Original Article

Clinical and histological evaluation of patients with refractory melasma treated with fractional Erbium:YAG laser

Avaliação clínica e histológica de pacientes com melasma refratário tratadas com laser de érbio: Yag fracionado

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ABSTRACT

Introduction: Melasma is an acquired hyperpigmentation that affects primarily the face and occurs more frequently in women with darker skin. There are several therapies for treating melasma, however its long-term management remains a challenge.

Objectives: To evaluate fractional Erbium:YAG laser's clinical effectiveness in treating refractory melasma through the histological analysis of usual characteristics and the amount of epidermal and dermal pigment before and after treatment.

Methods: Ten patients underwent three fractional Erbium:YAG laser sessions at monthly intervals. Biopsies were obtained before and after treatment. Subjective and objective clinical evaluations were carried out before, during, and after treatment.

Results: No statistical improvement in Melasma Area Severity Index score was observed during the treatment. Hyperpigmentation of the basal layer and pigment deposition in the dermis was observed histologically. In seven cases, there was a reduction in the degree of hyperpigmentation in the epidermis, which was not statistically significant.

Conclusions: The treatment of melasma with fractional Erbium:YAG laser was ineffective. Nonetheless, a decrease in Melasma Area Severity Index scores and in the degree of hyperpigmentation of the epidermis was detected, suggesting that fractional Erbium:YAG laser can clinically and histologically improve the degree of hyperpigmentation of the skin.

Keywords: *melanosis; lasers; erbium.*

RESUMO

Introdução: *Melasma é hiperpigmentação adquirida que afeta primariamente a face, e acomete mais comumente mulheres de pele escura. Diversas são as terapias utilizadas para seu tratamento; seu manejo clínico a longo prazo, entretanto, permanece um desafio.*

Objetivos: *Avaliar a eficácia do laser de érbio:YAG fracionado, analisar histologicamente as características usuais do melasma e a quantidade de pigmento na epiderme e derme antes e após o tratamento.*

Métodos: *Dez pacientes foram submetidas a três sessões do laser de érbio:YAG fracionado ablativo com intervalo de um mês de uma para outra. As pacientes foram biopsiadas antes e após o tratamento. Foram realizadas avaliações clínicas subjetivas e objetivas, antes, durante e após o tratamento.*

Resultados: *Não foi observada melhora do escore Masi ao longo do tratamento. Histologicamente foram observadas hiperpigmentação da camada basal e deposição de pigmento em derme superficial. Em sete casos observou-se redução no grau de hiperpigmentação da epiderme, sem significância estatística.*

Conclusões: *O tratamento do melasma com o laser de érbio:YAG fracionado ablativo não se mostrou efetivo, apesar de haver tendência a diminuição dos escore Masi e no grau de hiperpigmentação da epiderme, sugerindo que o laser de érbio:YAG pode ser capaz de melhorar tanto clínica quanto histologicamente o grau de hiperpigmentação da pele.*

Palavras-chave: *melanose; lasers; érbio.*

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INTRODUCTION

Melasma is an acquired hyperpigmentation, predominantly on the face, characterized by irregular brownish patches involving the cheeks, forehead, nose, upper lip, and chin. A great number of dermatological consultations relate to melasma, and 90% of cases seen are women. This condition can have a considerable psychological impact.[1]

Several factors can be involved in the pathogenesis of melasma, including genetic predisposition, exposure to the sun, pregnancy, oral contraceptives, and phototoxic drugs. [2, 3]

Traditional therapies include the use of sunscreens, whitening agents such as hydroquinone, retinoids, topical steroids, chemoexfoliation, laser and intense pulsed light, all of which produce variable results and involve frequent recurrences. Despite the various therapeutic modalities that are available, the long-term management of this condition remains a challenge. [4-6]

The energy emitted by the fractional ablative Erbium:YAG laser is highly absorbed by the epidermis, causing thin ablation that leads to fast healing with a low risk of complications. It is recommended for treating mildly to moderately photodamaged skin, small atrophic scars, rhytids, and dyschromia .[7-9]

This study's objective is to evaluate the effectiveness of fractional ablative Erbium:YAG laser in the treatment of melasma after one and three sessions); melasma's recurrence and typical histological features; and the amount of melanin pigment in the epidermis and dermis before and after treatment.

