolus; to apply in more superficial planes or to use blunt tip cannulas.

The superficial subdermal surface application technique of fluid polydensed monophasic hyaluronic acid suitable for surface applications – as described in the drug description leaflet – lends safety to the application for the correction of the lacrimal groove due to its greater local bio-integration, with low
risk of contour irregularities and color alterations – such as the Tyndall effect. The formation of hematomas can occur in any technique and is a less severe complication in these cases, since it does not entail compression risk to any important structure and may be minimized by applying local cooling before and immediately after the application. With this technique, given that the application is sub-epidermal, there is no risk of arterial obstruction or product migration. The most common complication is overcorrection, though this risk can be minimized with the slow application of the material and the use of a filler with low-density, good moldability, and good integration into the tissues properties.

It is worth noting that in cases with significant skin sagging, with the visualization of fat pads, traditional blepharoplasty is indicated for the removal of tissue and correction of the orbital septum. The filling procedure is complementary and indicated only for correcting the loss of local volume.

CONCLUSION

The superficial subdermal tear trough filling technique is a safe and easy to perform procedure, with a low risk of complications. It is mainly indicated for young patients without cutaneous sagging and as a complementary technique to blepharoplasty in patients who also have tissue laxity, and should be performed after surgical correction.

Hidradenitis is a chronic and recurrent inflammatory disease that affects flexural areas of the skin, such as the armpits, and the inframammary and groin regions. It is a painful and often disfiguring condition, which manifests after puberty and is characterized by deep inflammatory lesions in the region of the apocrine glands. The prevalence of hidradenitis in the general population is about 1%, affecting more women than men (4:1), and is associated with genetic and hormonal predisposition (androgen excess).

Hidradenitis initially emerges as an inflammation around the hair follicle, followed by a series of damaging events that lead to a rupture of the follicular infundibulum, forming deep painful nodules and abscesses that generate fistulas and scarring. This sequence of events tends to be recurrent in most patients. Thus, hidradenitis may arise in the form of abscesses, folliculitis, pyogenic granuloma, comedones, fistulas, scars, and keloids.

Given the variety of possible manifestations of this disease, the Hurley's staging system is used to classify the picture into three stages. During Stage I there are one or more separate abscesses, but an absence of fistulae or scars; in Stage II there are one or more separate abscesses, and scarring and fistula formation; and in Stage III there is a confluence of the lesions with interconnected fistulas and abscesses.

The lesions' pathophysiology involves both follicular innate immunity defect and hyper-reactivity to coagulase-negative staphylococci.

Hidradenitis can have significant clinical consequences, but most of all it can negatively affect a patient's quality of life.

Pharmacological treatments include topical and oral antibiotics, intralesional corticosteroids, hormone therapy, retinoids, immunosuppressants and biological agents. Surgical treatments vary from drainage and incision procedures to debridement and a wide surgical excision of fistulas and abscesses. Most recently, there have been reports of the use of technologies such as diode laser, CO2 laser, Nd:YAG (Neodinium:Yttrium Aluminum Garnet) and photodynamic therapy with good results in the treatment of hidradenitis.

Due to the success of some laser types in hidradenitis, the authors sought to evaluate the use of a new technology, the 1,340nm Nd:YAP (Neodinium:Yttrium Aluminum Perovskite). This laser was effective in the treatment of inflammatory acne through the organization of the collagen fibers and reduced inflammatory infiltrate. Thus, since it is also a chronic inflammatory disease, the authors sought to obtain positive results in the treatment of hidradenitis with 1,340nm Nd:YAP.

METHODS

Three female patients, all bearers of hidradenitis at Hurley’s Stages I or II, who were being treated at the Dermatology Ambulatory of the Faculdade de Medicina de São José do Rio Preto (FAMERP), were selected. The patients had already undergone drug treatments without success. They did not use systemic or topical therapy for three weeks and had not undergone previous surgical treatment. The diagnosis of pregnancy was excluded for the three patients. The study was approved by the Research Ethics Committee of FAMERP.

In a prospective study, the patients underwent four 1,340nm ND:YAP laser sessions (Etherea®, Industra Tecnologias Indústria e Comércio Ltda., São Carlos, São Paulo, Brazil), with the following parameters: 100mj, 100mtz and 8mm tip. The interval between sessions was one month. The response to the treatment was assessed through a comparison of photographs taken prior to and one month after the fourth laser therapy session.

Two dermatologists unrelated to the study compared the photographs and classified them as follows: 0 – worsening, 1 – lack of improvement, 2 – moderate improvement, and 3 – significant improvement. Each patient's degree of satisfaction was evaluated based on a rating scale of: 0 – unsatisfied; 1 – somewhat satisfied; 2 – satisfied; and 3 – very satisfied.

RESULTS

The objective analysis of the photographs carried out by dermatologists unrelated to the study was rated with “significant improvement” of the inflammation in all cases (Figures 1 and 2). The three patients were very satisfied with the outcome and showed only mild erythema and pain as adverse effects to the treatment. During the six months following the treatment, none of the patients had a recurrence.

A chronic inflammatory process with significant lymphocytic inflammatory infiltrate and disorganization of collagen fibers was observed in a histological examination performed.
prior to the treatment (Figures 3 and 4). After the treatment, however, a significant reduction of the inflammatory infiltrate and organization of collagen fibers became apparent (Figures 5 and 6).

**DISCUSSION**

Hidradenitis is a chronic inflammatory disease that adversely affects a patient’s quality of life and is associated with clinical morbidity. Nevertheless, there is a lack of effective and permanent treatment for this disease, since recurrences are frequent. Laser treatment has the advantage of being restricted to the affected body site and not being associated with systemic side effects.

1,340nm Nd:YAP laser (Neodymium:Yttrium Aluminum Garnet) laser has recently shown good results in the treatment of hidradenitis. According to Mahmoud et al. 2010, it is likely that the mechanism of action responsible for the therapeutic success is the follicular ablation and destruction of inflammatory lesions through selective photodermolysis.

In the present study, the authors describe the unprecedented success of 1,340nm Nd:YAP laser to treat hidradenitis. This technology has already proven effective in the treatment of inflammatory acne, with possible similar action in fibrosis and inflammation, which also characterize the hidradenitis. Thus, it was possible to guarantee satisfaction to patients and approval from a medical point of view, confirming this therapy’s efficacy in the histological examination.

The action of 1,340nm Nd:YAP in hidradenitis lesions (Stages I and II) was demonstrated to be durable, with no recurrence reported within the six months following the treatment. Side effects were minimal and localized. Therefore, the authors sought a safe and effective therapeutic alternative in the face of a condition having a great impact on the patient.

**CONCLUSION**

Since it is a case of a pathology associated with functional, aesthetic, and psychological damage, hidradenitis calls for effective therapeutic methods. In the present study, the authors conclude that 1,340nm Nd:YAP laser was effective and safe in three patients with hidradenitis, presenting a new therapeutic modality for the condition. Further studies on the different hidradenitis stages and with longer follow up are necessary.
Progressive macular hypomelanosis: an epidemiological study of 103 cases in Southeast Brazil

Hipomelanose macular progressiva: estudo epidemiológico com 103 casos da Região Sudeste do Brasil

ABSTRACT

Introduction: Progressive macular hypomelanosis is characterized by the emergence of hypopigmentation, predominantly in the trunk region of young women of mixed racial origin. Although recent studies suggest that Propionibacterium acnes may have an important role in the pathogenesis, its etiology remains unclear.

Objective: To evaluate the prevalence of the condition with regards to gender, age, skin phototype, affected areas and disease onset, and the relationship with ordinary acne and oily skin in the city of Niterói, Rio de Janeiro State, in the coastal region of Southeast Brazil.

Methods: Retrospective epidemiological study that uses the analysis of medical records of 103 patients with diagnosis of progressive macular hypomelanosis, from 2001 to 2012.

Results: Eighty-two percent of studied patients were women and 18% men, with a predominance of phototypes III (42.7%) and IV (42.7%). The average age of onset of the disease at diagnosis was 26 years. In 46.0% of patients the disease duration ranged from 1 to 4 years. When two areas were affected (50%), the dorsum was more frequent (79.0%), followed by the abdomen (20.0%). In 98% of cases, patients had oily skin, and 71.8% had active acne.

