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SHORT PAPER

Efficacy and safety of tranexamic acid 5% cream vs hydroquinone 4% cream in treating melasma: A split-face comparative clinical, histopathological, and antera 3D camera study

Rania El-Husseiny | Noha Rakha | Mohamad Sallam

Dermatology, Venerology and Andrology Department, Ain Shams University Hospitals, Cairo, Egypt

Correspondence
Rania El-Husseiny, Dermatology, Venerology and Andrology Department, Ain Shams University, Cairo, Egypt.
Email: raniaelhusseiny@yahoo.com

Abstract

Various tranexamic acid (TA) formulations have been evaluated for treating melasma, yet the effectiveness of this therapy has not been efficiently comparatively analyzed. To assess and compare the therapeutic efficacy and safety of TA 5% vs hydroquinone (HQ) 4% creams in treating melasma. 100 melasma female patients were treated with daily application of TA 5% cream on right-sided facial lesions and HQ 4% cream on left-sided lesions for 12 weeks. Photographic documentation using digital and Antera 3D camera, Wood's light examination, calculation of Hemi Melasma Area and Severity Index (Hemi MASI), Melasma quality of life (MELASQOL) scores and area% of melanin through histopathological examination was done before and after treatment. Both TA 5% and HQ 4% creams yielded significant improvement of all melasma lesions after 12 weeks of treatment, with no significant difference in treatment response regarding Hemi MASI, MELASQOL scores and Antera average level of melanin ($P > .05$); however, significant reduction in area % of melanin was recorded with TA 5% than HQ 4% creams ($P = .000$). TA appears to be a promising therapeutic option in treating melasma with fewer adverse effects, same or even better results in comparison to HQ cream.

KEYWORDS

hydroquinone, melasma, tranexamic acid

1 | INTRODUCTION

Traditionally, topical bleaching agents as hydroquinones (HQ) have been considered the mainstays of melasma treatment.[1] Meanwhile, Tranexamic acid (TA) which is a plasmin inhibitor and an anti-fibrinolytic, widely used to prevent and treat hemorrhages, has been evaluated for treatment of melasma in various formulations including topical, intradermal, and oral.[2] However, no definitive consensus on using TA in treating melasma currently exists, besides, comparison of its efficacy and safety vs conventional therapies requires further evaluation. Therefore, we aimed to assess and compare the therapeutic efficacy and safety of TA 5% cream vs hydroquinone 4% cream in treating different types of melasma.

2 | PATIENTS AND METHODS

This prospective split-face comparative study included 100 females with melasma, collected from dermatology out-patient clinic of Ain Shams University Hospitals, Cairo, Egypt. The study was approved by the Research Ethical Committee and all patients provided informed consents. Exclusion criteria included pregnant or lactating females, history of sensitivity to HQ, or TA, patients with severe systemic illness as hepatic, renal, coronary or cerebral artery diseases and those with history of coagulopathy, using anticoagulants or received any topical treatments or subjected to anti-melasma procedures during previous month.

All Patients were subjected to full history taking, general, dermatological and Wood's light examination (to determine type of melasma), photo documentation using digital Nikon D5300 camera (24.2 megapixels) and Antera 3D camera (Miravex, Ireland) that allows measurement of the average level of melanin (average melanin concentration per unit area relative to the area selected) before and after treatment. Furthermore, three 2 mm skin biopsies were collected from the melasma lesions in 30 patients for histopathological examination using hematoxylin and eosin (H&E) and Fontana-Masson stain (FM) for melanin. The first biopsy was taken at baseline, whereas the second and third ones were taken 12 weeks after treatment from both right and left sides of the face. Interpretation of the biopsies was carried out quantitatively by a dermatopathologist through counting the number of positive (active) melanocytes in the epidermis and dermis (melanophages) in five different captured non overlapping high-power fields using an image analyzer Leica Q win V.3 program installed on a computer connected to a Leica DM2500 microscope (Wetzlar, Germany) with measurement of the area % of melanin and mean value for each biopsy for the sum of 30 patients.