METHODS

Ten female patients, aged 38-53, were selected. All were treated at the Dermatology Outpatient Clinic of the Hospital de Clínicas da Universidade Federal Paraná between November 2008 and February 2009, having presented melasma with varying degrees of hyperpigmentation and duration, and having undergone several treatments with partial or no improvement. Fitzpatrick phototypes ranged from III to V.

Inclusion criteria were: presence of melasma for more than one year; partial or no response to previous treatment; regular use of sunscreen; and consent to participating in the study, biopsies, and photographic records. Exclusion criteria were: melasma with recent onset or good response to treatment with whitening; the presence of active infection in the face; intolerance to laser applications; and refusal to consent to undergo biopsies and photographic records. All patients were informed about the risks, benefits, and potential complications, and signed the term of informed consent according to the hospital's ethics and research committee.

All patients underwent three sessions of fractional 2,940 nm Erbium:YAG laser (Pixel, Harmony®XL platform, Alma Lasers Ltd, Israel) at monthly intervals. The procedure was carried out after washing the face with regular soap, without the application of anesthetic. All individuals in the procedure room – patients, doctor, and staff – wore eye protection to block the light emitted by the device.

The treatment was performed using the 7 x 7 tip, 1,400 mJ/P fluence, 2 Hz pulse per application per patient. Each session comprised three consecutive laser applications all over the face – each of which was performed in a separate aesthetical unit. The laser was applied in horizontal, vertical, and diagonal directions to allow a more uniform energy distribution on the skin.

All patients were instructed to apply ice packs on the treated area afterwards. No antibiotics or prophylactic antivirals were prescribed. During the study period, the patients were advised to avoid exposure to the sun and to use broad UVA/UVB spectrum sunscreen (SPF ≥ 50) at least four times a day.

Photographic records were made using a single camera (Sony Cybershot DSC-W30®, 6.0 MP, Japan) with consistent lighting parameters. All patients were photographed at baseline (D0), 30 days after each session (D30, D60, D90), and four months after the last session (D180).

All patients were biopsied (3 mm punch, in the hyperpigmented area) at baseline (D0) and four months after the end of treatment (D180). Biopsies were performed under local anesthesia, and the samples were fixated in 10% formalin solution. Hematoxylin-eosin staining (H&E) was used to assess the general histopathological alterations of the affected skin, and Fontana-Masson staining was used to visualize the melanin pigment. Specimens underwent blind analysis by experienced dermatopathologists employing an Olympus® BX50 microscope (Tokyo, Japan).

The patients were asked about their individual perceptions about the treatment's effectiveness 30 days after each session (D30, D60, D90) and four months after the last session (D180). The answers varied from: worsening, unchanged, slight improvement, moderate improvement, and marked improvement.

The medical evaluation was divided into subjective and objective, being carried out by experienced dermatologists. The subjective evaluation assessed overall improvement (modest, moderate, or marked improvement; unchanged; worsening). This evaluation was carried out through the comparative analysis of photographs between D0 and D90, D0 and D180, and D90 and D180.

The objective evaluation was carried out using Melasma Area and Severity Index (MASI) scores on D0, D30, D60, D90, and D180. The face was divided into four areas: forehead, right and left malar region, and mentum – corresponding to 30%, 30%, 30%, and 10% of the total area of the face, respectively. The severity of the melasma in each region was evaluated based on three variables: the area involved as a percentage of the total area (A), degree of pigmentation (P), and homogeneity (H). Numeric values were attributed to the percentage of the total area involved (0 = 0% involvement, 1 = <10% involvement, 2 = 10-29% involvement, 3 = 30-49% involvement, 4 = 50-69% involvement, 5 = 70-89% involvement, and 6 = 90-100% involvement. The degree of pigmentation (P) and the hyperpigmentation homogeneity (H) were graded on a scale from 0-4 (0 = normal skin color with no evidence of hyperpigmentation; 1 = hardly noticeable hyperpigmentation, some points of involve-

ment; 2 = mild hyperpigmentation, small areas of involvement with diameter less than 1.5 cm; 3 = moderate hyperpigmentation, areas of involvement with diameter less than 2 cm; 4 = severe hyperpigmentation, even involvement without light areas). To calculate the MASI, the sum of the degree of pigmentation severity and homogeneity was multiplied by the numeric value corresponding to the affected area and by the percentage representing the four areas of the face. Those values were added to produce the total score: forehead 0.3 x (P + H) x A + right malar 0.3 x (P + H) x A + left malar 0.3 x (P + H) x A + mentum 0.1 x (P + H) x A.