Conclusion: Progressive macular hypomelanosis is a chronic condition that primarily affects the skin of the dorsum and abdomen of young women with skin phototypes III and IV, who are also bearers of oily skin and acne. There are still many doubts regarding the true etiology and treatment of progressive macular hypomelanosis. The high percentage of association with skin oiliness and acne vulgaris suggests that these clinical conditions are possibly related.

Keywords: Hypopigmentation; epidemiology; acne vulgaris

RESUMO

Introdução: A hipomelanose macular progressiva se caracteriza pelo surgimento de hipopigmentação predominantemente na região do tronco de mulheres jovens de origem racial mista. Embora estudos recentes indiquem que o Propionibacterium acnes possa ter papel relevante na patogênese, sua etiologia permanece incerta.

Objetivo: Avaliar a prevalência da doença quanto a sexo, idade, tipo de pele, áreas afetadas e início da doença, relação com acne vulgar e pele oleosa na cidade de Niterói, RJ, região litorânea no sudeste do Brasil.

MÉTODOS: Estudo epidemiológico, retrospectivo, através da análise de prontuários de 103 pacientes com diagnóstico clínico de hipomelanose macular progressiva entre 2001 e 2012.

Resultados: Oitenta e dois por cento dos pacientes avaliados eram mulheres, e 18% homens, com predominância de fototipos III (42,7%) e IV (42,7%). A idade média de aparecimento da doença no momento do diagnóstico foi 26 anos; em 46% o tempo de doença variou entre um e quatro anos. Quando eram afetadas duas áreas (50%), o dorso foi mais frequentemente afetado (79%), seguido do abdômen (20%). Em 98% dos casos, os pacientes tinham pele oleosa e 71,8% delas apresentavam acne ativa.

Conclusão: A hipomelanose macular progressiva é doença crônica que principalmente afeta a pele do dorso e abdômen de mulheres jovens com fototipos III e IV, que também são portadoras de pele oleosa e acne. Existem ainda muitas dúvidas em relação à verdadeira etiologia e ao tratamento da hipomelanose macular progressiva. A alta porcentagem de associação com oleosidade cutânea e acne vulgar indica a possibilidade de essas condições clínicas estarem relacionadas.

Palavras-chave: Hipopigmentação; epidemiologia; acne vulgar
INTRODUCTION

Progressive macular hypomelanosis (PMH) is a cutaneous condition characterized by the emergence of hypopigmentation, predominantly in the trunk region of young women of mixed racial origin. It is a common, yet underdiagnosed pigmentary disorder. The condition can be found in patients worldwide, however it is more common in those from tropical and subtropical countries.

This entity was first described in 1987 by Borelli as cutis trunci variata and named by Guillet in 1988 as progressive macular hypomelanosis. Although this became the preferred terminology, it has been recognized by several authors around the world under a wide variety of denominations, such as: hypomelanosique maculée confluent et progressive du métis melanodermique, créole dyschromia, idiopathic macular hypomelanosis of the melanodermic, and progressive trunk hypomelanosis.

Its etiology remains unknown despite several factors having already been suggested as causes for the lesions: racial origin and, later on, a suggested correlation with tinea versicolor and pityriasis alba. The presence of Propionibacterium acnes producing a depigmentation factor has also been proposed, as well as disorders in the melanosomes. Hereditary factors may play an important role, although further investigations are necessary.

PMH is characterized by hypopigmented macules of undefined limits, usually 10-30 mm in diameter, located predominantly in the trunk region of the body. The condition generally affects skin areas rich in sebaceous glands. There is typically no reference to previous inflammatory occurrences or lesions of an infectious nature.

The diagnosis is mostly clinical and can be confirmed by examination using a Wood's lamp, which shows red fluorescent spots. Observation with confocal microscopy shows the "pigmented ring" around the dermal papillae in the lesions is intact, however its melanin content is less than the that of the surrounding normal skin. No spores, hyphae or bacteria are observed in the stratum corneum. Histological investigations show a slight reduction of melanin granules in the basal cell layer with a variable reduction of melanin transfer to keratinocytes. Nonetheless, the histological findings are not sufficient to characterize the definitive diagnosis of this condition.

It is necessary to exclude the possibility of pityriasis versicolor, pityriasis alba, leprosy and hypochromic fungal mycosis as differential diagnoses.

Several treatments are mentioned in the literature: topical and oral antibiotics, benzoyl peroxide, and phototherapy (PUVA and UVB-NB) – all of which are unstable and still produce results that are not fully satisfactory.

The present study is aimed at evaluating the prevalence of the dermatosis in regards to gender, age, skin phototype, affected areas and duration of the disease, and also considering its correlation with acne vulgaris and oily skin conditions.

METHODS

A retrospective study was performed through the analysis of medical records of patients with clinical diagnosis of PMH treated at private dermatology practices in the city of Niterói (Rio de Janeiro State), in the coastal region in southeastern Brazil, between 2001 and 2012. The study included 103 patients with complete personal and epidemiological data, and whose diagnosis was conclusive for this disease.

RESULTS

From Table 1 it is possible to note that roughly 82% of the patients were female (Figures 1 and 2), and 18% male (Figures 3 and 4). There was a predominance of phototypes III (42.7%) and IV (42.7%). The patients’ mean age at diagnosis was 26 years (min = 13 years, max = 50 years, mode = 22).

According to Table 2, patients had oily skin in 98% of cases, and 71% had active acne, indicating a possible association of the disease with oily skin and the presence of acne.

The results in Table 3 indicate that for most evaluated patients, the disease arose between the ages of 15 and 29, with 25% of cases between 15 and 19, 25% between 20 and 24, and 20% between 25 and 29 years. In addition, only 16% had developed the disease less than one year before, and in 46% the time of onset was one to four years before, with 18% with between five to nine years. It is worth noting that some patients had never noticed the lesion or did not exactly know when it had developed, with 4% of patients having more than 15 years of development without remission. One patient reported the development of the picture for about 20 years. Regarding the location, 51 patients had lesions only in one area, and 52 in two or more areas. When the patient had a single lesion, the dorsum was the most often affected area (79%), followed by the abdomen (10 cases, 20%) and chest (one case, 2%). Analyzing the association of affected areas, 47 patients (90%) had concomitant lesions on the dorsum and abdomen, and three patients (6%) had concomitant lesions in the dorsum, abdomen and chest.
DISCUSSION

Despite the fact that PMH is a considerably common disorder, its true prevalence is unknown.\textsuperscript{13} It mainly affects young individuals, predominantly between the ages of 18 and 25 years, with rare reports of cases in patients over the age of 50.\textsuperscript{16} The majority of cases occur in women, in proportions ranging from 3:1 to 7:1,\textsuperscript{9,13} though some authors have not found differences in the distribution between the genders.\textsuperscript{2,17} The present study evaluated 103 patients with clinical diagnosis of PMH. Of these, 82\% were female, with 70.8\% reporting the lesions' onset at between 15 and 29 years of age, thus corroborating the literature findings. It is important to note that in the present study it was possible to observe cases in men, in all skin phototypes and with onset of lesions between 9 and 49 years old.

Regarding the skin phototype, the literature has divergent data: while some authors found an increased incidence in patients of mixed ethnic origin (Negroids/Caucasoids),\textsuperscript{12,13,18} other studies deny this claim,\textsuperscript{1,2,12} explaining that the disease is probably more easily seen in patients with pigmented skin. Among the present study's patients, 85.4\% had Fitzpatrick phototypes III and IV.

Although some authors incriminate the \textit{Propionibacterium acnes} as the etiologic agent of this condition, the presence of acne vulgaris associated with HMP was an uncommon finding in some studies. It is also relevant to note that with conventional identification methods, there are still practical difficulties in distinguishing the species or subspecies of some specific genres that can play an important role in the pathogenesis of diseases. In this manner, the \textit{Propionibacterium acnes} species causing acne and progressive macular hypomelanosis could be of different subtypes.\textsuperscript{9} In a study by Rodriguez in Spain, of 10 patients with a clinical picture of PMH,
seven reported association with acne, however the author himself questions the possibility of different subtypes of this bacteria. In the present study, 71% of patients had acne vulgaris as an associated complaint. In addition, oily skin was observed in a significant percentage (98%), in line with studies from other authors.

