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Efficacy and Safety of Topical Tranexamic Acid Alone or in Combination with Either Fractional Carbon Dioxide Laser or Microneedling for the Treatment of Melasma

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ABSTRACT

Introduction: Tranexamic acid (TXA) is a promising treatment modality for melasma. Microneedling (MN) and fractional carbon dioxide (CO_2) laser were reported to enhance TXA transepidermal delivery.

Objectives: To compare efficacy and safety of topical TXA alone or in combination with either fractional CO_2 laser or MN for treatment of melasma.

Methods: Thirty females with facial melasma were divided randomly into 3 equal groups after excluding pregnant and lactating women and those using oral contraceptives or other hormonal therapy. Patients of group A were treated with fractional CO_2 laser and those of group B were treated with MN (4 sessions, 3 weeks apart for both) with immediate topical application of TXA 5% solution after sessions and daily application of 5% TXA cream for both groups. Patients of group C were treated by topical daily application of TXA 5% cream. Evaluation was done by modified melasma area and severity index scores (mMASI), patient satisfaction and dermoscopy.

Results: Statistically significant improvement of mMASI was reported in all studied groups with a significantly better improvement in patients of groups A and B than those of group C, meanwhile the difference between groups A and B was statistically insignificant.

Conclusions: Topical TXA is a safe and fairly effective treatment modality for facial melasma. Combining TXA with either fractional CO_2 laser or MN yielded significantly better improvement than when used alone. Fractional CO_2 laser carries the risk of post-inflammatory hyperpigmentation in patients with skin types III and IV and requires meticulous patient selection.

Introduction

Melasma is an acquired, chronic, recurrent hyperpigmentary disorder [1]. It is clinically characterized by symmetric light-brown to bluish-gray macules and patches, with irregular, sharp borders [2].

The etio-pathogenesis of melasma is complex and not completely understood. It appears that this disorder is an interplay of various internal and environmental factors, which may be responsible for triggering, maintaining or relapsing lesions [3].

Tranexamic acid (TXA) prevents blood loss by acting as a plasmin inhibitor. It's administered to prevent the abnormal fibrinolysis by preventing the plasminogen activator from converting plasminogen to plasmin. Moreover, plasmin elevates α-melanocyte-stimulating hormone, which activates melanin synthesis in melanocytes. TXA is thought to block melanogenesis and its efficacy in melasma and other light-induced pigmentary disorders might be through its anti-angiogenic and antimelanogenetic properties [4].

In comparison with other laser modalities, the fractional lasers have more advantage. With this modality, the recovery is faster and the risk of complications such as hyperpigmentation, hypopigmentation and scarring is lower. Fractional carbon dioxide (CO_2) laser is a hopeful potential therapeutic modality for melasma [5].

Skin microneedling (MN) or percutaneous collagen induction by needles, is a minimally invasive procedure that uses short fine needles to puncture the skin and stimulates fibroblast release of growth factors and collagen production. Long-term improvement of recalcitrant melasma after MN has been reported, however, the exact mechanism that promotes skin lightening is not known [6].

Both fractional CO_2 laser and MN have been used to increase the transepidermal delivery of several topical drugs with promising results. Both of them may add a beneficial effect to the topical TXA for treating facial melasma [7,8].

Objectives

This work aimed to compare the efficacy and safety of topical TXA alone or in combination with either fractional CO2 laser or MN for the treatment of melasma.

Methods

The study was conducted on 30 patients with facial melasma who were collected from the Outpatient Clinics of Dermatology and Venereology Department- Tanta University Hospitals. The approval was obtained from institutional review board-research Ethics Committee of Faculty of Medicine, Tanta University (approval code: 33006/03/20) and fulfilled all the ethical aspects required in human research. All patients signed an informed written consent before joining the study.

Only those patients not using any facial topical treatment for melasma within the preceding 8 weeks to incorporation in the study were included. Patients receiving hormonal treatment, oral contraceptives, systemic retinoids, anticoagulants, antiplatelets or chemotherapeutics were also excluded, in addition to pregnant females, lactating mothers and those with hypersensitivity to TXA or photosensitivity. Patients with blood disorders, other dermatological or systemic diseases causing hyperpigmentation (eg chronic liver, kidney or thyroid diseases) and those with unrealistic expectations were also excluded from the study.

All patients underwent a thorough history taking and clinical examination to assess Fitzpatrick skin phototype. Lesional examination and melasma pattern detection was done by Wood light and dermoscopy (dermalite 4, DL4, 3Gen. San Juan Capistrano, magnification x10) performed at fixed facial points per patient (guided by anatomical landmarks).

Patients were randomly divided into 3 equal groups. Patients of group A were treated with fractional CO_2 laser (4 sessions, 3 weeks apart) and immediate topical application of TXA 5% solution after session (Kapron® 500 mg/5 mL ampoules, Amoun Pharmaceutical Company, diluted to produce 5% TXA solution) with daily night application of topical 5% TXA cream thereafter. Fractional CO2 laser sessions were on the following parameters: power 8-10 W (according to the skin type, performed using CO2 laser [SmartXide Dot®-DEKA], spacing 1000 µm (5.3% density), dwell time 400 µs, and stack 1). Patients of group B were treated with MN (also 4 sessions, 3 weeks apart) and immediate topical application of TXA 5% solution with daily topical night application of 5% TXA cream. The dermapen

used was Dr. Pen ULTIMA-A1 device, 12 needles with needle length adjusted according to the skin thickness and site of melasma lesion (0.25-1 mm). The pen was placed perpendicular to the skin, and the technique includes a combination of horizontal, vertical, and oblique 4-5 passes. The end point was the appearance of erythema with pinpoint bleeding.

