Lasers in Medical Science
https://doi.org/10.1007/s10103-022-03547-7

ORIGINAL ARTICLE

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

Aysenur Botsali[1] · Pelin Esme[1] · Hakan Erbil[2] · Ercan Caliskan[1]

Received: 23 December 2021 / Accepted: 21 March 2022

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

✉ Aysenur Botsali
abotsali@hotmail.com

[1] Department of Dermatology, Gülhane Faculty of Medicine, University of Health Sciences, General Dr. Tevfik Sağlam Cad, SBÜ Gülhane EAH Dermatoloji AD, 06030 Keçiören, Ankara, Turkey

[2] Dr. Hakan Erbil, Private Clinic, Ankara, Turkey

Published online: 26 March 2022

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/cm^2 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/cm^2. 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, Quantificare, 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.

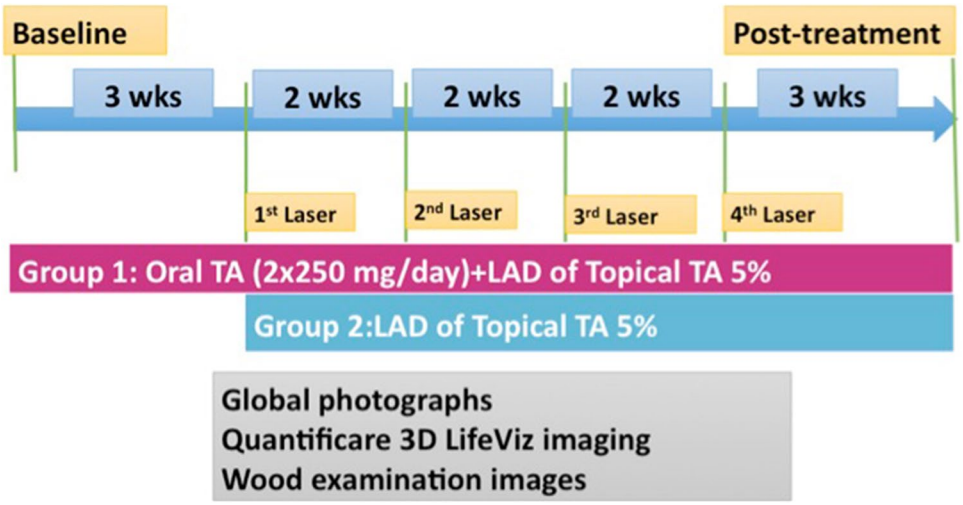

Fig. 1 The treatment scheme of the study groups

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 a 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

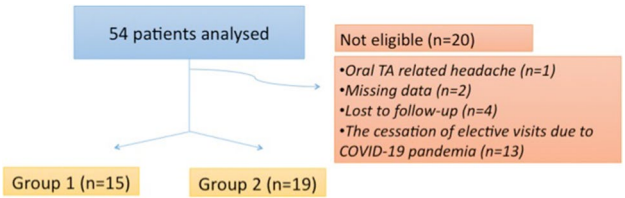

Fig. 2 The flowchart of the study population

(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

Table 1 The demographic and clinical features of the treatment groups

	Group 1				Group 2			
Age (mean ± SD)	40.8 ± 7.2				40 ± 5.5			
Fitzpatrick skin phototype	FP-2	FP-3		FP-4	FP-2	FP-3		FP-4
	5 (33.3%)	8 (53.3%)		2 (13.3%)	7 (36.8%)	10 (52.6%)		2 (10.5%)
Baseline mMASI	mean ± SD		min–max		mean ± SD		min–max	
	4.4 ± 4.2		0.6–18.6		2.7 ± 2.0		1–9.6	
Post-treatment mMASI	mean ± SD		min–max		mean ± SD		min–max	
	1.6 ± 1.5		0.6–6		1.6 ± 1.7		0–6.3	

Table 2 The mMASI score changes of the study population

mMASI score change	Group 1 ($n = 15$)	Group 2 ($n = 19$)
Excellent decrease	4 (26.6%)	4 (21%)
Very good decrease	7 (46.6%)	9 (47.3%)
Good decrease	2 (13.3%)	3 (15.7%)
Fair decrease	2 (13.3%)	3 (15.7%)
Increase		2 (10.5%)

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.