The biopsies were evaluated in order to histologically confirm the melasma diagnosis, compare the amount of melanin pigment in the epidermis before and after treatment, and compare the amount of melanin pigment in the dermis and its thickness before and after treatment. In the H&E staining, each biopsy was assessed according to the thickness of the epidermis (by counting the number of layers of the stratum spinosum) and the presence of solar elastosis and perivascular inflammatory infiltrate. In order to compare the amount of epidermal and dermal pigment in the biopsies before and after treatment, the slides stained with Fontana-Masson were evaluated. The two slides were placed side by side to allow the comparison of the intensity of pigmentation in the basal layer between them (more or less pronounced). To measure the thickness of the melanin pigment in the dermis, slides stained with Fontana-Masson were evaluated using a millesimal rule that measured the distance from the dermoepidermal junction to the depth where the pigment was located.

In the statistical analysis – used to provide a summary of the data and assist in defining the most appropriate statistical techniques – the normality of the data was not proven using the Lilliefors test. As a result, non-parametric statistical tests were applied.

The Friedman test (suitable for comparing three or more dependent samples) was used to compare MASI scores between the study's time points. The Wilcoxon test was employed to compare the thickness of the pigment and the number of layers before and after treatment. Fisher's exact test was used to compare the amount and distribution of pigment before and after treatment. The Mann-Whitney test was employed to assess the relationships involving the differences in the amount of pigment.

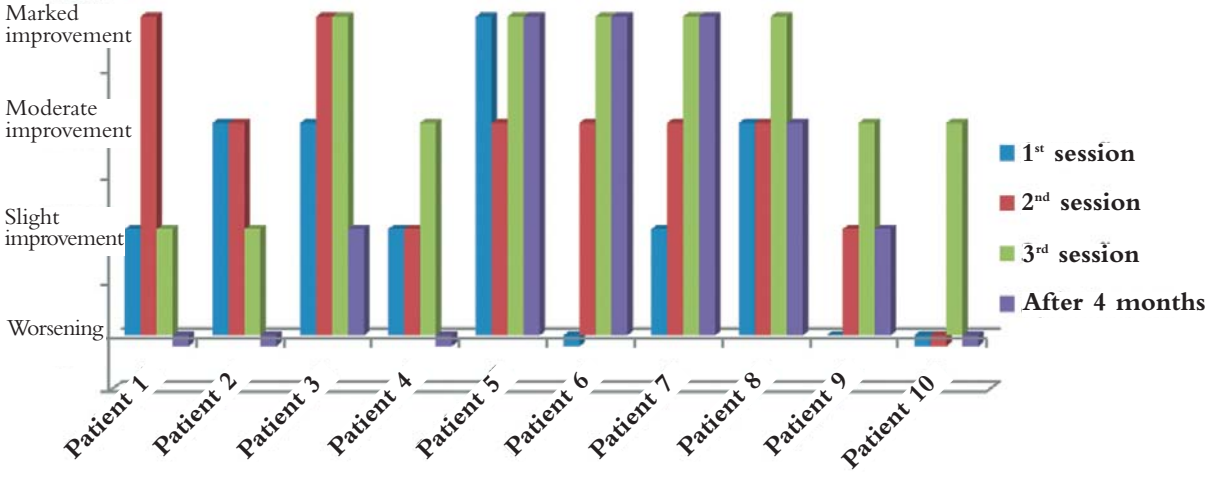
RESULTS

Most patients complained of mild to moderate intra-operative and post-operative discomfort for up to 48 hours. Re-epithelialization occurred within 3-5 days. No cases of scarring, ectropion, or bacterial or viral infection were observed. There was one case of post-inflammatory hyperpigmentation in the first session, which prompted the reduction of the following sessions' fluence to 1,000 mJ/P in the affected patient. Less frequent complications were facial and eyelid edema.