Patients of group C were treated only by topical daily night application of 5% TXA cream for 12 weeks. TXA cream was prepared as: white soft paraffin (13.5 gm), cetyle alcohol (13 gm), tween 80 (10 gm), propylene glycol (8 gm), TXA (5 gm) and water to complete 100 gm.

All included patients were instructed to avoid sun exposure as much as possible and to apply a proper daily sunscreen (SPF +50) throughout the treatment period.

Digital photographs were taken at base line, at the end of treatment then at follow up (after 3 months of treatment end) to assess treatment efficacy and recurrence. Scoring of melasma was done by using the modified melasma area and severity index score (mMASI). Assessment of treatment efficacy was done through physician evaluation (three dermatologists were asked to calculate mMASI score before and after completion of the treatment to assess percentage of improvement. Finally the minimum rate on which the three investigators agreed was considered as the investigator's view in the study), patient satisfaction (patients were asked at the end of treatment to rate the overall satisfaction comparing with the pretreatment condition using the following grades: very satisfied (≥ 75% improvement), satisfied (50%-74%), slightly satisfied (25%-49%), and not satisfied (0%-24%). Side effects were reported throughout the treatment period and during follow up.

Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 (IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level. The sample size was not estimated prior to the beginning of the study which is considered as a limitation of the present study.

Results

Age and clinical data of patients of studied groups are summarized in Table 1.

Regarding the percentage of improvement of mMASI score in the three studied groups, patients of groups A and B showed statistically significant higher percentage of improvement in mMASI score than those of group C (P = 0.039 and 0.011, respectively), while the difference between groups A and B was statistically insignificant (Table 1). Figures 1-3 show the clinical and dermoscopic results of some of the included patients in the three studied groups (representing the average response to the treatment).

Regarding the degree of patients satisfaction, a statistically significant better degree of patient's satisfaction was detected in groups A and B than group C, while the difference between groups A and B was statistically insignificant, (P value between A and C and between B and C is < 0.001, 0.006, respectively) (Table 1).

Regarding the recurrence of melasma, 3 patients in group A (37.5%), 2 patients of group B (20%) and 5 patients in group C (50%) showed recurrence of their melasma within 3 months after stoppage of treatment with statistically insignificant difference among the studied groups (Table 1).

Regarding the side effects, post inflammatory hyperpigmentation was reported in 3 patients (30%) of group A in the form of transient post laser hyperpigmentation of the facial skin which improved before the time of next session. Dryness and transient irritation were reported in only one patient (10%) in group A, 2 patients (20%) in group B and only one patient in group C (10%). No statistically significant difference was detected among the studied groups regarding side effects of treatment (Table 1).

Discussion

Results of the present study showed that the use of fractional CO_2 laser for drug delivery of TXA in group A resulted in a statistically significant improvement in facial melasma (P = 0.035). Thirty percent of patients of group A yielded very significant improvement and 50% of them yielded marked improvement of facial melasma. Several previous studies reported that fractional CO_2 laser has beneficial therapeutic effect in melasma [9,10]. It has been stated that the development of fractional resurfacing has led to improvements in melasma treatment with decreased incidence of post-inflammatory hyperpigmentation [11]. Moreover, TXA can also inhibit tyrosinase activity and combat melanin synthesis [12].

Trelles et al reported that melasma patients who underwent combined treatment with CO_2 laser and long-term topical lightening cream (Kligman formula) showed the greatest improvement than those treated by either methods solely and were able to maintain treatment benefits up to 12-month post-treatment [13].

El Sinbawy et alevaluated the effect of fractional CO_2 laser on facial melasma clinically and microscopically in eleven melasma patients treated by two sessions of fractional CO_2 laser one month apart and they concluded that repeated application of low energy fractional CO_2 laser on melasma skin may result in long lasting improvement due to its destructive

Table 1. Demographic data, clinical evaluation, treatment response and patient satisfaction of patients of the three studied groups.

	Group A (N = 10)	Group B (N = 10)	Group C (N = 10)	Test of significance	P
Sex Male, N (%) Female, N (%)	- 10(100)	- 10(100)	- 10(100)	-	-
Age (years) Range Mean (SD)	34-50 41.7(5.46)	37-50 44.2(4.96)	27-50 39.3(6.8)	F = 1.8	0.19
Duration of melasma in years Range Mean (SD)	3-15 10(4.16)	5-15 8.3(3.6)	3-13 9.9(3.4)	H= 2.2	0.33
Skin type, N (%) • III • IV • V	2(20) 3(30) 5 (50)	2(20) 4(40) 4 (40)	2 (20) 6 (60) 2 (20)	χ^2= 2.5	0.7
Melasma type, N (%) • Epidermal • Dermal • Mixed	2(20) 2(20) 6 (60)	3(30) 2(20) 5 (50)	2 (20) 2 (20) 6 (60)	χ^2= 20.82	0.96
Percentage of improvement in mMASI score Range Mean (SD)	0-88 51.5(31.4)	27-83 58.7(19.1)	20-50 32.2(8.5)	H^d=7.4	0.025
Significance between groups	$P_1 = 0.620^a$, $P_2 = 0.039^b$, $P_3 = 0.011^c$				
Patients satisfaction, N (%) • Not satisfied • Satisfied • Slightly satisfied • Very satisfied	2 (20) 1 (10) 5 (50) 2 (20)	1 (10) 2 (20) 4 (40) 3 (30)	2 (20) 8 (80) 0 0	χ^2= 19.1	0.001
Significance between groups	$P_1 = 0.693^a$, $P_2 = 0.001^b$, $P_3 = 0.006^c$				
Recurrence, N (%) • No • Yes	5(62.5) 3(37.5)	8(80) 2(20)	5(50) 5(50)	χ^2= 1.98	0.37
Side effects, N (%) • No • Post inflammatory hyperpigmentation • Dryness, transient irritation	6 (60) 3 (30) 1 (10)	8(80) 0 2(20)	9(90) 0 1(10)	χ^2= 5.3	0.2

