**Comparison of fractional erbium:YAG laser-assisted tranexamic acid delivery alone and in combination with oral tranexamic acid in melasma**

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**Abstract**
Tranexamic acid (TA) emerged as a promising agent for melasma. However, due to its hydrophilic structure, topical TA should be combined with a penetration-enhancing strategy to augment efficacy. To evaluate the efficacy of fractional erbium:YAG laser-assisted delivery (LAD) of topical TA 5% either with or without oral TA treatment in recalcitrant melasma patients. The authors retrospectively assessed the treatment outcomes of melasma patients treated by fractional erbium:YAG LAD of topical TA 5%. Patients receiving a standard protocol including four biweekly laser sessions were eligible. The study included two groups: group 1 patients received oral TA and LAD of topical TA 5%, and group 2 patients received only LAD of topical TA 5%. Two blinded dermatologists reported pre-treatment and post-treatment modified MASI (mMASI) scores. Mean mMASI scores in both group 1 (n = 15) and group 2 (n = 19) were significantly lower at the end of the treatment than baseline values (p = 0.001; p = 0.022, respectively). The decrease of mMASI scores were higher in group 1 (median = 2.1) (64.7%) than in group 2 (median = 1.2) (41.8%) (p = 0.027). Fractional erbium:YAG LAD of topical TA 5% is an efficient treatment regimen for melasma patients recalcitrant to conventional treatment approaches. The implementation of oral TA to this regimen improves the therapeutic outcomes.

**Keywords** Melasma · Pigmentation disorders · Laser-assisted delivery · Ablative fractional laser · Erbium:YAG laser · Tranexamic acid

**Introduction**
Melasma is a common acquired disorder of facial hyperpigmentation related to the complex interaction of genetic, hormonal factors, and UV exposure. The management of melasma is quite challenging for clinicians and deteriorates affected patients’ quality of life [1]. Rather than preferring a single treatment agent, various topical bleaching agents, chemical peels, mesotherapy, and laser treatments have been combined to enhance treatment outcomes, and relapses are almost inevitable. The hurdles to cure melasma led to efforts to further elucidate the pathogenetic mechanisms to determine new therapeutic targets. An ancient molecule, tranexamic acid (TA), emerged as a promising agent during this research. TA demonstrated multimodal efficacy in both pigmentation and vascular components of melasma along with the inhibition of UV-induced mast cell activation [2–5]. Oral TA demonstrated remarkable efficacy in recalcitrant melasma patients with low therapeutic doses (500 mg/day) compared to the conventional indications [6]. However, TA is an off-label treatment for melasma and concerns arose about the possibility of thromboembolic complications, attending major medicolegal implications [7]. Thus, clinicians should evaluate patients carefully for the presence of constitutional risk factors of thromboembolism, stroke, and heart diseases before introducing oral TA. The concerns about the possible systemic adverse effects propelled topical tranexamic acid to the forefront. However, due to its hydrophilic structure, TA is unable to permeate skin passively. Therefore, enhancement techniques such as liposomes or

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physical modalities (microneedling, lasers) are required to assist transdermal TA delivery [8–14].

The literature data on TA’s efficacy on melasma mainly includes Asian patients. On the other hand, as stated by Bala et al., there have been limited data for those with Hispanic, Caucasian, Mediterranean, Middle Eastern, or African-American backgrounds [15].

This study comparatively evaluated our experience with ablative fractional laser (AFL)–assisted delivery of topical TA in the presence or absence of oral TA treatment in recalcitrant melasma patients from the Mediterranean region.

Materials and method

The authors conducted this study on their clinical photographic archives and medical records. The institutional ethical committee approved this study (2021–33). One author (AB) extracted the data of the recalcitrant melasma patients receiving erbium:YAG laser delivery of topical TA at a single dermatology outpatient clinic of a tertiary center, from October 2019 to March 2020. Only participants who signed the written informed consent were enrolled. The cases who were not able to complete the pre-defined regimen or had to stop one of the administered treatments related to adverse effects were excluded as the cases with missing data.

The study included Turkish women. Turkish people are part of the Caucasian race. However, they are characterized with a darker skin phenotype and darker hair color that is further classified within the Mediterranean subgroup. The skin phototypes of the study population have been noted and analyzed. All of the patients were recalcitrant melasma patients and they had previously used at least two topical bleaching creams, including topical hydroquinone, unexceptionally. They had stopped these treatments due to the lack of efficacy or the emergence of adverse effects.