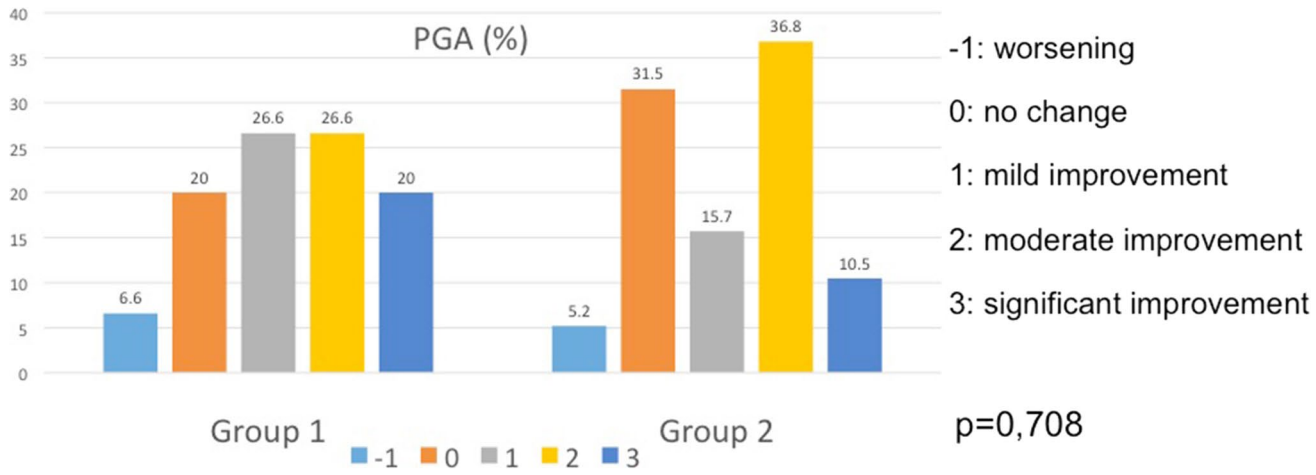

Fig. 3 The physician's global assessment scores of the study groups

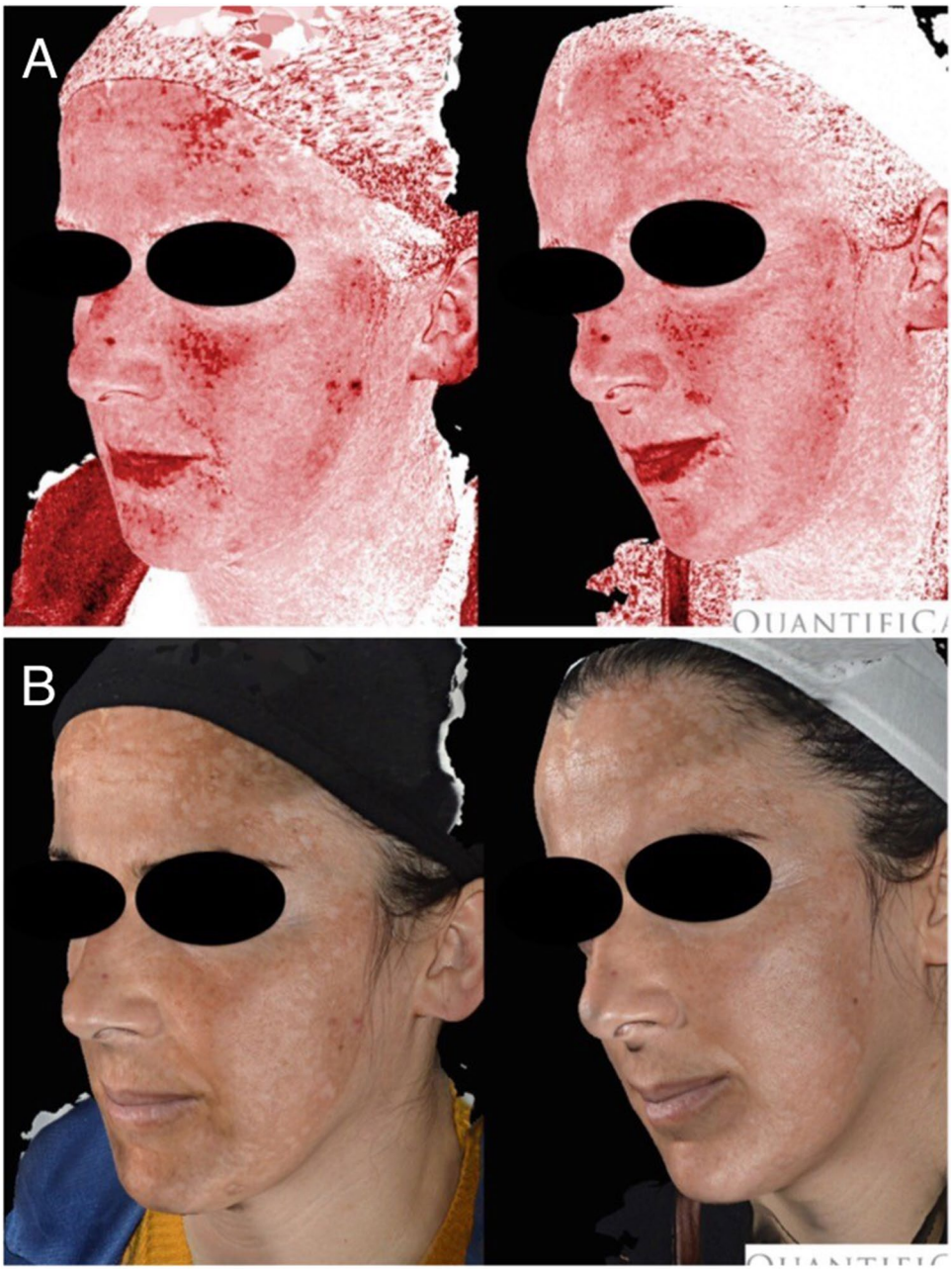

Fig. 4 The simultaneous resolution of the erythema and pigmentation components within different lesions of a patient in group 1

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/cm^2, 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/cm^2 [24]. The photomechanical acoustic effect

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, dose increments should not exceed 2 J/cm^2. However, a similar score increase was not present in group 1, suggesting the additional protective effect of the pre-conditioning regimen with oral TA.

The remaining categorical evaluation of mMASI scores did not reveal a difference for the two treatment regimens.

Due to recent advances in melasma etiopathogenesis, melasma is currently considered a unique photoaging phenotype rather than a simple pigmentary epidermal disorder [26]. 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, CO_2 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.

Acknowledgements Topical 5% tranexamic acid cream was prepared as a kind gift from Dermoskin® Cosmeceuticals (İstanbul, Turkey).

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.