2.1 | Treatment methodology

Patients were treated with TA 5% cream (liposomal formula prepared by fusion method) applied topically twice a day on right-sided melasma lesions of the face and commercially available HQ 4% cream applied on left-sided lesions once at night before sleep for 12 weeks. All patients were constructed to avoid sun exposure between 10 AM and 4 PM and to daily apply sunscreen 50+ SPF outdoors.

2.2 | Follow-up evaluation

Evaluation of the treatment efficacy was done through comparing Hemi Melasma Area and Severity Index (Hemi-MASI) score,[3] Melasma quality of life (MELASQOL) score,[4] and antera average level of melanin before treatment and after 4, 8, and 12 weeks of treatment as well as 1 month after stopping both treatments to assess the relapse rate. Furthermore, comparison between the area % of melanin for both right- and left-sided lesions in 30 patients before and after 12 weeks of treatment was done. All encountered side effects were also documented. The obtained data were tabulated and subjected to statistical analysis using different tests of significance. *P*-value was considered significant if ≤.05.

3 | RESULTS

3.1 | Demographic and clinical characteristics of studied patients

This study included 100 melasma female patients, aged 22 to 40 years (Mean ± SD; 32.48 ± 5.36) of type II, III, and IV Fitzpatrick Skin Type

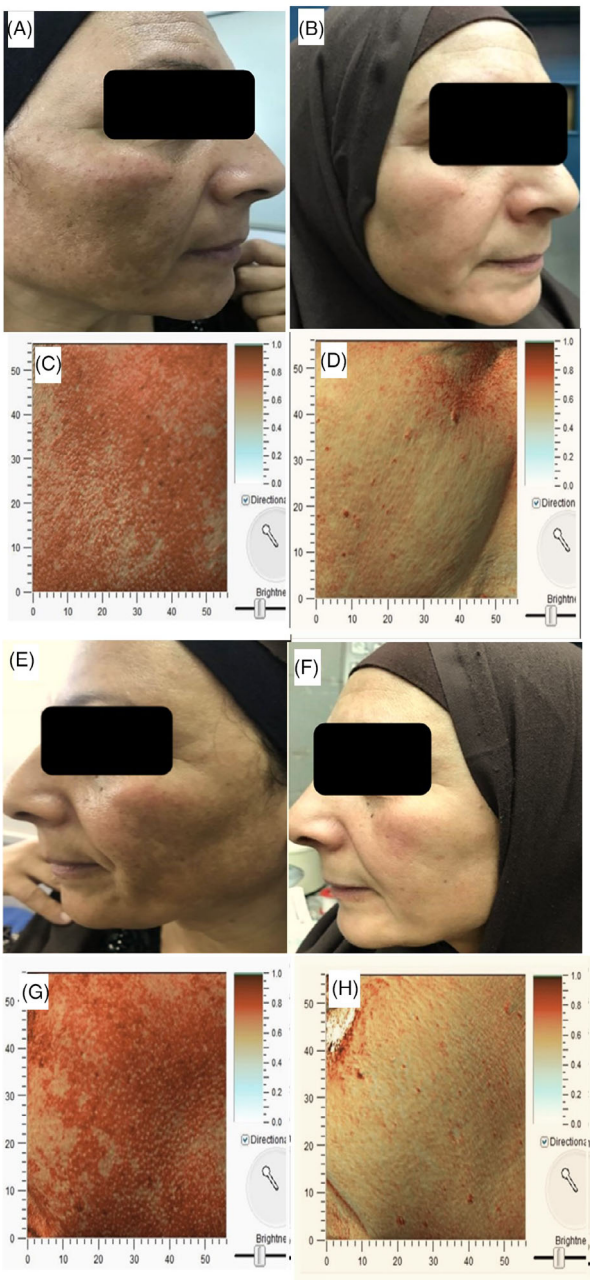

FIGURE 1 Digital clinical and Antera photography of 40-year-old-female with malar melasma of 5 years duration showing significant improvement of both sides of melasma lesions after 12 weeks of treatment. A, Clinical photograph for right-sided melasma lesions before treatment; Hemi MASI score 5.40, MELASQOL score 27. B, Clinical photograph for right-sided melasma lesions after 12 weeks of TA 5% cream; significant decrease in Hemi MASI score to 1.50, MELASQOL score to 16. C, Antera picture for right-sided melasma lesions before treatment; average melanin level 