Most patients noticed mild improvement after the first session. One patient reported worsening of the condition, while all others reported improvement after the second session. After the third session, all patients reported improvement. Four months after the last session, four patients reported either worsening or recurrence compared to one month after the last session. Six patients reported sustained improvement after that period (Graph 1).

In the subjective clinical evaluation, nine of ten patients presented improvement in the comparison of D0 vs. D90, albeit slight; and one case remained unchanged. In the comparison of D90 vs. D180, three patients presented mild improvement, four remained stable, and four worsened. In the comparison of D0 vs. D180, six patients had mild improvement, one had moderate improvement, and three did not change. No worsening was observed after the final assessment period compared to baseline (Figure 1).

The clinical evaluations obtained using MASI scores yielded conflicting data. In the comparison of D0 vs. D90, three patients worsened, six improved, and one remained unchanged. In the comparison of D90 vs. D180, two patients improved, four remained stable, and four worsened. In the comparison of D0 vs. D180, five patients worsened, four improved, and one remai-



Graph 1: Patients' subjective evaluation

ned unchanged (Tables 1 and 2).

The Friedman test did not find significant differences between MASI scores in the time points analyzed ($p > 0.10$). Nonetheless, although the data were not statistically significant, a decrease in mean MASI scores was observed between D0 and D90, and an increase was observed between D90 and D180 (Graph 2).

The pre-treatment biopsies revealed the presence of atrophy in the epidermis in half of the cases, in addition to solar elastosis and mild to moderate perivascular lymphocytic inflammatory infiltrate in all cases (Figure 2). Another observed alteration was mild to moderate perivascular edema, which was present in 60% of patients.

Post-treatment biopsies presented similar findings; epidermis atrophy was observed in 40% of patients. Mild to moderate perivascular edema was found in 80% of cases. There was no statistical difference in the number of layers in the epidermis before and after treatment ($p = 0.73$).

Epidermis hyperpigmentation was analyzed using Fontana-Masson staining. Before treatment, all cases presented epidermis hyperpigmentation, consistent with the diagnosis of melasma. Melanic pigment granules in varying quantities could be observed from the basal layer to the stratum corneum. The pigment distribution throughout the basal layer was homogeneous in most cases. The presence of melanin in the superficial dermis could also be observed in all samples, in varying amounts.

In the post-treatment evaluation of biopsies, the hyperpigmentation of the epidermis could be observed again – from the basal layer to the stratum corneum, with melanin distributed homogeneously in the basal layer in half of the cases. In the dermis, the melanin was restricted to the superficial dermis, as in