mMASI = modified melasma area and severity index scores; SD = standard deviation.
Group A = fractional CO2 laser + topical 5% tranexamic acid; Group B = microneedling + topical 5% tranexamic acid; Group C = topical 5% tranexamic acid.
[a] level of significance for comparing group A and group B; [b]: level of significance for comparing group A and group C; [c] level of significance for comparing group B and group C; [d]Kruskal Wallis test.

effect on melanocytes. No scarring or post inflammatory hyper or hypopigmentation was reported [14].

Tawfic et al assessed the combination of fractional CO_2 and TXA in melasma treatment and they found that the degree of improvement was higher on the side receiving fractional CO_2 laser combined with intradermal injection of TXA than on the side receiving fractional CO_2 laser alone [15].

Qu et alfound that low-power fractional CO_2 laser combined with topical TXA solution is a comparatively effective and safe method for melasma treatment [9].

It should be noted that in the present study, 20% of patients of group A (treated by fractional CO_2 laser and 5% TXA) showed no improvement and that could be attributed to the refractory nature of melasma, multiplicity of aggravating factors in some cases and skin type of Egyptian patients (mostly Fitzpatric III, IV and V) [16,17]. It has been previously mentioned that Q-switched Nd:YAG laser toning is thought to be significantly more effective than low power fractional CO_2 in the treatment of melasma when used separately [16].