0.78. D, Antera picture for right-sided melasma lesions after 12 weeks of TA 5% cream; significant decrease of average melanin level to 0.43. E, Clinical photograph for left-sided melasma lesions before treatment; Hemi MASI score 5.40, MELASQOL score 25. F, Clinical photograph for left-sided melasma lesions after 12 weeks of HQ 4% cream; significant decrease in Hemi MASI score to 1.45, MELASQOL score to 16. G, Antera picture for left-sided melasma lesions before treatment; average melanin level 0.80. H, Antera picture for left-sided melasma lesions after 12 weeks of HQ 4% cream; significant decrease of average melanin level to 0.38

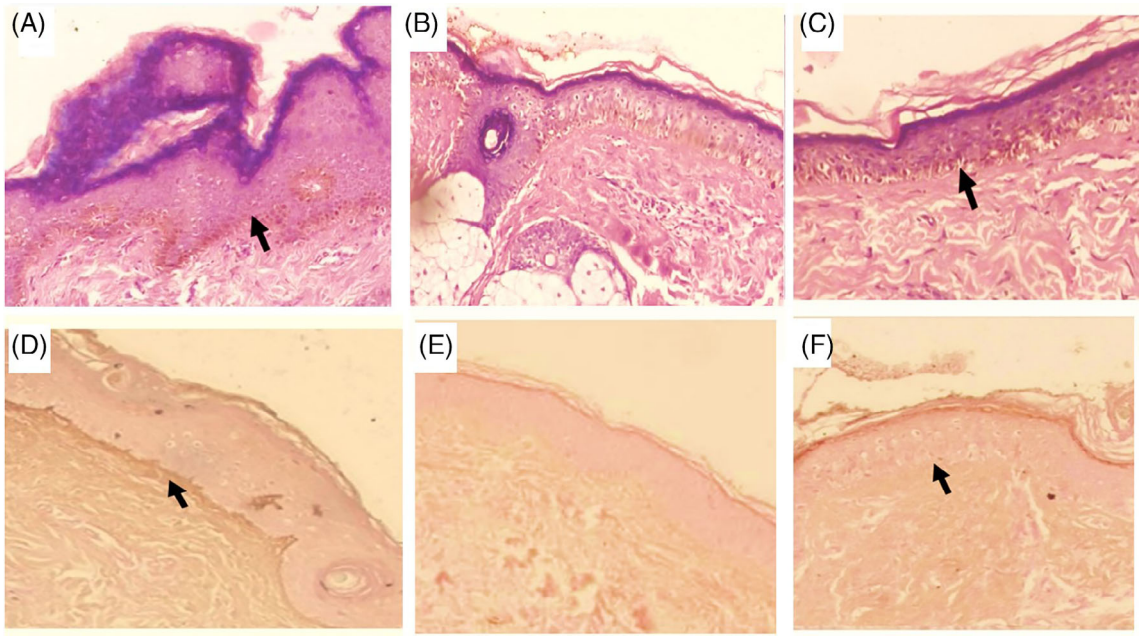

FIGURE 2 Histopathology of melasma lesions of the same patient stained with H& E and Fontana-Masson (FM) stains (40×) before and after treatment. A, Melasma lesion before treatment stained with H& E showing increased melanin in basal layer of epidermis. B, Right-sided melasma lesions after 12 weeks of TA 5% cream stained with H& E showing decreased in epidermal melanin. C, Left-sided melasma lesions after 12 weeks of HQ 4% cream stained with H& E showing decreased in epidermal melanin. D, Melasma lesion before treatment stained with FM showing increased melanin density (area% of melanin was 18.21 ± 6.38). E, Right-sided melasma lesions after 12 weeks of TA 5% cream stained with FM showing significant decrease of melanin density (area% of melanin 8.21 ± 4.48). F, Left-sided melasma lesions after 12 weeks of HQ 4% cream stained with FM showing significant decrease of melanin density (area% of melanin decreased to 12.46 ± 4.48, however, lower than the decrease on right side)

(15, 52, and 33 patients, respectively), Patients suffered from either epidermal (78 patients) or mixed (22 patients) type of melasma that was distributed on the malar (63 patients) or centrofacial areas (37 patients) for 1 to 15 years duration (Mean ± SD; 5.24 ± 3.73). Positive family history was present in 60% of patients.