According to the treatment regimens, the authors identified two study groups, including a standardized protocol of fractional erbium:YAG laser-assisted delivery (LAD) of topical TA 5% for all of the cohort. Topical 5% tranexamic acid cream was prepared as a kind gift from Dermoskin® Cosmeceuticals (İstanbul, Turkey). The treatment regimen includes four biweekly laser sessions, and topical 5% TA had been introduced immediately after the first laser intervention followed by consecutive once-daily applications until the 9th week. To ensure fractional erbium:YAG LAD, all fractional erbium:YAG laser applications had been immediately followed by topical TA 5% cream. AFL was performed by erbium:YAG laser (Fotona Dynamis, XS, Slovenia, Ljubljana). The fractional erbium:YAG laser settings were identical in all patients at baseline. The 1st pass of fractional erbium:YAG laser with 300 μsn pulse duration, 1.2 J/cm² fluency, and 5 mm spot size over the entire facial skin was followed by a 2nd pass specifically targeting the affected areas with the same settings. The energy settings were further adjusted according to the Fitzpatrick skin type and reaction patterns in consecutive treatment sessions and increased to fluencies of 3 to 6 J/cm². The patients did not report pain through the laser sessions; thus, the procedure was applied without anesthesia.

All of the included patients had been assessed and informed about adjuvant oral TA treatment. The patients with risk factors (an individual or familial history of thromboembolic incidents, connective tissue disorders, the possibility of drug interactions, etc.) were not prescribed oral TA. The remaining cases decided whether they wanted to receive oral TA treatment. The patients reluctant to receive the drug had undergone their laser sessions without oral TA treatment.

Group 1 (oral + topical + erbium:YAG laser) (O + T + L) patients were prescribed oral TA (2 × 250 mg/day) 3 weeks before the first laser session, and group 1 patients continued the treatment for a total duration of 12 weeks. Group 2 (topical + erbium:YAG laser) (T + L) consisted of patients receiving only AFL-assisted delivery of topical TA. Figure 1 represents the treatment scheme of the study groups.

The patients who did not complete this defined regimen were excluded as the cases with missing data.

Age, gender, previous treatments, and treatment outcomes were noted.

The standard clinical, 3D imaging (3D LifeViz® Mini, Quantificeare, Valbonne, France), and Wood’s lamp examination photographs of the patients before and after treatment were sorted according to the timeline and compared together by two blinded physicians (PE, EC). The quantitative evaluation included modified Melasma Area Severity Index (mMASI) scores calculated according to Pandya et al.’s description [16].

The primary outcome measure of this study is the mMASI score decreases detected at the 3rd week after the final laser session.

The mMASI changes were further evaluated for each patient as “excellent,” “very good,” “good,” and “fair” adapted from the criteria described by Mohamed et al. as the following: excellent: more than 75% decrease; very good: 50–75% decrease; good: 25–49% decrease; and fair: below 25% decrease in mMASI scores [17].

Additionally, the physicians reported a single score according to a 5-point physician’s global assessment grading (−1: worsening; 0: no change; 1: mild improvement; 2: moderate improvement; 3: significant improvement).

The adverse effects were extracted from patient charts.
Statistical analysis

Statistical analyses were performed using IBM SPSS (statistical package for social sciences) for Windows, Version 22.0 package program. Numerical variables were shown as mean ± SD or median (min–max). Categorical variables were shown by number and percentage. Differences in categorical variables between the groups were investigated by square test.

Normal distribution for variables was evaluated by histogram and Kolmogorov–Smirnov test. The significance of the difference of the two group’s average for independent groups is evaluated by Mann–Whitney U test for variables with a non-normal distribution and Student’s t-test for variables with a normal distribution. For repeated measurements with non-normal distribution, Wilcoxon test was conducted in case of comparison of 2 groups. For repeated measurements, with a normal distribution, Student’s t-test was performed in case of comparison for two groups. p-value < 0.05 was considered significant.

Results

A total of 54 patients had received at least one session of fractional erbium:YAG LAD of TA 5% between October 2019 and March 2020. According to the exclusion criteria, 20 were not eligible for analysis and the analysis have been conducted on 34 patients’ results (Fig. 2). The patient collection period was limited to the mentioned duration to resolve the confusion related to the spontaneous improvement of melasma frequently observed during the autumn and winter months. All study patients had epidermal melasma.

Thirty-four female patients between 23 and 54 years (age: 40.4 ± 6.2 years, mean ± SD) were eligible. The age distribution, skin phototype, and baseline mMASI scores of group 1 (O + T + L) (n = 15) and group 2 (T + L) (n = 19) were similar (Table 1).