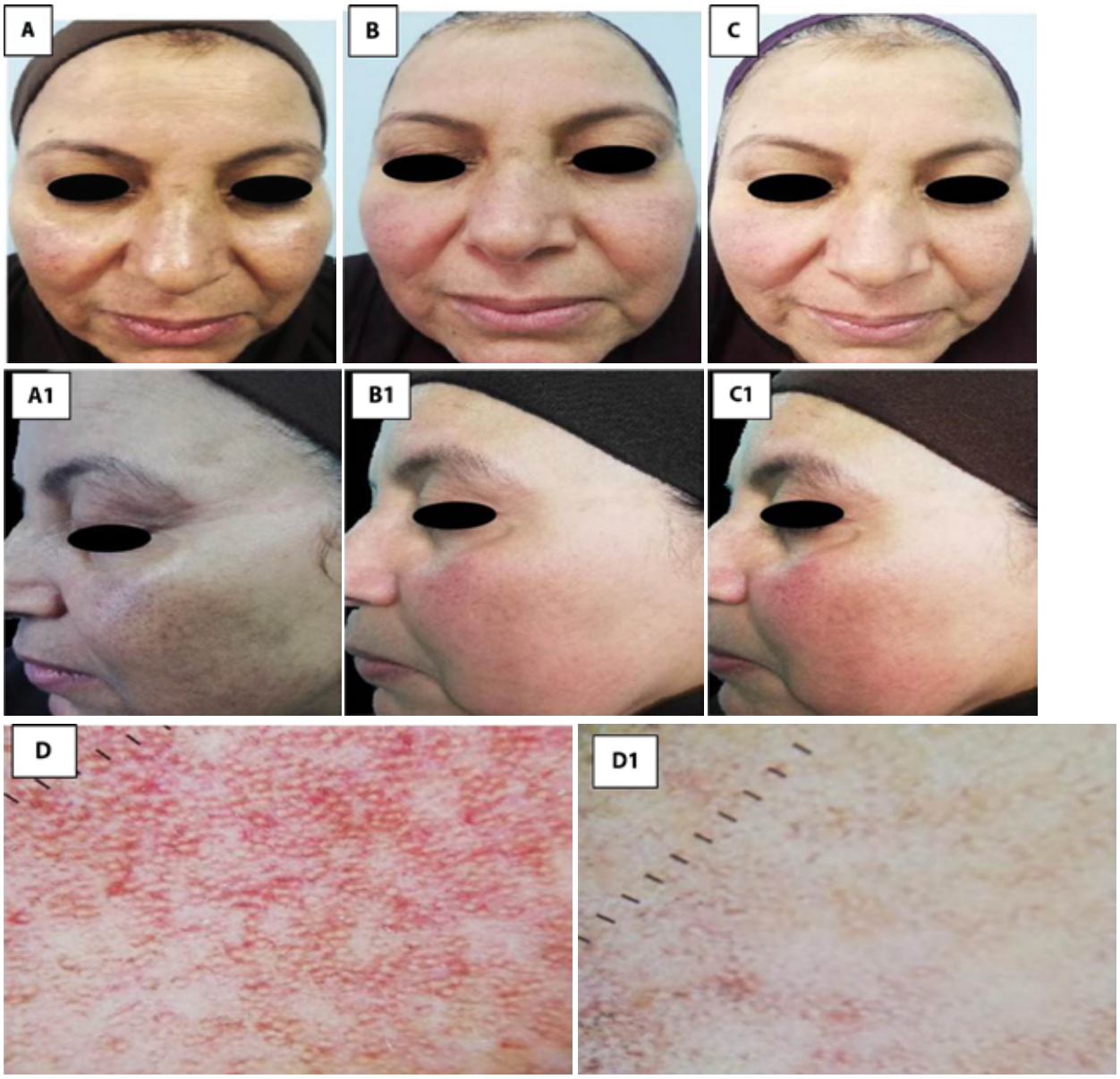

Figure 1. Fifty years old female patient with facial melasma treated by fractional CO2 laser plus topical 5% tranexamic acid. (A,A1) Before treatment. (B,B1) Very significant improvement after 1 months from the last treatment session. (C,C1) After 3 months of follow up (with no recurrence). (D) Dermoscopic picture of melasma showing pigmented network (red arrow) and hyper vascularity (black arrow). (D1) Very significant dermoscopic improvement after treatment showing the decrease in intensity of pigmentation.

In the present study, hyperpigmentation occurred as a side effect with fractional CO_2 laser sessions in 30% of patients of group A and this suggests that the fractional CO_2 laser is not always an optimal choice for treatment of facial melasma especially in patients of skin types IV and V and that meticulous patient selection and strict sun avoidance are key factors for improvement. A previous study reported that fractional CO_2 laser could increase TXA absorption in porcine skin, but when applied to humans, the risk of post inflammatory hyperpigmentation should be considered [18].

Delgado and Torre concluded that the use of fractional CO_2 laser in treatment of melasma for skin types IV to VI is risky. They claimed that in the best-case scenario in the long term, it will end up the same as the starting point, but there is a high possibility that it may worsen the condition [19].

This variation in the percentage of improvement among patients of group A in the present study, could be attributed to variations in patient skin type, type of melasma, season in which sessions were done, habitual sun exposure and adherence to sunscreen. The percentage of improvement was excellent in lighter skin color, epidermal type of melasma and with minimal sun exposure. On the other side, there was no or less improvement in dark skin color, dermal type of melasma and when sessions were done in summer. So proper patient selection must be kept in mind when using fractional CO_2 laser in facial melasma treatment.

The current study showed that the use of MN for drug delivery of TXA in group B (treated by MN and 5% TXA) resulted in a statistically significant improvement of facial melasma ($P = 0.005$), and that result was similar to many