References

1. Sheth VM, Pandya AG (2011) Melasma: a comprehensive update: part II. J Am Acad Dermatol 65(4):699–714
2. Li D, Shi Y, Li M, Liu J, Feng X (2010) Tranexamic acid can treat ultraviolet radiation-induced pigmentation in guinea pigs. Eur J Dermatol 20(3):289–292
3. Maeda K, Naganuma M (1998) Topical trans-4-aminomethylcyclohexanecarboxylic acid prevents ultraviolet radiation-induced pigmentation. J Photochem Photobiol B Biol 47(2–3):136–141
4. Maeda K, Tomita Y (2007) Mechanism of the inhibitory effect of tranexamic acid on melanogenesis in cultured human melanocytes in the presence of keratinocyte-conditioned medium. J Health Sci 53(4):389–396
5. Na JI, Choi SY, Yang SH, Choi HR, Kang HY, Park KC (2013) Effect of tranexamic acid on melasma: a clinical trial with histological evaluation. J Eur Acad Dermatol Venereol 27(8):1035–1039
6. Lee HC, Thng TGS, Goh CL (2016) Oral tranexamic acid (TA) in the treatment of melasma: a retrospective analysis. J Am Acad Dermatol 75(2):385–392
7. Bekassy Z, Åstedt B (1990) Treatment with the fibrinolytic inhibitor tranexamic acid—risk for thrombosis? Acta Obstet Gynecol Scand 69(4):353–354
8. Budamakuntla L, Loganathan E, Suresh DH et al (2013) A randomised, open-label, comparative study of tranexamic acid microinjections and tranexamic acid with microneedling in patients with melasma. J Cutan Aesthet Surg 6(3):139
9. Ghandehari R, Robati RM, Niknezhad N, Hajizadeh N, Tehranchinia Z (2020) Efficacy and safety of fractional CO2 laser and tranexamic acid versus microneedling and tranexamic acid in the treatment of infraorbital hyperpigmentation. J Dermatolog Treat. https://doi.org/10.1080/09546634.2020.1819527
10. Kaur A, Bhalla M, Thami GP, Sandhu J (2020) Clinical efficacy of topical tranexamic acid with microneedling in melasma. Dermatol Surg 46(11):e96–e101
11. Mekawy KMM, Sadek A, Seddeik Abdel-Hameed AK (2020) Micro-needling versus fractional carbon dioxide laser for delivery of tranexamic acid in the treatment of melasma: a split-face study. J Cosmet Dermatol 20(2):460–465
12. Menon A, Eram H, Kamath PR, Goel S, Babu AM (2020) A split face comparative study of safety and efficacy of microneedling with tranexamic acid versus microneedling with Vitamin C in the treatment of melasma. Indian Dermatol Online J 11(1):41
13. Shamsi Meymandi S, Mozayyeni A, Shamsi Meymandi M, Aflatoonian M (2020) Efficacy of microneedling plus topical 4% tranexamic acid solution vs 4% hydroquinone in the treatment of melasma: A single-blind randomized clinical trial. J Cosmet Dermatol 19(11):2906–2911
14. Xing X, Chen L, Xu Z, Jin S, Zhang C, Xiang L (2020) The efficacy and safety of topical tranexamic acid (liposomal or lotion with microneedling) versus conventional hydroquinone in the treatment of melasma. J Cosmet Dermatol 19(12):3238–3244
15. Bala HR, Lee S, Wong C, Pandya AG, Rodrigues M (2018) Oral tranexamic acid for the treatment of melasma: a review. Dermatol Surg 44(6):814–825
16. Pandya AG, Hynan LS, Bhore R et al (2011) Reliability assessment and validation of the Melasma Area and Severity Index (MASI) and a new modified MASI scoring method. J Am Acad Dermatol 64(1):78-83.e2
17. Abdel-Raouf Mohamed H, Ali Nasif G, Saad Abdel-Azim E, Abd El-Fatah Ahmed M (2019) Comparative study of fractional erbium: YAG laser vs combined therapy with topical steroid as an adjuvant treatment in melasma. J Cosmet Dermatol 18(2):517–523
18. Grimes PE, Bhawan J, Guevara IL et al (2010) Continuous therapy followed by a maintenance therapy regimen with a triple combination cream for melasma. J Am Acad Dermatol 62(6):962–967
19. Shin JU, Park J, Oh SH, Lee JH (2013) Oral tranexamic acid enhances the efficacy of low-fluence 1064-nm quality-switched neodymium-doped yttrium aluminum garnet laser treatment for melasma in Koreans: a randomized, prospective trial. Dermatol Surg 39(3pt1):435–442
20. Cho HH, Choi M, Cho S, Lee JH (2013) Role of oral tranexamic acid in melasma patients treated with IPL and low fluence QS Nd: YAG laser. J Dermatolog Treat 24(4):292–296
21. Haedersdal M, Erlendsson AM, Paasch U, Anderson RR (2016) Translational medicine in the field of ablative fractional laser (AFXL)-assisted drug delivery: a critical review from basics to current clinical status. J Am Acad Dermatol 74(5):981–1004
22. Lee WR, Shen S-C, Lai H-H, Hu C-H, Fang J-Y (2001) Transdermal drug delivery enhanced and controlled by erbium: YAG laser: a comparative study of lipophilic and hydrophilic drugs. J Control Release 75(1–2):155–166
23. Forster B, Klein A, Szeimies RM, Maisch T (2010) Penetration enhancement of two topical 5-aminolaevulinic acid formulations for photodynamic therapy by erbium: YAG laser ablation of the stratum corneum: continuous versus fractional ablation. Exp Dermatol 19(9):806–812
24. Fang JY, Lee WR, Shen SC, Fang YP, Hu CH (2004) Enhancement of topical 5-aminolaevulinic acid delivery by erbium: YAG laser and microdermabrasion: a comparison with iontophoresis and electroporation. Brit J Dermatol 151(1):132–140
25. Shen SC, Lee WR, Fang YP, Hu CH, Fang JY (2006) In vitro percutaneous absorption and in vivo protoporphyrin IX accumulation in skin and tumors after topical 5-aminolevulinic acid application with enhancement using an erbium: YAG laser. J Pharm Sci 95(4):929–938
26. Nelson JS, McCullough JL, Glenn TC, Wright WH, Liaw L-HL, Jacques SL (1991) Mid-infrared laser ablation of stratum corneum enhances in vitro percutaneous transport of drugs. J Invest Dermatol 97(5):874–879
27. Attwa E, Khater M, Assaf M, Haleem MA (2015) Melasma treatment using an erbium:YAG laser: a clinical, immunohistochemical, and ultrastructural study. Int J Dermatol 54(2):235–244