Twenty patients had lesions limited to the dorsum; eight had lesions only in the abdomen; 20 had lesions in both the dorsum and abdomen; two had concomitant lesions in the chest in addition to the dorsum and abdomen; and only one had lesions exclusively in the chest. These findings are consistent with the literature, showing the lesions’ predominant distribution to be in the dorsal and abdominal regions.

The progression of the lesions is uncertain. Spontaneous regression usually occurs within 3 to 5 years, though some cases persist for more than ten years. Menke et al. do not believe in spontaneous remission. On the contrary, they observed stability of the lesions in a 10-year follow up of patients, with no repigmentation being observed in any of them. Lesuer et al. showed that lesions may persist for in excess of 25 years. In the patients evaluated in the present study, the lesions’ time progression at diagnosis ranged from two months to 240 months, with 11 of the 103 patients being unable to specify the exact onset time of the disease due to the fact they had not noticed its presence, and because the lesions were only identified at the dermatological examination.

| TABLE 2: Epidemiological profile of patients with PMH - oily skin and acne (n = 103) |
|---------------------------------|-----------------|-----------|
| OILINESS                        | Frequency       | Percentage|
| Yes                             | 101             | 98,1      |
| No                              | 2               | 1,9       |
| ACNE                            |                 |           |
| Yes                             | 73              | 71        |
| No                              | 29              | 28        |
| NL                              | 1               | 1         |

| TABLE 3: Epidemiological profile of patients with PMH - age of lesion onset, disease development, location (n = 103). |
|---------------------------------------------------------------|-----------------|-----------|
| AGE OF LESION ONSET                                          | Frequency       | Percentage|
| 0-11 months                                                  | -               | -         |
| 1-4 years                                                    | -               | -         |
| 5-9 years                                                    | 1               | 1         |
| 10-14 years                                                  | 6               | 5,8       |
| 15-19 years                                                  | 26              | 25,2      |
| 20-24 years                                                  | 26              | 25,2      |
| 25-29 years                                                  | 21              | 20,4      |
| 30-34 years                                                  | 5               | 4,9       |
| 35-39 years                                                  | 4               | 3,9       |
| 40-44 years                                                  | 1               | 1         |
| 45-49 years                                                  | 2               | 1,9       |
| Did not know                                                 | 11              | 10,7      |

| PROGRESSION TIME                                              | Frequency       | Percentage|
| 0-11 months                                                  | 17              | 16,3      |
| 1-4 years                                                    | 48              | 46,2      |
| 5-9 years                                                    | 19              | 18,3      |
| 10-14 years                                                  | 4               | 3,8       |
| 15-19 years                                                  | 3               | 2,9       |
| 20-24 years                                                  | 1               | 1         |
| 25-29 years                                                  | -               | -         |
| 30-34 years                                                  | -               | -         |
| 35-39 years                                                  | -               | -         |
| 40-44 years                                                  | -               | -         |
| 45-49 years                                                  | -               | -         |
| Did not know                                                 | 11              | 10,6      |

<table>
<thead>
<tr>
<th>LOCATION OF LESIONS</th>
<th>Single area (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdomen</td>
<td>10</td>
</tr>
<tr>
<td>Dorsum</td>
<td>39</td>
</tr>
<tr>
<td>Dorsum (sacrum)</td>
<td>1</td>
</tr>
<tr>
<td>Chest</td>
<td>1</td>
</tr>
</tbody>
</table>

| Two or more areas (n = 52)                                   | Abdomen/dorsum      | 47       | 90,4    |
| Dorsum/Thorax Chest                                         | 1                   | 1,9      |
| Abdomen/Dorsum/Thorax Chest (axillary)                      | 3                   | 5,8      |
CONCLUSION

PMH is a chronic disease that primarily affects the skin of the dorsum and abdomen of young women with phototypes III and IV, oily skin, and acne.

Although several studies have been previously carried out, there are still many doubts regarding PMH, and its true etiology and effective treatment remain under question. The present review reinforces the findings described in the literature, with the high number of patients with skin oiliness and acne vulgaris inducing the authors’ belief that the condition’s etiology is related to these clinical conditions. Further studies are necessary to confirm the actual involvement of *P. acnes* or subtypes of this bacterium in the etiology of PMH and to further elucidate this disease.
Applicability of platelet-rich plasma in dermatology

ABSTRACT
Platelet-rich plasma has been proven to be promising in regards to its applicability in dermatology, especially in the healing of chronic ulcers and for soothing signs of aging. The autologous platelet-rich plasma is obtained through blood centrifugation, in a way that its components are separated by density gradient. The final product is a gel rich in growth factors that act in tissue repair, activating fibroblasts and inducing the extracellular matrix remodeling.

Keywords: platelet-derived growth factor; platelet-rich plasma; transforming growth factors; vascular endothelial growth factors; wound healing

INTRODUCTION
Cutaneous ulcers are characterized by tissue loss involving epidermis, dermis, and sometimes adipose tissue, as well as muscle fascia. The etiology of these lesions is diverse, including peripheral vascular disease, infectious diseases, and trauma. It can also be secondary to neurological, immune, neoplastic disorders and iatrogenic injury. Cutaneous ulceration is a rather common occurrence, with a current prevalence rate ranging from 0.18 – 0.32%, an incidence rate of 0.78% and a clear trend toward an increase in frequency as the average age of the global population increases. Additionally, there is an inevitable socio-economic cost impact. Chronic skin ulcers have a significant effect on a patient’s quality of life, and also drive up public health costs in Brazil and worldwide. The European Union directs 2% of its annual health care budget for the treatment of such lesions.
Wound healing is a complex process brought about by signals of molecular interaction involving cellular mediators and events, and is followed by the recruitment of mesenchymal cells, and extracellular matrix proliferation and regeneration. The healing process is a response of innate immunity to restore tissue integrity. It is regulated by a standard sequence of events including coagulation, inflammation, granulation tissue formation, epithelialization, and tissue remodeling. These events are mediated and modulated by cytokines and growth factors that stimulate and modulate such cellular activities. More recently, platelet-rich plasma (PRP) has also drawn attention to the field of cosmetics regarding skin rejuvenation. The aging of human skin results from a combination of a gradual decline in its function over time (intrinsic process) and the cumulative damage caused by environmental factors (extrinsic process), such as smoking and, in particular, exposure to ultraviolet B radiation (UVB). In the dermis, UVB exposure has been shown to stimulate the production of collagenase by fibroblasts. In skin continuously exposed to UVB rays, degradation of collagen and the altered elastic tissue deposition result in damage to the structural integrity of the dermal extracellular matrix, causing wrinkling of the skin. Cutaneous elasticity is also reduced. Given that PRP produces several growth factors linked to skin regeneration, it can be assumed that PRP is capable of inducing the synthesis of collagen and other extracellular matrix components through the stimulation of fibroblasts, thus leading to the rejuvenation of the skin. In this research field, however, studies that have confirmed the effect of PRP on aged fibroblasts are still considerably limited.\(^2\)

A brief literature review

Studies already carried out have shown that PRP has been effective in several control-cases and uncontrolled clinical trials.\(^3\) Crovetti et al.\(^1\) published a prospective study on the efficacy of platelet gel in the healing of chronic skin ulcers. The lesions of the 24 patients involved in the study ranged in etiology, including vascular disease, infectious disease, post-traumatic ulcers, and also conditions related to diabetes mellitus, neuropathy, and vasculitis. The study’s protocol consisted of weekly applications of platelet gel, and at the time of publication, nine patients had been completely cured, two had received skin grafts, four had halted the treatment, and nine had a partial response and continued to be treated.\(^1\)

McAleer et al.\(^4\) found that the use of autologous PRP worked satisfactorily in the healing of chronic ulcers of the lower extremities in a case study of a 57-year-old man with type II diabetes mellitus. The treatment with PRP was established after the unsuccessful application of a skin graft. The autologous PRP was synthesized at the assistant physician’s practice, with inspection and debridement of the wound and an application of platelet gel performed weekly. The complete healing of the ulcer was achieved in the fourth week of treatment. Despite the fact that the study involved only one patient, this evidence nonetheless suggests that PRP can be used successfully in healing ulcers that do not heal with other treatment techniques.\(^4\)