3.2 | Evaluation of treatment response

There was significant improvement of all melasma lesions for both sides of the face after 8 and 12 weeks of treatment regarding hemi-MASI score, MELASQOL score and Antera average level of melanin as well as mean difference of area % of melanin after 12 weeks of treatment ($P \leq .05$, Paired t test) (Figure 1-4), although slight non-significant recurrence was observed 1 month after stopping both treatments ($P > .05$, Paired t test).

Furthermore, on comparison between the treatment response of both sides of the face, there was no significant difference regarding Hemi-MASI score, MELASQOL score and average level of melanin at baseline, 4, 8, 12, and 16 weeks of follow up ($P > .05$). However, the mean difference of the area % of melanin for right-sided lesions (11.01 ± 6.38 SD) was significantly higher than the mean difference of left-sided lesions (3.21 ± 4.03 SD) ($P = .000$, Paired t test) (Table 1).

Meanwhile, there was no significant difference in treatment response of TA 5% and HQ 4% creams for epidermal vs mixed type of melasma regarding the mean difference of Antera average level of melanin, Hemi MASI score nor MELASQOL score ($P = .750$ & 0.107, $P = .092$ & 0.049, and $P = 715$ & 0.446, respectively, Mann Whitney test), although lower in mixed than epidermal type.

Furthermore, no significant relations were found between the treatment response and patients' age, skin type, duration of disease, family history, and site (pattern) of melasma ($P > .05$). However, there was positive significant correlation between patient's age and MELASQOL score on both sides of the face at baseline, 4, 8, and 12 weeks of follow up ($P \leq .05$, Pearson correlation coefficients).

On comparison between reported side effects of both treatments, no side effects were found with TA 5% cream, while skin irritation, erythema, and burning sensation were noticed in 21.21% of patients and post inflammatory hyperpigmentation (PIH) in 2% of patients with HQ 4% cream.

4 | DISCUSSION

Despite the advances with technology and new formulations of medications, melasma remains challenging to treat.[2] Topical