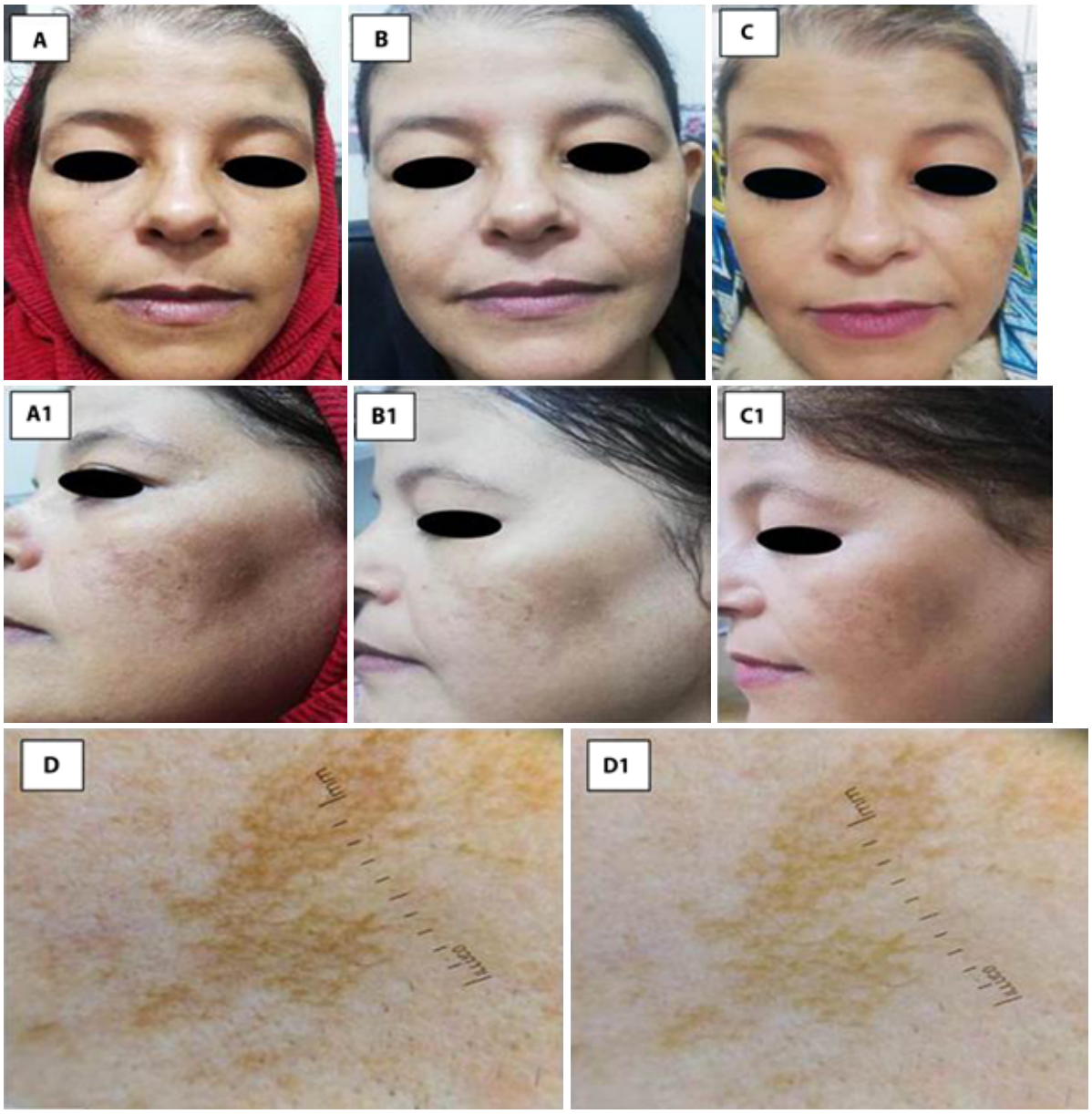

Figure 2. Forty-three year old female patient with malar melasma treated by microneedling plus topical 5% tranexamicacid. (A,A1) Before treatment. (B,B1) Marked improvement after 1 month from the last treatment session. (C,C1) Recurrence of melasma after 3 months of follow up. (D) Dermoscopic picture of melasma showing melanin pigment (red arrow). (D1) Dermoscopic picture after treatment showing the decrease in intensity of pigmentation.

previous studies which assisted the pleasant effect of MN in treatment of melasma [10,20,21].

Based on low-quality evidence, MN may play a role in the treatment of melasma through facilitation of delivery of topical therapies to the epidermis and dermis, and one ancillary benefit of this approach being the very low risk of postinflammatory hyperpigmentation [22].

Lima et al concluded that MN alone, without the addition of any active medication, can cause lightening of skin stains in patients with recalcitrant melasma. Through their histological findings, it was found that MN therapy promotes the proliferation of fibroblasts and helps in superior dermal neocollagenesis, decreases the contact of the melanocytes with melanogenic stimuli and improves the protection against UVR owing to epidermal thickening [2].

Moreover, MN can provide a minimally invasive means of painless delivery of therapeutic molecules through the skin barrier with precision and convenience. Physically opening micro tunnels for drug delivery with MN involves a different mechanism of action than lasers and is not accompanied by the risk of post inflammatory hyperpigmentation [21].

A split face comparative study of safety and efficacy of MN with TXA versus MN with vitamin C in the treatment of melasma concluded that improvement was more with TXA than with vitamin C, although not statistically significant [23].