Driver et al.\(^5\) carried out the first multicenter prospective, randomized, and controlled trial in the U.S., on the use of autologous PRP for the treatment of diabetic foot ulcers. Among the participants were 72 patients with type I and type II diabetes, aged between 18 and 95 years, and with lesions having set on at least four weeks prior. In this study, researchers compared the autologous PRP’s effectiveness to that of the usual saline gel, for 12 weeks. The study’s primary objective was to evaluate PRP’s safety and the incidence of the complete closure of the wound (defined as 100% re-epithelialization), as compared to the treatment administered to the control group. The secondary objective concerned the closing rate. At the end of the study, it was found that patients treated with PRP had their ulcers healed in 68.4% of cases when compared with 42.9% for the saline group. Furthermore, in the PRP group, healing occurred in about 42.9 days, while it took 47.4 days on average in the control group.\(^5\)

Salimi et al.\(^6\) recently conducted a study evaluating the effectiveness of the combination of PRP and autologous adipose tissue in an ulcer in the lower extremity of a 65-year-old non-diabetic patient, whose condition had been in development for three years. This study lasted for four weeks, with follow-up events after one, three, six, and fifteen months. Despite the absence of statistical analysis in this study, the researchers noted that the graft integrated well and the patient suffered no local infection or other complications. In the thirteenth month of follow-up, the wound was completely healed and there was restoration of the limb’s function.\(^6\) Other authors have used this technique for the treatment of ulcers in the lower limb.\(^7\) Cho JM et al.\(^8\) led a study involving genetically modified mice, with naked skin, photogaged through exposure to UVB radiation. They were divided into three groups (untreated, injected with saline, and injected with PRP). After four weeks the degree of wrinkle formation was compared between the three groups using replica analysis; skin biopsies were also performed. An additional in vitro trial with growth factors neutralizing antibodies has also been developed to assess whether the growth factor contained in PRP could accelerate fibroblast proliferation and collagen production. The promising results of the study indicated that PRP is effective in rejuvenating photodamaged skin.\(^8\)

**PRP composition**

Plasma plays an important role in creating an appropriate microenvironment for tissue repair.\(^9\) The presence of some leukocytes in PRP lends some natural resistance to the infectious processes of this compound, improving the treatment’s prognosis. The platelets, in turn, correspond to the most important component regarding the modulation of tissue healing due to its ability to release growth factors. They are responsible for regulating a number of cellular events such as DNA synthesis, chemotaxis, cytokidifferentiation, and matrix synthesis. The alpha granules of the platelets release numerous growth factors, which act by joining cellular receptors located on the cell membrane and which transmit the signal from the exterior to the interior of the cell, by coupling different proteokinas, which in turn phosphorylate and activate a cascade of signals that end with the activation of one or several genes (signal transduction). The platelet-derived

---

growth factor (PDGF) was one of the first identified growth factors. It is the main factor contained in platelets, due to the fact that it is the first to be present in the wound and to guide the re-vascularization, collagen synthesis, and tissue repair processes. The PDGF is probably produced in megakaryocytes and is stored in the platelets’ alpha granules. Macrophages, endothelial cells, and osteocytes are additional sources of PDGF. They are released from their original granules when platelets adhere to the sites of vessel breakage and/or basal membranes area. The platelets’ PDGF start the repair process, while that present in the macrophages continues to heal the wound. Moreover, the PDGF stimulates DNA synthesis, chemotaxis, and collagen synthesis, processes that are essential to wound healing and tissue repair.

The beta transforming growth factors (TGF-b) constitute a superfamily of local mediators that regulate the proliferation and functions of most cells in the body. This family is composed of b1, b2, b3, b4 and b5 TGFs. The TGFs most commonly present in the PRP are TGF-b1 and TF-b2, which are factors related to connective tissue healing. Their most important functions regarding tissue repair are the chemotaxis of inflammatory cells and extracellular matrix synthesis. Also known as somatomedins, insulin-like growth factors (IGF) are produced in the liver and circulate when bound to proteins and such substances. Types 1 and 2 (IGF1 and IGF2) are involved in the tissue repair process, by regulating the availability of amino acids for protein synthesis, collagen and other connective tissue molecules. The epidermal growth factor (EGF) is a peptide that produces a variety of biological responses—most of them involving replication, movement, and cell survival regulation. It belongs to a family of related ligands (which includes the alpha transforming growth factor, TGF-α), which share a homologous amino acid sequence with high affinity for the same receptor, the EGFR. The vascular endothelium growth factor (VEGF) plays an important regulatory role in the physiological vascular development, increasing the tissue’s vascularization, hence improving the supply of oxygen and nutrients to a particular site.

**PRP Collection**

Platelet-rich plasma is obtained from autologous blood via a process that uses the cell separation principle of differential centrifugation. At least 16 PRP preparation systems are currently available. The resulting PRP volume and final platelet and leukocyte concentrations differ in the divergent preparation systems. According to Saucedo et al., Dohan Ehrenfest et al. classified PRP according to the concentration of leukocytes and fibrin while Mishra et al. accomplished this according to the concentration of platelets, presence of leukocytes, and the inclusion of an activator. In order to create PRP, whole blood is usually collected in the presence of an anticoagulant that binds to calcium and prevents the start of the coagulation cascade, thus preventing the conversion of prothrombin into thrombin. Although there are various anticoagulants available, only two were deemed suitable for the process so as not to damage the platelets: acid citrate dextrose A, and citrate phosphate dextrose. Once the whole blood sample is obtained, it is subjected to one or two centrifugation stages, depending on the desired characteristics of the final product. An amount of 10-20 ml of blood is then collected and distributed in 5 ml tubes containing a 10% sodium citrate solution. The tubes are then centrifuged at room temperature, resulting in three basic components: red blood cells, PRP and PPP, from the lowest to the uppermost portion, respectively. After this process, plasma is collected. The volume of about 1.2 ml per tube is associated with 5 ml of 10% calcium chloride, and approximately five minutes after, the gel is formed.

**Safety in the use of PRP**

Given the autologous nature of PRP, safety concerns are minimal at this time. The complications reported in most clinical series have been limited to transient pain and inflammation at the site of application. A laboratory study showed that PRP has an antimicrobial effect against *Staphylococcus aureus* and *Escherichia coli*, potentially reducing the risk of infection by these organisms.

**Dose-response effect**

*In vitro* studies demonstrated that the majority of the growth factors for dose-response curves is non-linear, meaning that from a certain point, increasing the concentration of growth factors brings no additional effects, as cell surface receptors would be fully occupied. On the other hand, some growth factors can effectively exert an inhibitory effect on cell functions once a sufficiently high concentration is reached. Thus, not only is there a presence of growth factors that dictates the level of the healing response, but also the presence and ability of target-cells to use these factors appropriately.

**DISCUSSION**

Due to increased life expectancy and hence the significant aging of the global population, the prevalence of chronic skin ulcers is expected to become higher, mainly those resulting from atherosclerotic and microangiopathic processes. The same can be said of skin aging, given the longer cumulative exposure to UVB rays. In this respect, there is a need to develop techniques that will assist in the process of wound healing and skin repair. The PRP arises as a tool that allows the application of large amounts of growth factors that stimulate the production of collagen and extracellular matrix through minimal amounts of plasma. Growth factors promote a rapid increase in the number of undifferentiated mesenchymal cells in the healing site during the repair and healing processes. Thus, PRP has the advantage of accelerating the regenerative process via the amount of growth factors present in platelets. Conversely, it has the disadvantages of short platelet life (about three to five days), and the fact that the growth factors expire in seven to ten days. Despite the platelets’ short life span, it was proved that PRP is able to promote a faster and qualitatively better skin repair. However, there are many potentially confounding variables in the studies—both regarding the variation in patients’ and in the PRP’s characteristics. Hence the difficulty in carrying out standardized studies.
CONCLUSION

Based on the literature referred to here, it is possible to conclude that the use of PRP in dermatology, while recent, is a very promising technique. PRP is a preparation of organic, non-immunoreactive, non-toxic, and low morbidity, with production costs that are reasonably low. Regarding the healing of chronic skin ulcers, treatment with PRP can result in a shorter healing and recovery time of the limb's function, and decrease the amputation rate, thereby improving the patient's quality of life. Regarding its use in cosmiatry, one may suggest that stimulation with growth factors is able to promote skin rejuvenation. Finally, further studies are necessary on PRP's mechanism of action and ideal preparations standardization, either for the healing of chronic ulcers or for the mitigation of signs resulting from aging. Many questions remain unanswered regarding the use of PRP in dermatology; however, despite these remaining issues, PRP promises to be an effective treatment modality.