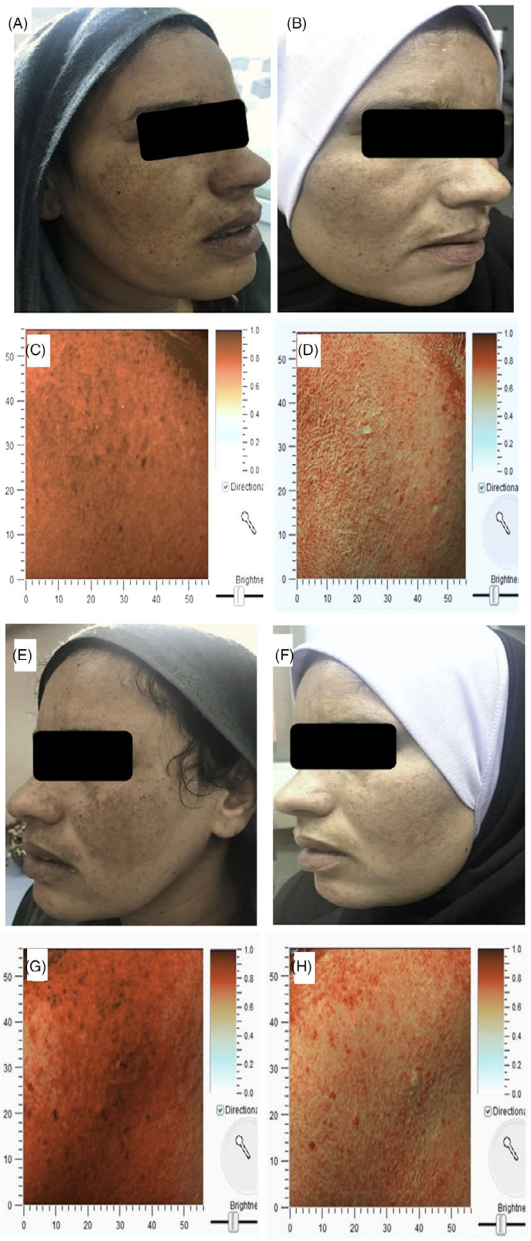

FIGURE 3 Digital clinical and Antera photography of 34 year old female with centrofacial melasma of 12 years duration showing significant improvement of both sided of melasma lesions after 12 weeks of treatment. A, Clinical photograph for right-sided melasma lesions before treatment; Hemi MASI score 9.00, MELASQOL score 27. B, Clinical photograph for right-sided melasma lesions after 12 weeks of TA 5% cream; significant decrease in Hemi MASI score to 3.60, MELASQOL score to 18. C, Antera picture for right-sided melasma lesions before treatment; average melanin level 0.62. D, Antera picture for right-sided melasma lesions after 12 weeks of TA 5% cream; significant decrease of average melanin level to 0.44. E, Clinical photograph for left-sided melasma lesions before treatment; MASI score 10.00, MELASQOL score 27. F, Clinical photograph for left-sided melasma lesions after 12 weeks of HQ 4% cream; significant decrease in MASI score to 4.00, MELASQOL score to 18. G, Antera picture for left-sided melasma lesions before treatment; average melanin level 0.64. F, Antera picture for left-sided melasma lesions after 12 weeks of HQ 4% cream; significant decrease of average melanin level to 0.48

hydroquinone is a conventional therapeutic choice for hyperpigmentary disorders, which inhibits dihydroxyphenylalanine (DOPA) conversion to melanin through inhibition of tyrosinase enzyme, thus suppresses the formation, melanization and degradation of melanosomes, and induces melanocyte damage by inhibiting RNA and DNA synthesis.[5]

Tranexamic acid can be used as a skin brightening agent through disrupting keratinocyte-melanocyte interactions. Plasminogen exists in human epidermal basal cells where hyper-activated melanocytes and keratinocytes are located. TA blocks the lysine binding sites on plasminogen and inhibits plasminogen conversion to plasmin, thus, secretion of different substances that stimulate melanogenesis cannot occur.[6]

Given the potential for serious adverse effects with systemic use of TA, there has been interest in formulating and evaluating topical TA for cosmetic indications.[2] Although previous reports have proposed initial promise, currently available data are limited by small sample sizes, short treatment durations and follow-up, lack of different doses evaluation, and comparison with various conventional therapies.

This study aimed to assess and compare the therapeutic efficacy and safety of TA 5% cream applied on the right-sided facial melasma lesions in 100 female patients vs HQ 4% cream applied on their left-sided lesions for 12 weeks.

Antera 3D is a multi- led handheld camera with accompanying software that captures three dimensional high resolution images using an innovative optical method and complex mathematical algorithms, which allow to quantify the efficacy of treatments and monitor changes over time in terms of topography, roughness index, indentations index, average melanin level, and hemoglobin.[7] In our study, the camera was operated using the melanin mode, which allows to map the distribution of melanin and measure its average concentration and uniformity. To the best of our knowledge, this is the first study that used Antera 3D camera in evaluating the treatment efficacy of anti-melasma agents.

Our results showed that both TA 5% and HQ 4% creams proposed significant improvement of different types of melasma without significant difference regarding Hemi MASI score, MELASQOL scale score, and average level of melanin. However, the area % of melanin showed significant higher reduction after 12 weeks of treatment with TA 5% than HQ 4% cream.