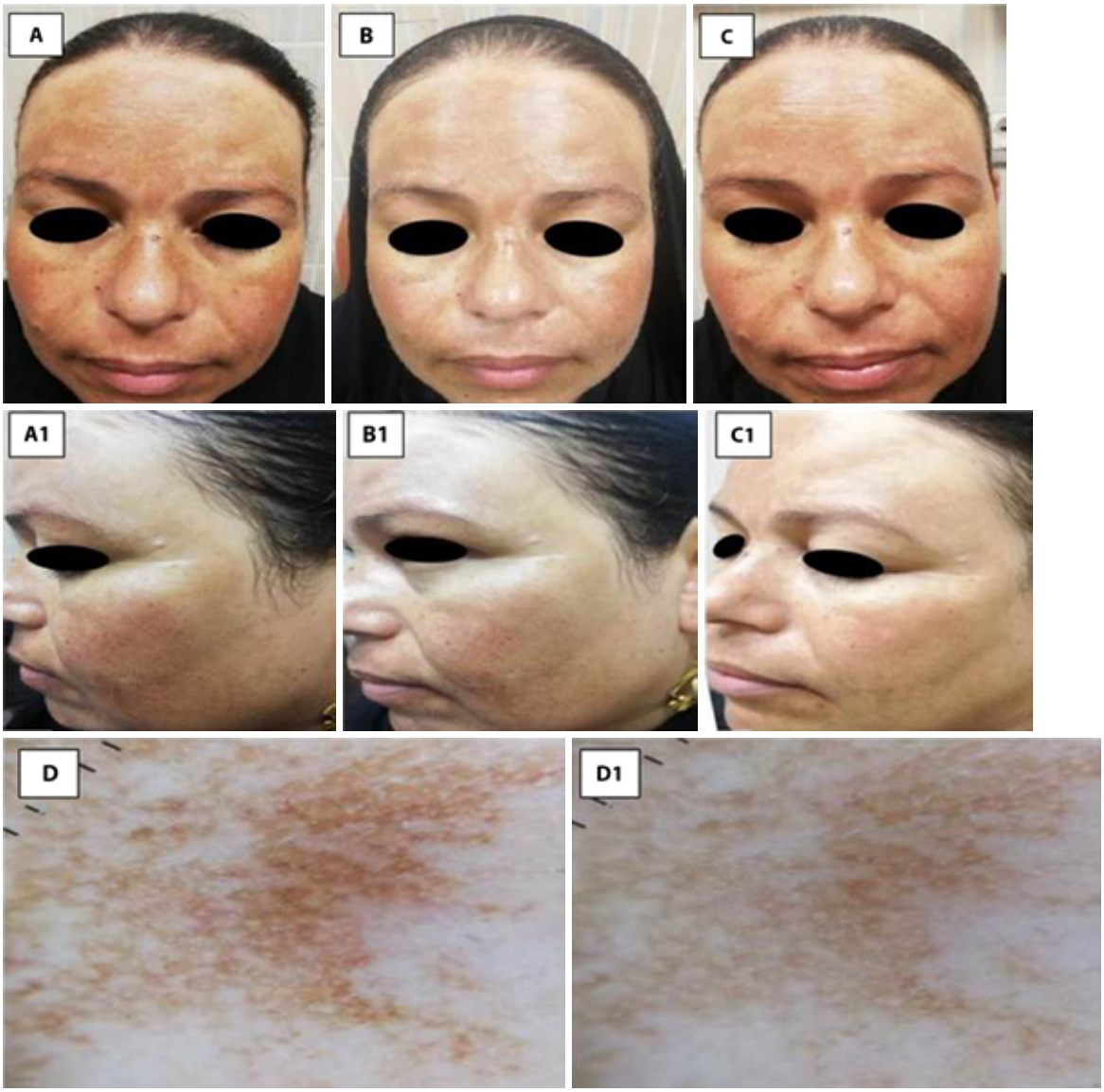

Figure 3. Forty-four year old female patient with facial melasma treated by 5% topical tranexamic acid cream. (A,A1) Before treatment. (B,B1) Moderate improvement after 1 month from the end of treatment. (C,C1) Recurrence of melasma after 3 months of follow up. (D) Dermoscopic picture of melasma showing pigmented network (red arrow), deep melanin pigment (yellow arrow) deposition and hypervascularity (black arrow). (D1) Dermoscopic picture after treatment showing the decrease in intensity of pigmentation.

Saleh et al used TXA with MN versus MN alone in treatment of melasma, they concluded that although MN alone produced significant lightening effect, topical TXA combined with MN achieved more satisfactory results [24].

Farshi and Mansouri concluded that both MN and mesoneedling are effective in decreasing melanin content in the epidermal melasma lesions [25].

On the other hand, Mekawy et al compared both fractional CO_2 laser and MN for delivery of TXA in the treatment of melasma, they found that both methods were equally effective and safe in treatment of facial melasma [10].

In the present study, MN was safe in melasma treatment without side effects as hyperpigmentation that happened with fractional CO_2 laser. The irritation and dryness that happened occasionally in group B was mostly due to TXA cream.

In the present study both fractional CO_2 laser and MN were equally effective in TXA delivery and melasma treatment with no statistically significant difference in either the percentage of improvement or patient satisfaction. Meanwhile, MN can be preferable in melasma treatment than fractional CO_2 laser which carries the risk of hyperpigmentation in patients with darker skin complexion.

The present study also showed that application of daily TXA cream 5% in group C (treated by 5% TXA cream only) improved facial melasma significantly ($P = 0.005$).

The role of topical TXA in melasma has been studied in several previous researche. Similar to the present work, most

of the previous studies had small sample sizes ranging from 13 and 50 patients and most of them demonstrated significant differences in mMASI scores after treatment [26-29]. A multitude of topical preparations and methodologies of treatment were used. Those ranged from 3% TXA cream [27], 5% gel [28], 3 % solution and 5% liposome-based formulation [29]. All were used twice daily for 12 weeks. In a previous comprehensive review of clinical studies, no statistically significant differences were collectively detected between topical TXA and baseline treatment options of melasma including topical hydroquinone [27,29], or combination of topical hydroquinone and dexamethasone [27].

Kaleem et al compared the efficacy of TXA mesotherapy versus 0.9% normal saline for melasma by split-face study. They observed significant improvement in TXA side and considered it cost-effective and safe therapy for melasma [30].

On the contrary, Kanechorn et al] treated 23 women with bilateral epidermal melasma in their split-face trial for 3 months by using topical 5% TXA gel versus its vehicle [28]. They reported that improvement of pigmentation induced by TXA gel was neither superior nor different compared to its vehicle although it caused more irritation to the treated site.

Four patients in the present study experienced dryness and irritation from TXA application that was similar to the result of Kanechorn et al observed irritation and dryness by using local TXA [28].

As melasma is claimed to respond better to treatment with oral and/or locally injected TXA than to topical application, and as topical TXA is not readily available in the markets, it seems to be a worthy research point to improve the pharmacokinetic transepidermal carriage with different vehicles and to handle the matter of irritation [31,32].

It has been claimed that TXA alone is not strong enough to fight a previously settled melasma by itself and it should be better used in combination with other treatment modalities. TXA is thought to improve UV-induced pigmentation and hinders the progress of melanogenesis [31].

This has been furtherly proved in the present study, as combining TXA with either fractional CO_2 laser or MN gave a statistically significant better improvement of melasma than when used alone.

It is worthy saying that combing of TXA with fractional CO_2 laser or MN in the present study raised the degree of patient satisfaction.

In the present study, dermoscopy was done at the beginning of treatment to confirm diagnosis and classify the type of melasma. A statistically significant better improvement in epidermal melasma than dermal type was detected in the studied groups. Dermoscopic improvement included fainting the color of melanin pigment and decreasing the red color of the vascular component of melasma.

All patients in the current study were re-evaluated after 3 months from the end of the study to detect the percentage of the recurrence. Thirty percent in group A, 20% in group B and 50% in group C experienced recurrence during follow-up. It should be taken in consideration that recurrence can be considered as a role in different treatment modalities of facial melasma and appropriate maintenance therapy should be selected to avoid relapse of melasma after improvement [33].

Lueangarun et al studied 4mg/mL intradermal TXA injection for treatment of melasma. They found significant efficacy at16th week; however, melasma recurrence occurred during the 48-weeks of follow-up, so they concluded that maintenance therapy and sun protection should be considered for patients with melasma [34].

In general, pretreatment and post-treatment topical regimens in conjunction with laser, light treatments and other treatment protocols help to reduce the risk of rebound hyper-pigmentation, post-inflammatory pigmentation, and increase the longevity of the lightening effect on melasma [35].