REFERENCES

Wood’s light in the determination of the surgical borders of the hypomelanotic lentigo maligno melanoma
Luz de Wood na determinação das bordas cirúrgicas de lentigo maligno melanoma hipomelanótico

RESUMO
A lâmpada de Wood é instrumento diagnóstico de baixo custo, seguro, de fácil manuseio e perfeitamente disponível em consultórios. Apesar disso, sua aplicação na dermatologia tem-se restringido à detecção de infecções cutâneas, avaliação e classificação de distúrbios de pigmentação, como melasma e vitiligo, além de análise de distúrbios no metabolismo das porfirinas. No presente relato demonstramos o uso da lâmpada de Wood como opção à microscopia óptica confocal, na delimitação da margem cirúrgica de um lentigo maligno melanoma hipomelanótico, cuja ausência de pigmentação melânica, bem como a localização do tumor em área de fotodano, dificultava a programação cirúrgica da paciente. Palavras-chave: luz; melanoma; melanoma amelanótico; microscopia confocal

ABSTRACT
A Wood’s lamp is a cost effective, safe, easy to use diagnostic tool that is readily available at medical practices. However, its dermatological application has been restricted to the detection of cutaneous infections, the evaluation and classification of pigmentary disorders (such as melasma and vitiligo), and the analysis of disturbances in the metabolism of porphyrins. In the present report the authors demonstrate the use of a Wood’s lamp as an alternative to confocal optical microscopy, in the delimitation of the surgical margins of a hypomelanotic lentigo maligna melanoma, whose lack of melanin pigmentation and tumor location in a photodamaged area had hampered a patient’s surgical planning. Keywords: light; melanoma; melanoma, amelanotic; microscopy, confocal;

INTRODUCTION
The Wood’s light (WL) has been used by dermatologists as a diagnostic device in pigmentedary disorders, skin infections, and porphyria for more than a century. Although it is an easy to use and cost effective tool, it is also often an underutilized tool. Very few publications explore its new applications. Paraskevas et al. demonstrated its use in the detection of recurring pigmentation in surgical scars, in the differentiation between agminated nevus and spilus nevus, and in the delimitation of surgical margins in lentigo maligna.

The present paper describes a case of hypomelanotic lentigo maligna melanoma, where visual inspection and dermoscopy were insufficient to define the lesion’s surgical borders.
CASE REPORT

A seventy-four year-old female patient, Fitzpatrick skin phototype II, with a history of multiple basal cell carcinomas, complained of an erythematous lesion that she had noticed in the right infraclavicular region ten months earlier. Dermatological examination showed a 4.2 cm x 3.1 cm erythematous-brownish macule with irregular and poorly defined borders (Figures 1 and 2). Dermoscopy evidenced a lesion with an erythematous background, without evident pigmentation, and rare punctate, irregular vessels that intermingled with areas of photodamage (Figure 3). After a clinical evaluation, an incisional biopsy was carried out with the histological study of the sample suggesting the diagnosis of hypomelanotic lentigo maligna melanoma (HLMM) in a radial growth phase, with a thickness of 0.25 mm.

The WL was used in the pre-operative evaluation in order to delimit the surgical margins of the HLMM (Figure 4A). The patient then underwent tumor exeresis and a primary closure (Figure 4B). The authors decided to carry out the resection with a 1 cm margin due to the possibility of performing the primary closure as well as concerns about the loss of the case follow-up. The histology revealed the proliferation of atypical epithelioid melanocytes, and voluminous, hyperchromatic, pleomorphic nuclei with evident nucleoli, in addition to lentiginous distribution in the dermoepidermal junction. It was also possible to notice the absence of ulceration or mitotic figures, a Breslow index of 0.32 mm, Clark level III and free margins (Figure 4C). The patient is currently being followed up at the Dermatology Service, without signs of recurrence.
DISCUSSION

The WL is an observation and diagnosis tool based on the fluorescence phenomenon of the cutaneous surface. The long wave ultraviolet radiation (UVR) emitted by the WL originates from a high-pressure mercury arc passing through a barium silicate filter containing 9% of nickel oxide, called Wood filter. This filter allows the passage of UVR waves that are in the range 320nm - 400nm, with a peak at 365nm. Melanin is responsible for the absorption of most of the radiation emitted by the WL. In cases of skin lesions with an increased concentration of epidermal melanin, the dermatologist will see it in darker contrast to the circumscribed normal skin. In cases of a lower concentration of melanin, lesions will tend to be lighter and more difficult to distinguish.

In the evaluation of lesions with poor melanin pigmentation or in regions of extensive photodamage, examination under visible light is often insufficient to distinguish areas of fair pigmentation from normal skin areas, due to lack of contrast. This is mainly due to the fact that the longer wavelengths of light present in the visible light spectrum penetrate deeper into the dermis than the shorter wavelengths. The dermis reflects longer wavelengths and thus reduces the contrast of the image that is perceptible to the examiner’s eye. When only shorter wavelengths of WL are used to illuminate the skin, the interference caused by the longer wavelengths is avoided, consequently improving the contrast between superficial pigmented lesions and the normal epidermis.

Due to this ability to emphasize the different pigmentation of the skin, WL becomes a tool of considerable value in the pre-operative evaluation of hypomelanotic tumors or tumors located in areas of extensive sun damage. Although most melanomas are characterized by a pigmentation that ranges between shades of brown and black, there are numerous reports in the literature of amelanotic malignant melanoma (AMM), which is characterized by the complete absence of pigment, or more frequently, with melanin pigmentation in less than 25% of the total lesion area, called hypomelanotic malignant melanoma (HMM).

AMMs correspond to a range of 1 - 8% of melanomas. Any cutaneous melanoma subtype can be amelanotic, although the subungual and desmoplastic variants have the highest rates (15% to 20% and 50%, respectively). Therefore, the amelanotic or hypomelanotic lentigo malignant melanoma is rare, constituting a diagnostic challenge, especially when the dermatologist needs to define its borders for surgery. Although laser assisted confocal microscopy is the most accurate technique for the pre-operative study, its high cost and limited availability in most dermatology services in Brazil make WL by contrast an indispensable tool for dermatologists.

REFERENCES

New Techniques

Steps for performing a nasolabial flap in a single surgical time

Passos para um retalho nasolabial em único tempo cirúrgico

ABSTRACT

The upper lip is commonly affected by cutaneous carcinomas. The excision of the neoplasia with safe oncologic margins calls for a large incision, and sometimes flaps are necessary. In addition to its aesthetic value, a successful lip reconstruction includes the maintenance of perfect oral functionality. The authors describe a nasolabial rotation cutaneous flap associated with an advancement flap of the oral mucosa in a single surgical event, performed on a patient bearing basal cell carcinoma involving the left side portion of the upper lip.

Keywords: surgical flaps; carcinoma, basal cell; mouth mucosa

INTRODUCTION

Lip carcinomas account for approximately 25% of all oral tumors.1 Late diagnosis and the need for safety margins often result in the primary defect covering a quarter to one third of the upper lip, thus preventing direct suture.2 The reconstruction of defects in the upper lip has been shown to be a surgical challenge. There is no specific method to be used for lesions in the lateral area of the upper lip.

METHODS

The present paper reports the case of a 48-year-old female patient bearing for the span of one year an erythematous plaque, 2 cm in diameter, having pearly borders and well-defined contours in the lateral third of the upper lip. Ovoid nests and arboriform vessels were evidenced by dermoscopy. The invasive micronodular basal cell carcinoma diagnosis was confirmed by an incisional biopsy. In the absence of lymphadenopathy and any signs and symptoms, the lesion was classified as Stage I (T1N0M0).3

Due to the essential need for a complete exeresis of the tumor, combined with the preparation of a local flap, the excision...
Nasolabial flap in a single surgical time

and surgical reconstruction were carried out in one single event. The objective of the present report is to describe the reconstruction technique and demonstrate its surgical applicability, as well as its aesthetic and functional outcomes.