The mean mMASI of the study population is 3.4 ± 3.1. The average mMASI score at the 3rd week after the last laser session was 64.7% (1.6 ± 1.5) and 41.8% (1.6 ± 1.7) lower than that at baseline for group 1 (4.4 ± 4.2) and group 2 (2.7 ± 2.0), respectively (p = 0.001; 0.022). The comparison of mMASI score changes between the two groups revealed higher mMASI score decreases in group 1 (p = 0.027).

mMASI score changes were evaluated further for each patient (Table 2). mMASI score increase was detected only in 2 patients among the study population with 1.8 and 3.2 points. Both patients were in group 2 with Fitzpatrick skin types III and IV.

The mean PGA scores of both groups have been depicted in Fig. 3. Improvement was detected in 73.2% of group 1 and 63.3% of group 2 patients. The difference between the two study groups’ PGA scores did not reach statistical significance.

Despite not being considered within the primary outcomes of the current study, the authors assessed melasma’s vascular component through 3D imaging software. The serial 3D pigmentation and erythema imaging of the same patient has been presented in video-1 and video-2. As a conspicuous finding, erythema was not prominent for the lesions with a longer duration. However, the new-onset
obscure lesions revealed erythema. The treatment led to the simultaneous resolution of the erythema and pigmentation components within different lesions (Fig. 4). However, laser associated widespread erythema appeared as a significant pitfall upon the global evaluation of the study patients’ vascular imaging results. Thus, the authors could not conduct grading to evaluate the changes regarding erythema within the study population.

Through the evaluation of side effects, six women had menstrual irregularities and additionally, two patients in group 1 reported mild gastrointestinal intolerance. One patient had stopped oral tranexamic acid treatment related to headache and she had been withdrawn from the analysis. Her complaints resolved within several days.

### Discussion

Melasma is a common disorder remaining a challenging topic of cosmetic dermatology. Topicals are among the most commonly prescribed agents for melasma. Although the triple combination with topical hydroquinone, topical tretinoin, and topical steroid has been considered the most effective approach, an unmet need exists for most patients who are not satisfied by the results of topical treatment combinations [18].

Tranexamic acid has the potential to target multiple discrete pathogenic steps of melasma. Furthermore, several studies in melasma patients with intense pulsed light (IPL) and Q-switched Nd:YAG laser reported an additional benefit with a conditioning regimen of oral TA, pointing out TA’s efficacy to inhibit laser-induced melanogenesis [19, 20]. Furthermore, TA has been shown to modulate vascularization within melasma lesions, but only for systemic use.
LAD is a novel prospect to improve the bioactivity of topical agents [21]. The current study investigated two melasma treatment regimens, including fractional erbium:YAG LAD of topical tranexamic acid. Both regimens were successful in achieving melasma severity score decreases. Fractional erbium:YAG laser is commonly used for LAD and the available data demonstrate that the depth of substrate removal by erbium:YAG laser is precisely controlled by a fixed energy density per pulse [22, 23]. According to previous descriptions for low fluences below 8 J/cm², fractional erbium:YAG laser ablation has been shown to cause only damages within the SC at a mean depth of 12.5 ± 7.8 μm and the laser channels last for a maximal duration of 24–48 h, even after full-field applications [22, 23]. The efficacy of erbium:YAG laser-assisted delivery for another hydrophilic molecule, topical 5-aminolaevulinic acid (ALA), has been extensively investigated [24, 25]. The results point out that compared to the removal of stratum corneum with tape stripping, laser ablation provides better drug permeation for ALA [26]. Forster et al. suggested that ultrastructural alteration of the epidermis by laser treatment might explain this phenomenon [23]. Furthermore, Fang et al. noted a linear relationship between ALA flux and Er:YAG laser fluences for only low fluences but not for higher settings between 2.1 and 2.6 J/cm² [24]. The photomechanical acoustic effect

Fig. 4 The simultaneous resolution of the erythema and pigmentation components within different lesions of a patient in group 1
related to erbium:YAG fractional laser treatment was hypothesized to lead to loosening of the epidermis and the formation of transient channels followed by greater drug permeation across the skin. As higher influences induce more condensation and homogenization within the stratum corneum, the drug permeation may decrease even in the presence of deeper ablation [24]. According to the available data, the current study’s laser settings can be regarded effective for the enhanced penetration of topical TA 5%.