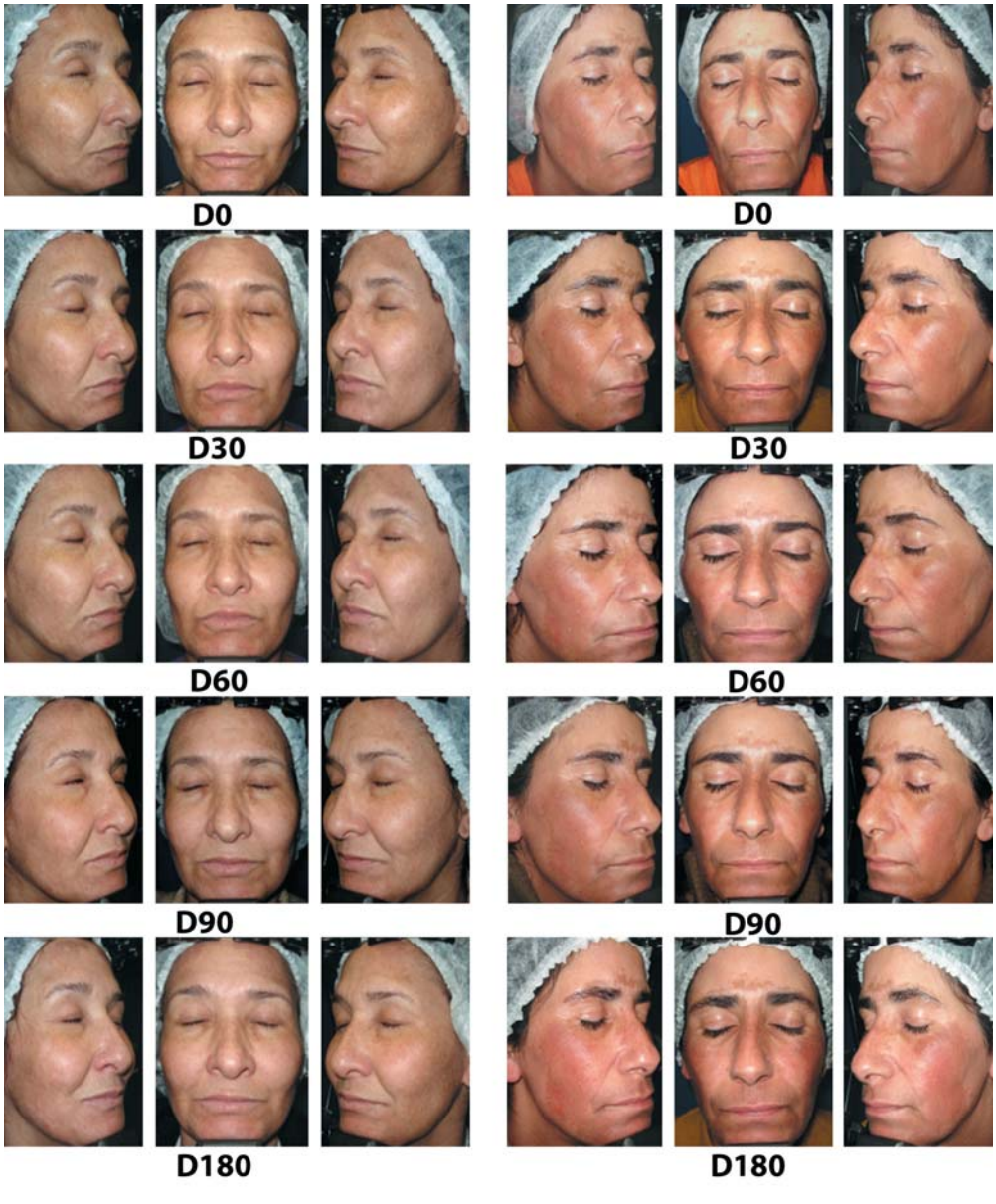


Figure 1: Pictures of two patients at time points D0, D30, D60, D90, and D180

Table 1: MASI scores per patient per time point

	MASI score D0	MASI score D30	MASI score D60	MASI score D90	MASI score D180
Patient 1	22,5	22,8	22,8	22,8	25,2
Patient 2	26,7	23,7	23,7	22,5	26,7
Patient 3	8,7	10,7	12,0	12,0	10,8
Patient 4	11,1	8,1	8,1	8,1	7,5
Patient 5	29,8	23,4	23,4	23,4	23,4
Patient 6	19,2	22,8	22,8	20,1	20,1
Patient 7	7,2	7,2	7,2	6,0	6,0
Patient 8	20,1	17,7	18,9	18,9	18,9
Patient 9	14,4	16,8	16,8	14,4	15,6
Patient 10	16,2	16,2	16,2	14,1	17,7

Table 2: Mean, minimum, and maximum MASI scores per time point

MASI	n	Mean	Minimum	Maximum	Standard deviation
D0	10	17,59	7,2	29,8	7,50
D30	10	16,89	7,2	23,7	6,46
D60	10	17,19	7,2	23,7	6,30
D90	10	16,23	6	23,4	6,26
D180	10	17,19	6	26,7	7,21

the pre-treatment examinations.

In the qualitative comparative analysis of the epidermis' degree of hyperpigmentation before and after treatment, there was a considerable reduction in the amount of melanin pigment in the basal layer in 70% of cases (Figure 3). In the remaining cases, there was increased pigmentation in the basal layer compared to baseline (Figure 4). However, the data was not statistically significant ($p = 0.09$).

There was a decrease in dermal pigmentation in 60% of cases (and an increase in 40%) after treatment – however without statistical significance ($p = 0.33$), and without correlation to the improvement or worsening of the degree of hyperpigmentation in the epidermis ($p = 0.16$).