The tumor was identified and underwent resection with a 5 mm surgical margin (Figure 1). A rotation flap in the nasolabial fold was used to fill the open area of skin in the upper lip (Figure 2). The reconstruction of the submucosa was performed with an advancement flap of the buccal mucosa (Figure 3). Finally, the suture of the primary and secondary defects was carried out.

The histologic examination of the removed specimen confirmed the presence of margins free of neoplastic involvement. The patient developed post-surgical stress labial herpes, but showed good response to treatment with oral acyclovir in a weekly follow up during the first month. Figure 4 shows the two-week outcome after the surgery.

**RESULTS**

The single-stage procedure, combining an upper lip reconstruction after excision of basal cell carcinoma, was performed on the patient using a nasolabial rotation flap associated with an advancement flap of the buccal mucosa, with margins free of neoplastic involvement and an excellent aesthetic appearance.

**DISCUSSION**

The reconstruction of the upper lip has consistently been a challenge for surgeons, since the contour, symmetry and cupid’s bow positioning of the lip must be kept unchanged,4,5 and the functionality of the mouth opening preserved as well.1,4

For minor lesions, “V” and “W”-shaped excisions followed by suturing are sufficient.5,6 However, when lesions extend from one to two thirds of the lip, local flaps are the best choice – such as i) the Abbé,6 ii) the Estlander,2,6,7 iii) the Gillies unilateral,5 iv) the Karapandzic unilateral,6 and v) the “V-Y”-shaped.8

Primary defects affecting 80% or more of the lip can be reconstructed with i) bilateral Karapandzic and Gillies flaps,5,6 ii) Fujimori flap,9 iii) Bernard von Burrow Webster technique,2,6,10 and iv) antebrachial microsurgical flap.2

In the present example, a primary suture was contraindicated due to the displacement it would cause to the philtrum...
and the general asymmetry that would result. The Abbé flap would be a plausible option for the case, however it would have disadvantages such as scar formation in the lower lip, the inconvenience of having to be performed in two stages, in addition to the patient’s discomfort of not being able to open the mouth in the first 14 to 21 days post-operatively. 5

CONCLUSION
Comparing the technique used in this example with the flaps described to date in the literature, it is possible to conclude that the aesthetic and functional outcomes provided to the patient were excellent. The practical demonstration of the nasolabial and submucosal flap, carried out in a single surgical procedure, allowed for an absence of tension, reconstruction of the skin and submucosa without distortion of the upper lip, a minimal surgical scar hidden in the nasogenian fold and the maintenance of the oral function in a young adult patient.

REFERENCES
Case Reports

Atypical presentation of a granular cell tumor

Apresentação atípica de tumor de células granulares

ABSTRACT

Case report of a male patient bearing a rare granular cell tumor in the left arm, confirmed by histology and immunohistochemistry (positive S100 and CD68 proteins).

Keywords: arm; granular cell tumor; skin neoplasms

RESUMO

Relato do caso de paciente do sexo masculino com raro tumor de células granulares em braço esquerdo, comprovado com histopatológico e imuno-histoquímica (proteína S100 e CD68 positivas).

Palavras-chave: braço; neoplasias cutâneas; tumor de células granulares

INTRODUCTION

The granular cell tumor (GCT), originally known as the Abrikossof tumor, is rare and of unknown origin. 1

Formed by cells with granular cytoplasm, it has benign features, and cases of malignancy are rare. It is slightly more frequent in women and people of African origin, and mainly occurs within the third to the fifth decade of life. 1,3

It is clinically characterized as a solitary, asymptomatic nodule, usually located in the head and neck (45-65%). Of these, 70% are located in the oral cavity (tongue and oral mucosa), although there are reports of its presence in other organs. 4

The diagnosis is performed with histological and immunohistochemical examinations. It has a typical histology that shows a poorly defined, non-encapsulated nodule with polygonal cells, abundant granular cytoplasm, with small round nuclei and prominent nucleoli. Its cells are strongly S-100 positive in the immunohistochemical tests.

The authors describe a case of this tumor having a rare location, not previously described in the literature.
CASE REPORT
A 30-year-old male patient attended a consultation for an asymptomatic nodular cystic lesion in the left arm measuring 1.3 x 0.8 cm that had been developing for two years. (Figure 1).
An excisional biopsy of the lesion was carried out, with the histological study suggesting an absence of alterations in the epidermis and dermis with non-encapsulated and circumscribed neoplastic proliferations up to the deep dermis, consisting of cells in a solid arrangement, with broad granular eosinophilic cytoplasm and small, regular monomorphic nuclei. The skin appendages were atrophic (Figure 2).
The S-100 (Figure 3) and CD68 (Figure 4) proteins were dimly positive in the immunohistochemical test – clone KP1. The other proteins – such as p53, Melan-A, HMB45, desmin, CK5, CD34, AML, AE1+AE3 came out negative, invalidating the hypothesis of melanocytic epithelial, muscular, or vascular neoplasia.

DISCUSSION
There are scarce reports of GCT in the literature. Typical locations for the tumor are the head and neck, with the oral mucosa being the most common. In the literature there were no reports of the tumor being present in the upper limbs, as in the case described in this paper.
Its origin is still unknown. In the past it was believed that this cell type originated in the smooth muscles, however some studies assume it arises from the nerve sheath cells – the Schwann cells – in which there is positivity for the S-100 protein. 5
In recent years, immunohistochemical markers that are positive for GCT, with positive immunoreactivity for alpha-1-antitrypsin and CD68 have been developed. CD68 is closely linked to the lysosomal membrane glycoprotein. The positive immunoreactivity for alpha-1-antitrypsin and CD68 in GCT may reflect the intracytoplasmic accumulation of phagolysosomes and does

not imply histiocytic origin for these tumors. From a practical point of view, therefore, only S-100 staining could be used to confirm the diagnosis.

Tumor treatment is performed through surgical resection within adequate margins, with the material being sent to histologic examination, as done in the present case. On rare occurrences of multiple tumors, intralesional injection of glucocorticoids can be carried out with an aim at temporarily reducing the size of the lesions, with spontaneous regression occurring in some cases.7

The malignancy of the tumor is controversial, since there have already been reported cases of malignant GCT. Its malignant variant can metastasize, and is more common in children and in the gingival region.

In face of this tumor’s atypical and not yet published location, in addition to the scarcity of reported cases, the authors emphasize the necessity of further studies aimed at deepening the knowledge on the subject. The authors also highlight the importance of surgical resection as it can possibly be a malignant lesion.

REFERENCES

The use of fractional CO2 laser therapy for the treatment of an in situ squamous cell carcinoma in the glans penis of a patient with hypospadias

Laser fracionado de CO2 para o tratamento de carcinoma espinocelular in situ da glande em paciente com hipospádia

ABSTRACT

Erythroplasia of Queyrat is an in situ squamous cell carcinoma of the glans penis. Due to its unusual location, surgical treatment can cause mutilation. CO2 laser-assisted vaporization is a treatment option with excellent aesthetic and functional results, but it requires strict follow up owing to its high recurrence rates. The authors describe a case of erythroplasia of Queyrat treated with fractional CO2 laser, with an absence of recurrence during a one-year follow up.

Keywords: carcinoma, squamous cell; carcinoma in situ; foreskin; laser coagulation; lasers; lasers; gas; penis; penile neoplasms

INTRODUCTION

The traditional treatment for squamous cell carcinoma of the penis is resection with a 2 cm safety margin. This procedure, however, is considered mutilating, and conservative treatments are accepted for in situ lesions. Treatments with imiquimod, 5-fluorouracil, and laser are described in the literature. CO2 laser is absorbed by water and produces deep, predictable cutaneous vaporizing regardless of the color of the tissue. The authors report a case of a patient with erythroplasia of Queyrat treated with CO2 fractional laser.