28. Otb S, Shaarawy E, Sadek A et al (2021) A split face comparative study between intradermal tranexamic acid and Erbium-YAG laser in treatment of melasma. J Dermatolog Treat:1–5
29. Kwon S-H, Hwang Y-J, Lee S-K, Park K-C (2016) Heterogeneous pathology of melasma and its clinical implications. Int J Mol Sci 17(6):824
30. Li JY, Geddes ER, Robinson DM, Friedman PM (2016) A review of melasma treatment focusing on laser and light devices. Semin Cutan Med Surg 35(4):223–232
31. Zhang Y, Zheng X, Chen Z, Lu L (2020) Laser and laser compound therapy for melasma: a meta-analysis. J Dermatolog Treat 31(1):77–83
32. Berardesca E, Rigoni C, Cantu A et al (2020) Effectiveness of a new cosmetic treatment for melasma. J Cosmet Dermatol 19(7):1684–1690
33. Caniglia RJ (2004) Erbium:YAG laser skin resurfacing. Facial Plast Surg Clin North Am 12(3):373–7, vii
34. El-Domyati M, Abd-El-Raheem T, Abdel-Wahab H et al (2013) Fractional versus ablative erbium:yttrium-aluminum-garnet laser resurfacing for facial rejuvenation: an objective evaluation. J Am Acad Dermatol 68(1):103–112
35. El-Domyati M, Abd-El-Raheem T, Medhat W, Abdel-Wahab H, Al AM (2014) Multiple fractional erbium: yttrium-aluminum-garnet laser sessions for upper facial rejuvenation: clinical and histological implications and expectations. J Cosmet Dermatol 13(1):30–37
36. Hiramoto K, Yamate Y, Sugiyama D, Matsuda K, Iizuka Y, Yamaguchi T (2018) Tranexamic acid inhibits the plasma and non-irradiated skin markers of photoaging induced by long-term UVA eye irradiation in female mice. Biomed Pharmacother 107:54–58
37. Hiramoto K, Yamate Y, Sugiyama D, Matsuda K, Iizuka Y, Yamaguchi T (2019) Ameliorative effect of tranexamic acid on physiological skin aging and its sex difference in mice. Arch Dermatol Res 311(7):545–553
38. Riggs K, Keller M, Humphreys TR (2007) Ablative laser resurfacing: high-energy pulsed carbon dioxide and erbium:yttrium-aluminum-garnet. Clin Dermatol 25(5):462–473