There was no statistical difference regarding the pigment distribution in the basal layer before and after treatment ($p = 0.22$). The Wilcoxon test did not find a significant difference between the thickness of the pigment in the dermis before and after treatment ($p = 0.173$). However, there was a tendency of reduction. No correlation was observed between the difference in pigment thickness in the dermis and qualitative improvement in the degree of epidermal hyperpigmentation ($p = 0.183$). Also, there was no correlation between the difference in pigment

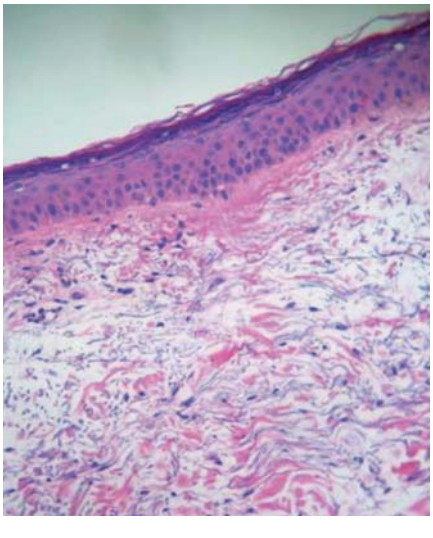


Figure 2: Biopsy showing atrophy of the epidermis, marked solar elastosis, mild perivascular lymphocytic inflammatory infiltrate and mild perivascular edema (H&E, 400x 2x)

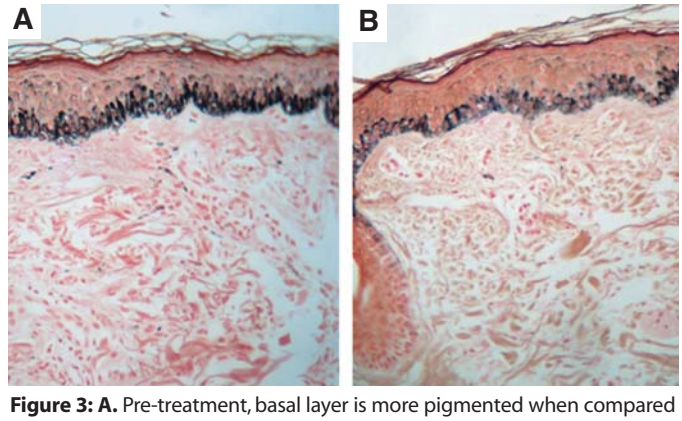


Figure 3: A. Pre-treatment, basal layer is more pigmented when compared with; **B.** after the treatment (Fontana-Masson, 400x 2x)

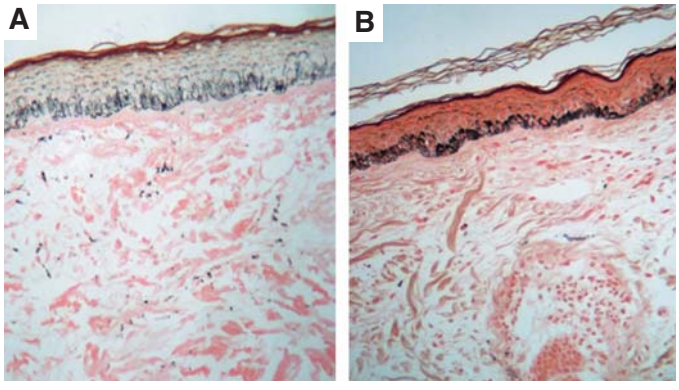
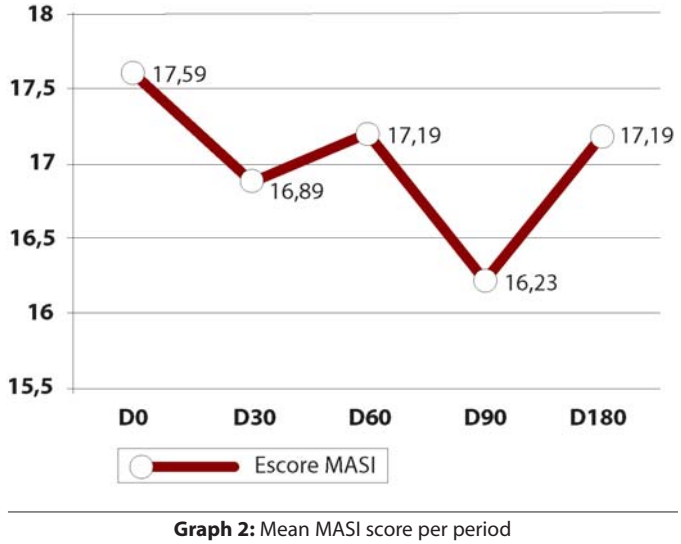


Figure 4: A. Pre-treatment, basal layer is less pigmented when compared with; **B.** after the treatment (Fontana-Masson, 400x 2x)



Graph 2: Mean MASI score per period

thickness in the dermis and qualitative improvement in the degree of pigmentation of the dermis (p = 0.067).