CASE REPORT

An 80-year-old man with hypospadias complained of a reddish lesion, progressive in growth that had appeared in the periurethral region one year earlier. On examination it was possible to observe an erythematous plaque in the ventral portions of the glans and foreskin (Figure 1). Biopsies were performed on four specimens, each obtained from one of four quadrants of the lesion, in addition to the exeresis of its most elevated part. The histological examination revealed a squamous cell carcinoma (SCC)
in situ: erythroplasia of Queyrat (Figure 2). The patient refused to undergo excision of the lesion, preferring the treatment with CO2 fractional laser (eCO2®, Lutronic, Sowon-Ro, South Korea). The procedure was performed monthly under topical anesthesia with 4% lidocaine cream (Dermomax®, Laboratório Aché, São Paulo, Brazil). During each procedure the coagulation of all the spongy area was carried out with a 5 mm margin. The parameters used were: 500μm tip, 100mJ/cm² density, and 60 to 80J/cm² fluence. Five sessions were performed (Figures 3 and 4). There were no complications between sessions. By the time this paper was approved for publication, the patient had not presented recurrences for a period of one year and would be followed up with for five years after the end of the treatment.

DISCUSSION
The erythroplasia of Queyrat (EQ) is an SCC in situ that develops in the glans or foreskin. Its extension up to the distal urethra – where the pseudostratified urethral epithelium becomes squamous stratified – has already been described. The EQ usually arises in the glans and inner foreskin as a single plaque or multiple plaques that are slightly elevated and erythematicous. When compared to SCC in situ of the epidermis, the EQ has a high rate of progression into invasive neoplasia (10-33%).

Conventional treatment of penile carcinoma involves full or partial amputation with good oncologic control of the lesion, however aesthetic and functional alterations may affect psychosexual function in important ways. Conservative therapy is an option for in situ lesions, and although survival is seldom affected, it has a higher recurrence rate when compared to the surgical treatment described.

Mohs micrographic surgery is a conservative treatment option, however it has a relatively high recurrence rate (21%) when compared to partial penectomy (0-7%). Due to the extent of the lesion, even undergoing Mohs micrographic surgery would be unacceptable to the patient because of the great loss of tissue.

Of the topical alternatives, 5-fluorouracil is the most studied, even though it causes great discomfort and a local inflammatory process during different treatment cycles. When the urethra is affected, however, this treatment is not recommended by some authors, since there is no guarantee that it will be possible to perform applications along the entire length of the intraurethral lesion.

According to the last U.S. directive, CO2 or ND:YAG laser therapy are among the options for penile SCC in situ, and some consider this as the first choice due to the favorable aesthetic and functional outcomes. On the other hand, local recurrence rates are high, reaching 26%; therefore, patients should be
followed up with more often than those who underwent amputation – every three months for the first two years and every six months up until five years after the treatment. Recurrences can be treated with the same procedure.\footnote{Mikhail GR. Cancers, precancers, and pseudocancers on the male genitalia. A review of clinical appearances, histopathology, and management. J Dermatol Surg Oncol. 1980;6(12):1027-35.}


The use of a liquid silicone implant for aesthetic treatment: coursing with late local and systemic adverse reactions

ABSTRACT
Since ancient times, humans have had an interest in improving their body contour. Liquid silicone has been used for this purpose, in order to improve deformities. The authors present a case of a female patient with paralysis in the right lower limb, who underwent improper injections of a large volume of injectable silicone in the affected limb aimed at correcting its contour. Ten years later, the patient developed local complications linked to the silicone injections – localized scleroderma lesions and superficial lipomatous nevus with progressive growth in the affected limb – and clinical and laboratory pictures of rheumatoid arthritis. Injectable liquid silicone should be contraindicated as a substance for implants.

Keywords: postoperative complications; silicones; skin neoplasms

INTRODUCTION
Between 1960 and 1970, physicians and lay people worldwide used silicone oil injections or industrial silicone to enlarge breast size and improve the body’s contour. After a variable period ranging from three to twenty years, many of the individuals who received such injections developed serious complications, ranging from product migration causing siliconoma (foreign body reaction), auto-inflammatory disease, and even carcinomas, leading to the cessation of this technique and its prohibition by the Food and Drug Administration (USA) and the Dimed in Brazil. In a retrospective study carried out from 1960 to 1996 with more than seven thousand patients who underwent silicone breast implantation, it was possible to observe the presence of a probable risk of rheumatoid arthritis, lupus erythematosus, scleroderma or Sjögren’s syndrome development.
The superficial cutaneous lipomatous nevus is an idiopathic abnormality, being considered a variant of the connective tissue nevus. It is histologically characterized by the presence of ectopic mature adipose tissue in the dermis. The rarest is the Hoffmann-Zurhelle variant, which consists of nodular or “mamillated” lesions grouped in cerebriform plaques in a segmental arrangement. It is usually congenital or emerges in the first three decades of life, having the pelvis and buttocks as its primary location.3

METHODS

The present study describes the case of a 50-year-old Caucasian married female patient, with polio sequelae in the right leg. She described having undergone a large volume implant of injectable silicone in the affected limb in procedures performed by physicians in 1994, aimed at improving the contour of the thigh and leg, which had been disfigured by the polio sequelae (Figure 1).

Approximately 10 years after the procedure had been carried out, the patient attended her first medical visit at the Fundação Pró-Hansen, describing cutaneous complications consisting of hardening of the skin of the right lower limb, with formation of asymptomatic erythematous plaques – possibly characterizing the clinical picture of morphea – and of a verrucous erythematous-pigmented plaque of approximately 15 cm x 25 cm and with progressive growth in the right gluteal region, which led to the suspected diagnosis of lipomatous nevus (Figure 2). The clinical and laboratory diagnosis of rheumatoid arthritis was also made at the time. According to the patient’s report, there was no family history of the condition.

In 2011, the patient sought care at the Fundação Pró-Hansen presenting a poorly healing ulcer on the right leg following a trauma on the hardened plaque. The wound’s debridement and cleansing were carried out, with the daily change of dressings with healing ointment and the administration of systemic antibiotics. Complete re-epithelialization occurred after four months of treatment, resulting in a depressed and unsightly scar (Figure 3). Laboratory tests, incisional biopsies of the hardened plaque and the verrucous lesion, as well as a MRI of the affected limb were carried out. The rheumatoid arthritis continued to be treated with 7.5 mg/week methotrexate and 1g/day paracetamol.

RESULTS

Histology

Hardened plaques: dermis and adipose tissue diffusely infiltrated by silicone droplets of different sizes, in addition to the presence of silicone within the macrophages and alteration of collagen fibers (Figure 4).

Late complications due to silicone injection

Verrucous lesion: tapered epidermis, with great accumulation of adipose cells of varying sizes, compatible with histological diagnosis of superficial lipomatous nevus (Figure 5).

MRI: atrophy of all muscles, sharp increase in volume of the right thigh due to edema and infiltration of the subcutaneous. It was possible to observe a marked morphostructural alteration and architectural distortion of the soft tissues in the gluteal region due to the diffusion of silicone (siliconoma). Presence of joint effusion in the knee and hip joints (Figure 6).

Laboratory tests: FAN (-), AntiRO (-), AntiLA (-), ESR 50mm/h, rheumatoid factor (+) 60UI/ml, blood count (normal) and liver function tests (normal).

DISCUSSION

Almeida Jr, Gevehr and Pinto reported a case of late onset of superficial lipomatous nevus, which is the only publication to date featuring this content. The pathogenesis in superficial lipomatous nevus is not well understood. Some authors suggest...
that this lesion originates from adipose precursor cells, as they were observed in the vicinity of the nevi, however this fact was not confirmed by electron microscopy.

The patient whose case is described in the present case report also referred to the late onset of the lesion, after 40 years of age.

Brotas et al.\(^5\) reported a case of a 40-year-old female patient who presented coalescing erythematous papules, forming a scleroderma plaque throughout the gluteal region two years after the application of liquid injectable silicone in the region.

A syndrome called ASIA (Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants) has recently been incorporated into the “siliconoses”, a term referring to the various events that occur after exposure to silicone. This syndrome’s pathogenesis is based on the hypothesis that early exposure to an adjuvant can trigger a chain of biological and immunological events, which in susceptible individuals, can lead to the development of autoimmune diseases. The hypothesis that allowed linking breast implants with the development of autoantibodies was that of the presence of an adjuvant action.\(^6\)

The silicone can migrate from the site of application to nearby or even distant body sites, with the presence of granulomas in the anterior and posterior sides of the lower limbs – resulting from the application of substances for increasing the thighs and buttocks – becoming increasingly common. The cause for the product’s migration is the large volume applied at short intervals, a fact that allows the silicone to travel to distant sites through the tissular planes.\(^7\)

In an article published by Silva,\(^8\) a patient received injectable industrial liquid silicone in the breast, with complications ten years later. The patient developed abscesses that led to a bilateral mastectomy 35 years later, due to complications caused by the silicoma.