In agreement to our results, previous studies which compared the efficacy of TA with conventional HQ creams in treating melasma reported that; both treatments are effective with non-significant difference in their treatment responses regarding MASI score, although side effects were significantly less prominent with TA.[8,9] On the other hand, a split-face controlled trial performed by Saki et al.,[10] where 37 melasma patients were randomized to receive three monthly sessions of TA intradermal injections on one side of the face and topical HQ once at night on other side, stated

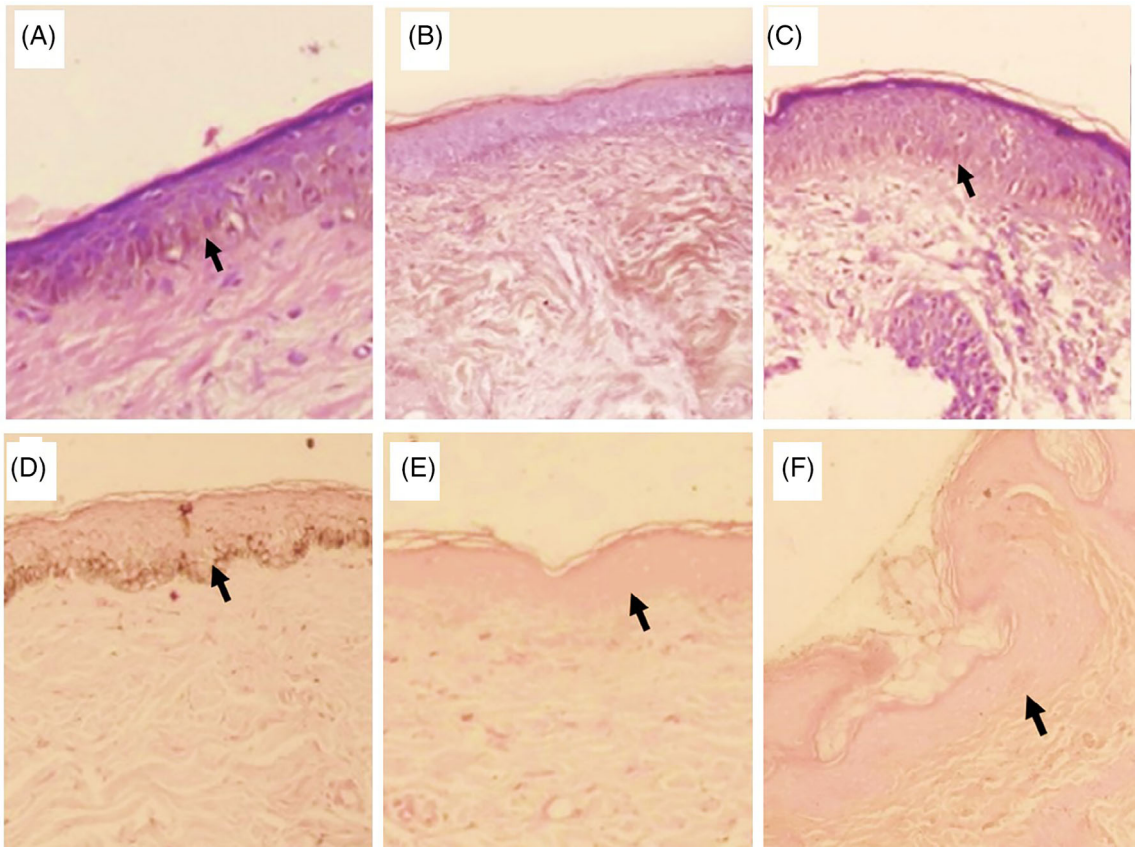

FIGURE 4 Histopathology of melasma lesions of the same patient stained with H& E and Fontana-Masson (FM) (40×) before and after treatment. A, Melasma lesion before treatment stained with H& E showing increased melanin in basal layer of epidermis. B, Right-sided melasma lesions after 12 weeks of TA 5% cream stained with H& E showing decreased in epidermal melanin. C, Left-sided melasma lesions after 12 weeks of HQ 4% cream stained with H& E showing decreased in epidermal melanin. D, Melasma lesion before treatment stained with FM showing increased melanin density (area% of melanin was 29.87 ± 5.48). E, Right-sided melasma lesions after 12 weeks of TA 5% cream stained with FM showing significant decrease of melanin density (area% of melanin decreased to 6.26 ± 2.38). F, Left-sided melasma lesions after 12 weeks of HQ 4% cream stained with FM showing significant decrease of melanin density (area% of melanin decreased to 12.64 ± 2.78; however, lower than the decrease on right side)

that the mean satisfaction values had statistically supported TA than topical HQ ($P < .001$). In addition, previous studies reported that combination of TA with HQ creams yielded better results than TA alone.[11,12] Contradicting, a split-face trial by Ayuthaya et al.[13] using topical 5% TA in 23 women with melasma for 12 weeks, found no extra benefit from topical TA use compared to a vehicle; even more irritation was caused by TA.