Conclusions

Topical TXA is a safe and fairly effective treatment modality for facial melasma. Combining TXA with either fractional CO_2 laser or MN yielded significantly better improvement of melasma than when it is used alone. No significant difference regarding mean mMASI reduction, degree of improvement, or the level of patients satisfaction was detected between MN and fractional CO_2 laser when combined with topical TXA for melasma treatment. MN is more recommended instead of CO_2 fractional laser as a combination with TXA in melasma treatment due to the similar efficacy but more favorable side-effect profile. Fractional CO_2 laser carries the risk of post-inflammatory hyperpigmentation when used in melasma treatment, so proper patient selection with adequate parameters must be kept in mind.

References

1. Handel AC, Miot LDB, Miot HA. Melasma. A clinical and epidemiological review. *An Bras Dermatol.*. 2014;89(5):771-782. DOI: 10.1590/abd1806-4841.20143063. PMID: 25184917. PMCID: PMC4155956.
2. Freitag FM, Cestari TF, Leopoldo LR, Paludo P, Boza JC. Effect of melisma on quality of life in a sample of women living in Southern Brazil. *J Eur Acad Dermatol Venereol.* 2008;22(6):655-662. DOI: 10.1111/j.1468-3083.2007.02472.x. PMID: 18410339.
3. Polnikorn N. Treatment of refractory melasma with the Med Lite C6 Q-switched Nd. YAG laser and alpha arbutin. a prospective study. *J Cosmet Laser Ther.* 2010;12(3):126-131. DOI: 10.3109 /14764172.2010.487910. PMID: 20482238.