In addition, there was a report of a case of a woman who underwent the application of injectable liquid silicone in both buttocks, with a late onset of difficult to resolve ulcerations.\(^9\)

In the present case report, the ulcer that wouldn’t heal was located on a hardened plaque, and infiltrated with silicone, according to the pathological examination.

Shvartsbeyn et al.\(^10\) published a case of a 35-year-old transsexual woman with bilateral masses in the buttocks, in which the histopathological evaluation revealed a collection of cells with cytoplasmic vacuoles containing lipids similar to lipoblasts. This pattern can be clinically and histologically mistaken for neoplastic processes, particularly when this adverse effect of the industrial silicone develops several years after injection.

Among the environmental factors that compromise the immune system are the adjuvants (silicone, aluminum, pristine and infections, among others), which can be deemed as being the “triggers” that initiate autoinflammatory diseases in humans.\(^7\)\(^-\)\(^11\)

CONCLUSION

The etiopathogenesis of localized scleroderma (morphoea) can be explained by the presence of silicone in the body turning into silica or silicon, and producing an autoimmune response with macrophages that phagocytoses silicon and releases humoral factors. The latter, in turn, trigger the biosynthesis of collagen by fibroblasts that induce lymphocyte alterations in the subpopulations CD2 +, CD8 + y T-DR (+)\(^11\) (Figure 7).

ACKNOWLEDGEMENTS

We would like to thank Dr. Maurizio Pedrazzani from X-Leme diagnostic imaging; Dr. Lismari A.F. Mesquita, Dermatopathologist Physician at the Dermatology Service of the Santa Casa de Curitiba; Dr. Samuel Regis de Araújo, Pathologist Physician at Laboratório Master pathology and cytopathology.
REFERENCES


Cutaneous leiomyosarcoma: a case report

ABSTRACT
Cutaneous leiomyosarcoma is a rare neoplasm with a tendency to recur, and with possible metastases. The authors report a case of a female patient who was being treated with triamcinolone injections in a dermal leiomyosarcoma lesion that was misdiagnosed as keloid.

Keywords: keloid; leiomyosarcoma; skin neoplasms

INTRODUCTION
Cutaneous leiomyosarcoma (LMS) is a rare neoplasm corresponding to 2–3% of soft tissue sarcomas.1 It is likely derived from piloerector smooth muscle (dermal LMS) or from smooth muscle of the vascular wall in the subcutaneous (subcutaneous LMS),1-6 with a different biological behavior. It is prevalent in Caucasian men in their 5th and 6th decades of life.2

Its subcutaneous form consists of a bulging covered with normal and mobile skin over the lesion. Recurrence is high (up to 70%) and there is a risk of metastases.1

Primary cutaneous LMS (dermal) has a relatively indolent behavior. The recurrence rate is around 30%,3 but can be absent in some series.2 Its extension up to the subcutaneous level brings a higher risk of recurrence,1 though the risk of metastasis is low2-4 and even controversial.3,5 It comes in the form of a single tumor of up to 3 cm,2-5 well-defined, lobulated, pedunculated or umbilicated and varying in color (erythematous to brownish).2 When grouped in nodules, the presence of an extracutaneous primary neoplasm should be investigated, especially in its retroperitoneal or uterine forms.1 There may be pain on compression, as well as exulceration and bleeding.1,5 It mainly affects areas in the thighs having a high hair density, as well as the head and neck.1,2,6
Histology shows a smooth muscle cell tumor, with proliferation of fusiform cells with elongated, “cigar-shaped” nuclei, pleomorphism, and mitosis. Immunohistochemistry identifies the smooth muscle cells, with smooth muscle actin, desmin, and vimentin as its main markers.\(^1^6\)

The authors describe a case of leiomyosarcoma in which, due to the rarity of the condition, there had been a delay in the treatment due to lack of previous clinical suspicion.

**CASE REPORT**

A 49-year-old female patient was referred by a plastic surgeon for a differential diagnosis evaluation of a keloid lesion, after unusual response to corticosteroid injection.

There had been an onset of a painful lesion with keloidal appearance on the lateral side of the right leg, six years earlier. The patient underwent excision with three recurrence episodes of the lesion, the last of which was three years before the submission of the present paper. She reported previous histologies with no malignancy, however the results were not in her possession. After eight monthly sessions of local injections of triamcinolone, she developed erythema, a worsening of pain, and changes in the lesion’s appearance. Clinical examination showed an erythematous tumor of 4.5 cm x 4 cm, having an irregular surface and exulceration in the anteroposterior pole (Figure 1). The incisional biopsy revealed a clearly differentiated spindle cell neoplasm (Figure 2-4) with positive immunohistochemistry for smooth muscle actin, desmin, and S-100, and weakly positive for AE1/AE3. The diagnosis was consistent with leiomyosarcoma. Laboratory tests for the detection of a possible primary focus of neoplasia came back negative.

The resection of the lesion was performed with a 1 cm margin and a dissection depth up to the muscle fascia. A decision was made for the purse string suture with the aim at hemostasis and the plan for a later reconstruction. After the histological examination evidenced an excessively narrow deep margin, the dissection was extended up to the muscle layer (Figure 5). A total skin graft was performed in the third surgical stage. The patient

**FIGURE 1:** Side view of the right leg. Erythematous-hyperchromic tumor with 4.5 cm x 4 cm, irregular surface, and exulceration in the lesion’s anteroposterior pole

**FIGURE 2:** Spindle cell neoplastic lesion involving the entire dermis, showing storiform arrangement and in fascicles; (A) Small magnification; (B) Higher magnification

**FIGURE 3:** (A) Marked cellular pleomorphism and numerous mitotic figures (black arrows); medium magnification; (B) Marked cellular pleomorphism and multinucleation (red arrows)

**FIGURE 4:** Focus of coagulation necrosis (arrow); large magnification

**FIGURE 5:**
progressed without complications or signs of recurrence during the observation period (eight months) and remains under clinical follow up (Figure 6).

DISCUSSION

The cutaneous leiomyosarcoma is a rare neoplasm and arises as a tumor that varies in color, shape, and size, and is more common in men. In the case described, the patient is female, phototype IV, and the disease emerged with a topography that was diverse from the usual.

Due to its nonspecific clinical features, diagnosis of leiomyosarcoma depends on the histologic examination and immunohistochemistry. In the present case, the patient had started treatment motivated by a clinical suspicion of keloid. However, she did not have a typical lesion and therefore her case deserved further investigation, given that various tumors and even infectious diseases may have a keloidal aspect.

The benefit of imaging examinations for pre-operative/diagnostic staging is not clear, and results are often negative. Although there is no clear guidance in the literature, a decision was made in this case to research and rule out other neoplasms (retroperitoneal, uterine) or metastases (lymph node, lung).

The lesion exeresis is the treatment of choice, with safety margins being suggested at 1 cm or the use of Mohs micrographic surgery (MMS). Adjuvant radiation therapy is mentioned, especially for lesions in excess of 5 cm, deep or where it is impossible to widen margins. The main prognostic factor is the status of the surgical margins, in addition to the size of the tumor, extension of the subcutaneous involvement and mitotic index.

In the present case, the surgery depth was increased, since the deep, free margin was deemed excessively narrow. A decision was made for not closing the surgical wound during the first operative time and to wait for confirmation from pathology that the removal of the lesion was complete, before the implementation of the graft. This technique is also described by other authors for the treatment of leiomyosarcomas and other tumors.

The patient’s elapsed follow up time after the surgery is still short, however she remains under monitoring. The literature does not specify whether there is a necessary and limited follow up time or whether it should be continued, as is the case in the authors’ dermatological service.

The present case exemplifies the importance of considering the differential diagnosis in dermatology. Although the clinical aspect is sufficient in a great number of cases, the histology is crucial for the identification of rare dermatoses that demand different therapeutic approaches. When considering lesions of a keloidal aspect, the absence of previous trauma, a positive personal and family history and the presence of pain should trigger an alert.
REFERENCES