Our study showed no significant difference in the treatment response of epidermal vs mixed type of melasma with both therapies, although lower in mixed than epidermal type. This could be attributed to the higher number of epidermal than mixed type of melasma patients among studied participants.

The non-significant relations, which were found in our study between the treatment response and each of patients' age, skin type, family history, duration, and site of melasma deny the importance of these factors in determining the clinical outcome of TA and HQ creams in treating melasma. However, the positive significant correlation, which was found between patient's age and MELASQOL score could be explained by the lower self-esteem and more concern of beauty experienced usually by older-aged population.

Limitations of our study include; relative short duration of treatment and follow-up and lack of evaluation of combined treatments.

5 | CONCLUSION

TA appears to be a promising therapeutic option in treating melasma. It has fewer adverse effects, same or even better results in comparison to the conventional topical melasma targeting therapies as HQ cream.

TA could be considered in conjunctions with other treatment modalities of melasma to increase the treatment efficacy and decrease possible relapse rate.

TABLE 1 Comparison between right & left sides of the face regarding Hemi-MASI score, MELASQOL score, Antera average melanin level and area % of melanin before and after treatment

Evaluation of treatment response		Right *N* = 100	Left *N* = 100	Test value[a]	*P*-value
Hemi-MASI score	Mean ± SD	5.60 ± 2.79	5.86 ± 2.97	−1.178	0.248
Baseline (before treatment)	Range	1.5-12	1.5-12		
4 weeks	Mean ± SD	4.94 ± 3.00	5.36 ± 3.21	−1.688	0.101
	Range	1.2-12	0.9-12		
8 weeks	Mean ± SD	3.80 ± 2.54	4.35 ± 2.57	−2.134	0.110
	Range	0.6-10.5	0.9-9		
12 weeks	Mean ± SD	3.05 ± 2.03	3.23 ± 2.22	−0.529	0.601
	Range	0.6-7.2	0.6-8.4		
Mean difference	Mean ± SD	2.63 ± 1.59	2.55 ± 2.02	0.179	0.859
16 weeks	Mean ± SD	3.21 ± 1.93	3.45 ± 2.07	−0.742	0.464
	Range	0.6–7.2	0.6–8.4		
MELASQOL score	Mean ± SD	21.24 ± 4.07	21.06 ± 3.79	1.139	0.263
Baseline (before treatment)	Range	15-27	15-27		
4 weeks	Mean ± SD	20.79 ± 3.92	20.70 ± 3.64	0.432	0.669
	Range	13-26	13-26		
8 weeks	Mean ± SD	18.18 ± 3.18	18.42 ± 3.26	−1.187	0.244
	Range	12-24	13-24		
12 weeks	Mean ± SD	17.91 ± 3.08	17.97 ± 3.02	−1.233	0.227
	Range	11-20	12-20		
Mean difference	Mean ± SD	3.85 ± 3.98	3.27 ± 4.31	0.568	0.572
16 weeks	Mean ± SD	18.58 ± 3.64	23.82 ± 3.90	−0.812	0.423
	Range	12-21	17-28		
Antera average melanin level	Mean ± SD	0.765 ± 0.115	0.769 ± 0.118	0.464	0.646
Baseline (before treatment)	Range	0.52-0.96	0.53-0.93		
4 weeks	Mean ± SD	0.75 ± 0.13	0.75 ± 0.13	0.296	0.769
	Range	0.47-0.97	0.42-0.93		
8 weeks	Mean ± SD	0.68 ± 0.13	0.70 ± 0.12	−1.706	0.098
	Range	0.39-0.9	0.4-0.9		
12 weeks	Mean ± SD	0.63 ± 0.14	0.66 ± 0.12	−1.561	0.128
	Range	0.33-0.82	0.38-0.85		
Mean difference	Mean ± SD	0.14 ± 0.09	0.11 ± 0.05	−1.640	0.099
16 weeks	Mean ± SD	0.65 ± 0.12	0.68 ± 0.10	−1.588	0.122
	Range	0.42-0.84	0.47-0.87		
Area% of melanin	Mean ± SD	11.01 ± 6.38	3.21 ± 4.03	−4.623	**0.000**
Mean difference					