4. Cheng L, Pettersen D, Ohlsson B, et al. Discovery of the fibrinolysis inhibitor AZD 6564, acting via interference of a protein–protein interaction. *ACS Med Chem Lett*. 2014;18(5): 538-543. DOI: 10.1021/ml400526d. PMID: 24900876. PMCID: PMC4027757.
5. Alexiades-Armenakas MR, Dover JS, Arndt KA. The spectrum of laser skin resurfacing, non-ablative, fractional, and ablative laser resurfacing. *J Am Acad Dermatol*. 2008;58(5):719-737. DOI: 10.1016/j.jaad.2008.01.003. PMID: 18423256.
6. Tuan-MahmoodTM, McCrudden MT, Torrisi BM, et al. Microneedles for intradermal and transdermal drug delivery. *Eur J Pharm Sci*. 2013;50(5):623-637. DOI: 10.1016/j.ejps .2013.05.005. PMID: 23680534. PMCID: PMC4119996.
7. Alegre-Sánchez A, Jiménez-Gómez N, Boixeda P. Laser-assisted drug delivery. *Actas Dermosifiliogr*. 2018;109(10):858-867. DOI: 10.1016/j.ad.2018.07.008. PMID: 30266385.
8. Shende P, Sardesai M, Gaud RS. Micro to nanoneedles. A trend of modernized transepidermal drug delivery system. *Artif Cells Nanomed Biotechnol*. 2018;46(1):19-25. DOI: 10.1080/21691401.2017.1304409. PMID: 28355887.
9. Qu Y, Wang F, Liu J, Xia X. Clinical observation and dermoscopy evaluation of fractional CO_2 laser combined with topical tranexamic acid in melasma treatments. *J Cosmet Dermatol*. 2021;20(4): 1110-1116. DOI: 10.1111/jocd.13992. PMID: 33565243.
10. Mekawy KMM, Sadek A, Seddeik Abdel-Hameed AK. Micro-needling versus fractional carbon dioxide laser for delivery of tranexamic acid in the treatment of melasma: A split-face study. *J Cosmet Dermatol*. 2021;20(2):460-465. DOI: 10.1111 /jocd.13537. PMID: 32562337.
11. Neeley MR, Pearce FB, Collawn SS. Successful treatment of malar dermal melasma with a fractional ablative CO_2 laser in a patient with type V skin. *J Cosmet Laser Ther*. 2010;12(6):258-260. DOI: 10.3109/14764172.2010.538412. PMID: 21142733.
12. Kim HJ, Moon SH, Cho SH, Lee JD, Kim HS. Efficacy and Safety of Tranexamic Acid in Melasma: A Meta-analysis and Systematic Review. *Acta Derm Venereol*. 2017;97(7):776-781. DOI: 10.2340/00015555-2668. PMID: 28374042.
13. Trelles MA, Velez M, Gold MH. The treatment of melasma with topical creams alone, CO2 fractional ablative resurfacing alone, or a combination of the two: a comparative study. *J Drugs Dermatol*. 2010;9(4):315-322. PMID: 20514787.
14. El-Sinbawy ZG, Abdelnabi NM, Sarhan NE, Elgarhy LH. Clinical & ultrastructural evaluation of the effect of fractional CO2 laser on facial melasma. *Ultrastruct Pathol*. 2019;43(4-5):135-144. DOI: 10.1080/01913123.2019.1673861. PMID: 31575311.
15. Tawfic SO, Abdel Halim DM, Albarbary A, Abdelhady M. Assessment of combined fractional CO_2 and tranexamic acid in melasma treatment. *Lasers Surg Med*. 2019;51(1):27-33. DOI: 10.1002/lsm.23032. PMID: 30431171.
16. Esmat S, Z Elramly A, Shahin D, Hilal RF. Combining Low Power Fractional CO_2 With QS-NdYAG Toning in the Treatment of Melasma Reduces the Incidence of Punctate Leukoderma. *Lasers Surg Med*. 2021;53(10):1325-1340. DOI: 10.1002/lsm.23441. PMID: 34164829.
17. Nourmohammadi Abadchi S, Fatemi Naeini F, Beheshtian E. Combination of Hydroquinone and Fractional CO_2 Laser versus Hydroquinone Monotherapy in Melasma Treatment: A Randomized, Single-blinded, Split-face Clinical Trial. *Indian J Dermatol*. 2019;64(2):129-135. DOI: 10.4103/ijd.IJD_240_17. PMID: 30983609. PMCID: PMC6440181.
18. Hsiao F, Lin YC, Huang CC. Efficacy and safety of a single treatment using a 10,600-nm carbon dioxide fractional laser for mild-to-moderate atrophic acne scars in Asian skin. *Dermatologica Sinica*. 2013;31(2):59-63. DOI: 10.1016/j.dsi .2012.09.009.
19. Delgado RE, Torre Mde L. Use of fractional laser in mixed-race patients. *Facial Plast Surg*. 2013;29(3):161-166. DOI: 10.1055/s-0033-1347006. PMID: 23761119.
20. Lima Ede A. Microneedling in facial recalcitrant melasma: report of a series of 22 cases. *An Bras Dermatol*. 2015;90(6):919-921. DOI: 10.1590/abd1806-4841.20154748. PMID: 26734882. PMCID: PMC4689089.
21. Xu Y, Ma R, Juliandri J, et al. Efficacy of functional microarray of microneedles combined with topical tranexamic acid for melasma: A randomized, self-controlled, split-face study. *Medicine (Baltimore)*. 2017;96(19):e6897. DOI: 10.1097/MD.0000000000006897. PMID: 28489798. PMCID: PMC5428632.
22. Wu SZ, Muddasani S, Alam M. A Systematic Review of the Efficacy and Safety of Microneedling in the Treatment of Melasma. *Dermatol Surg*. 2020;46(12):1636-1641. DOI: 10.1097 /DSS.0000000000002763. PMID: 32897944.
23. Menon A, Eram H, Kamath PR, Goel S, Babu AM. 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*. 2019;11(1):41-45. DOI: 10.4103/idoj.IDOJ_22_19. PMID: 32055507. PMCID: PMC7001392.
24. Saleh FY, Abdel-Azim ES, Ragaie MH, Guendy MG. Topical tranexamic acid with microneedling versus microneedling alone in treatment of melasma. Clinical, histopathologic, and immunohistochemical study. *J Egypt Womens Dermatol Soc*. 2019;16(2):89-96. DOI: 10.4103/JEWD.JEWD_25_19.
25. Farshi S, Mansouri P. Study of efficacy of microneedling and mesoneedling in the treatment of epidermal melasma: A pilot trial. *J Cosmet Dermatol*. 2020;19(5):1093-1098. DOI: 10.1111/jocd .13369. PMID: 32196865.
26. Steiner D, Feola C, Bialeski N. Study evaluating the efficacy of topical and injected tranexamic acid in treatment of melasma. *Surg Cosmet Dermatol*. 2009;1(4):174–177.
27. Ebrahimi B, Naeini FF. Topical tranexamic acid as a promising treatment for melasma. *J Res Med Sci*. 2014;19(8):753-757. PMID: 25422661. PMCID: PMC4235096.
28. Kanechorn Na Ayuthaya P, Niumphradit N, Manosroi A, Nakakes 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(3):150-154. DOI: 10.3109/14764172.2012.685478. PMID: 22506692.
29. Banihashemi M, Zabolinejad N, Jaafari MR, Salehi M, Jabari A. Comparison of therapeutic effects of liposomal Tranexamic Acid and conventional Hydroquinone on melasma. *J Cosmet Dermatol*. 2015;14(3):174-177. DOI: 10.1111/jocd.12152. PMID: 26177992.
30. Kaleem S, Ghafoor R, Khan S. Comparison of efficacy of Tranexamic Acid Mesotherapy versus 0.9% normal Saline for Melasma; A split face study in a Tertiary Care Hospital of Karachi. *Pak J Med Sci*. 2020;36(5):930-934. DOI: 10.12669/ pjms.36.5.2379. PMID: 32704266. PMCID: PMC7372652.
31. Tse TW, Hui E. Tranexamic acid: an important adjuvant in the treatment of melasma. *J Cosmet Dermatol*. 2013;12(1):57-66. DOI: 10.1111/jocd.12026. PMID: 23438143.

32. Ng SP, Marcant M, Davis AF. In vitro human skin concentrations following topical application of 2% tranexamic acid in co-enhancer cream and branded cream formulations. *J Cosmet Dermatol.* 2020;19(10):2656-2662. DOI: 10.1111/jocd.13301 . PMID: 31961048.
33. Arora P, Sarkar R, Garg VK, Arya L. Lasers for treatment of melasma and post-inflammatory hyperpigmentation. *J Cutan Aesthet Surg.* 2012;5(2):93-103. DOI: 10.4103/0974-2077.99436. PMID: 23060704. PMCID: PMC3461803.
34. Lueangarun S, Sirithanabadeekul P, Wongwicharn P, et al. Intradermal Tranexamic Acid Injection for the Treatment of Melasma: A Pilot Study with 48-week Follow-up. *J Clin Aesthet Dermatol.* 2020;13(8):36-39. PMID: 33178380. PMCID: PMC7595366.
35. Trivedi MK, Yang FC, Cho BK. A review of laser and light therapy in melasma. *Int J Womens Dermatol.* 2017;3(1):11-20. DOI: 10.1016/j.ijwd.2017.01.004. PMID: 2849204.; PMCID: PMC5418955.