The addition of oral TA to erbium:YAG LAD of topical TA enhanced treatment outcomes by further improving the mMASI score decreases from 41.8 to 64.7%. The study’s baseline mMASI scores were substantially lower than those in Asian melasma studies. This difference is most probably related to the study region as the studies from European countries also reported lower baseline mMASI scores [25, 26].

Although no serious adverse effects were noted, two patients experienced mMASI score increases with 1.8 and 3.2 points among the study population. Both patients were in group 2 and thus were not receiving oral TA. These score increases might be related to the current study’s relatively aggressive fractional laser dose settings. Although the initial laser parameters of this study were similar to the previous studies, the authors increased the doses upon consecutive sessions [17, 27, 28]. Thus, herein, the authors suggest that dose increments should be reserved for patients with Fitzpatrick skin phototype II, and especially for patients with darker skin. Thus, in addition to therapeutic approaches with a direct effect on pigmentation, an ideal treatment plan should correct the signs of photoaging such as vascular alterations, basal membrane disruption, dermal changes, and increased mast cells to achieve overall rejuvenation [29].

Numerous rejuvenating therapeutic modalities have been implemented in melasma patients. Especially in Caucasian patients, light and laser treatments can provide substantial treatment outcomes [30, 31]. However, paradoxical worsening is a significant concern for these treatments [32]. Among the active treatments of this study, erbium:YAG laser’s potential for rejuvenation has been established by numerous studies [33–35]. Furthermore, TA has been shown to inhibit the plasma and non-irradiated skin markers of photoaging and ameliorate physiological skin aging in animal studies [36, 37].

The most suitable wavelength to target melanin is 650–850 nm. Although characterized with a substantially higher wavelength to target water as the preferential chromophore, isolated fractional ablative laser applications can provide remarkable treatment outcomes for melasma patients [28]. Among ablative lasers, CO₂ lasers are particularly avoided upon melasma management as the post-inflammatory hyperpigmentation is frequently related to their inherent features [38]. The findings of this study cannot denote the discrete effects of topical TA and fractional erbium:YAG laser; instead, they demonstrate that fractional erbium:YAG laser-assisted delivery of TA is successful in treating melasma. However, the dose settings should be minimized, and probably the number of laser sessions should be increased to improve treatment outcomes.

Furthermore, the addition of oral TA to this regimen increases the therapeutic potential and prevents paradoxical hyperpigmentation. The authors detected excellent resolution of the vascular component in a limited proportion of group 1 patients. Despite the improved penetration of topical TA, in the current study, topical TA was not able to ameliorate the vascular component of melasma. The ablative fractional laser applications may enhance erythema and lead to confusion. Thus, the authors did not conduct a detailed comparison of the 3D images to assess the presence of erythema.

The major limitation of the current study is that it was a non-randomized retrospective study. Furthermore, in addition to topical TA 5% cream applications provided immediately after the fractional erbium:YAG laser sessions, the study population continued daily applications for 9 weeks. Although it is a pitfall for assessing the isolated efficacy of erbium:YAG LAD of TA 5% cream, our results derived from recalcitrant melasma patients were impressive that could not be achieved with the isolated use of topical TA 5% cream. Additional limitations include the high drop-out rate and the lack of long-term follow-up to search for recurrences related to the unexpected emergence of COVID-19 within the study region and the cessation of elective outpatient admissions. Furthermore, although a 3D imaging software was used to evaluate concurrent vascularization and pigmentation within melasma lesions, assessments were based on subjective investigator evaluation. The authors intentionally preferred this method as the quantitative values depicted by the 3D system are also subjected to bias and can be manipulated by minor selection differences, thus, instead used global evaluation.

**Conclusion**

The findings of this study reveal that laser-assisted delivery of TA is an effective treatment strategy in melasma patients of Mediterranean descent. The addition of oral TA to this regimen substantially improves treatment outcomes.
Supplementary Information  The online version contains supplementary material available at https://doi.org/10.1007/s10103-022-03547-7.

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Author contribution  AB: applied the treatments, drafting the manuscript, acquisition of data, literature search. PE, EC: evaluation of treatment outcomes, literature search. AB, EC and HE: concept design. PE, EC, HE: critical revision of the manuscript.

Declarations

Ethics approval and consent to participate  Gülhane Faculty of Medicine’s ethical committee approved this study (2021–33). Only participants who signed the written informed consent were enrolled in this study.

Consent for publication  The patients in this manuscript have given written informed consent to publication of their case details.

Conflict of interest  The authors declare no competing interests.

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