[a]Paired *t* test.
Note: *P*-value ≤ 0.05: Significant.
Abbreviations: Hemi-MASI, hemi-melasma area and severity index; **MELASQOL,** Melasma quality of life; **N,** number.

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CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Rania El-Husseiny https://orcid.org/0000-0002-0028-4686

REFERENCES

1. Dashore S, Mishra K. Tranexamic acid in melasma: why and how? *Indian J Drugs Dermatol*. 2017;3:61-63.
2. Wang JV, Jhawar N, Saedi N. Tranexamic acid for melasma: evaluating the various formulations. *J Clin Aesthet Dermatol*. 2019;12(8):E73-E74.
3. Wang X, Li Z, Zhang D, Li L, Sophie S. A double-blind placebo controlled clinical trial. Evaluating the efficacy and safety of a new skin whitening combination in patients with chloasma. *J Cosmet Dermatol Sci Appl*. 2014;4:475-482.

4. Balkrishnan R, Alikhan A, Daly M, Wu J, Feldman SR. Cost-effectiveness of a hydroquinone/tretinoin/ fluocinolone acetonide cream combination in treating melasma in the United States. *J Dermatol Treat*. 2010;21(5):276-281.
5. Ferreira Cestari T, Hassun K, Sittart A. A comparison of triple combination cream and hydroquinone 4% cream for the treatment of moderate to severe facial melasma. *J Cosmet Dermatol*. 2007;6:36-39.
6. Na J, Choi S, Yang S. Effect of tranexamic acid on melasma: a clinical trial with histological evaluation. *J Eur Acad Dermatol Venereol*. 2013; 27:1035-1039.
7. Matias AR, Ferreira M, Costa P, Neto P. Skin colour, skin redness and melanin biometric measurements: comparison study between Antera 3D, Mexameter and colorimeter. *Skin Res Technol*. 2015;21(3):346-362.
8. Banihashemi M, Zabolinejad N, Jaafari MR. Comparison of therapeutic effects of liposomal tranexamic acid and conventional hydroquinone on melasma. *J Cosmet Dermatol*. 2015;14:174-177.
9. Atefi N, Dalvand B, Ghassemi M, Mehran G, Heydarian A. Therapeutic effects of topical tranexamic acid in comparison with hydroquinone in treatment of women with melasma. *Dermatol and Ther*. 2017;7(3):417-424.
10. Saki N, Darayesh M, Heiran A. Comparing the efficacy of topical hydroquinone 2% versus intradermal tranexamic acid microinjections in treating melasma: a split-face controlled trial. *J Dermatol Treat*. 2018;29:405-410.
11. Lajevardi V, Ghayoumi A, Abedini R. Comparison of the therapeutic efficacy and safety of combined oral tranexamic acid and topical hydroquinone 4% treatment vs. topical hydroquinone 4% alone in melasma: a parallel-group, assessor-and analyst-blinded, randomized controlled trial with a short-term follow-up. *J Cosmet Dermatol*. 2017; 16:235-242.
12. Tehranchinia Z, Saghi B, Rahimi H. Evaluation of therapeutic efficacy and safety of Tranexamic acid local infiltration in combination with topical 4% hydroquinone cream compared to topical 4% hydroquinone cream alone in patients with Melasma: a Split-face study. *Dermatol Res Pract*. 2018;2018:8350317.
13. Ayuthaya PKN, Niumphradit N, Manosroi A. Topical 5% tranexamic acid for the treatment of melasma in Asians: a double-blind randomized controlled clinical trial. *J Cosmet Laser Ther*. 2012;14: 150-154.

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