DISCUSSION

Melasma is a common cause of acquired hyperpigmentation, especially in patients with higher phototypes, including Latin Americans. It is a common and chronic complaint in dermatologic practices, and presents variable responses to treatment and a tendency to recur.

The management of melasma poses a challenge. Although there are many therapeutic modalities, including whitening agents, chemical peels, and laser treatments, many patients are unresponsive to those therapies. Moreover, due to its recurring nature, maintenance treatments and the removal of possible etiologic factors become necessary. [10-13]

The Erbium:YAG laser has become an interesting ablative tool for the treatment of melasma. Its energy is highly absorbed by tissues that contain water, and its pulse duration is shorter than the thermal relaxation time of the skin. Those characteristics limit the dissipation of heat, creating a zone of thermal damage less than 50 m deep. As a result, the recovery time after surgery is reduced and the risk of post-inflammatory hyperpigmentation is potentially decreased. [8, 14.15]

In this study, the treatment was well tolerated and had a low complication rate. Only one case (a phototype III patient) presented post-inflammatory hyperpigmentation. The other patients – even those with higher phototypes – did not present this complication. The treatment was well accepted by the patients, with most reporting improvement, albeit mild, in at least one of the three treatments. Regarding the overall medical assessment, an improvement in the degree of hyperpigmentation was observed from baseline to 30 days after the last session (D0 vs. D90) in nine of the ten patients. While not statistically significant, a trend towards reduced MASI scores between D0 and D90 (with an score increase observed four months after the end of treatment, consistent with the recurrent behaviour of the disease) was clinically observed. No treatment other than photoprotection was used after the sessions.

The recurrence of hyperpigmentation at the end of the study period may have resulted from several factors, including the tendency for the condition to recur in the absence of treatment, or the lack of treatment associated with the use of sunscreen. It is possible that combining the laser treatment with topical depigmenting agents would maintain the results obtained after the third session.

Regarding the histologic features, in addition to the hyperpigmentation of the epidermis, all cases revealed the presence of variable solar elastosis and perivascular inflammatory infiltrate, consistent with the data found in the literature. Perivascular edema was common in several examinations – both pre-and post-treatment – however there are no similar reports in the literature. [16-23]

From the histological point of view, while not statistically significant, treatment with Erbium:YAG laser led to a reduction in the amount of melanin pigment in the basal layer of the epidermis in 70% of patients – which did not correlate with clinical improvement or worsening. Likewise, it did not affect the depth of pigmentation in the dermis. [24-26]

Therefore, the application of fractional Erbium:YAG laser in isolation, using high fluence and long pulse with three passes at monthly intervals, cannot be considered highly effective for treating melasma. Notwithstanding, the data shows that it promotes histological changes in the skin that persist even after a long period without treatment.

Dermatologists should always be aware of adjuvant methods in the management of patients with melasma, since the negative psychological impact can affect the patients' quality of life. The advice to avoid sun exposure and to use sunscreen in a systematic manner, and the prescription of therapies including whitenings, are essential for successful treatment.

CONCLUSION

The treatment of melasma with fractional Erbium:YAG laser was proven safe and well tolerated, with a rapid post-operative recovery, however the decline in MASI scores were not

significant. For most patients it was a well-accepted treatment that led to subjective improvement.

Despite the small sample size, the data suggested that the Erbium:YAG laser can improve, both clinically and histologically, the degree of epidermal hyperpigmentation. The study treatment was not curative, for it presented a great potential for recurrence. It is possible that combining the laser treatment with the use of depigmenting agents between sessions may lead to an improvement in the clinical response and a decrease in the risk of recurrence. New technologies can be used to treat this condition, however their results are inconsistent and need to be carefully evaluated. ●

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