The Use of Tranexamic Acid and Microneedling in the Treatment of Melasma: A Systematic Review

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PRACTICE **POINTS**

- Combination therapy with tranexamic acid (TXA) and microneedling is a safe and effective treatment for melasma.
- Combining TXA with microneedling may result in decreased melasma relapse rates.

Melasma is a chronic pigmentary disorder that results in hyperpigmented patches in sun-exposed areas. Tranexamic acid (TXA) and microneedling are potential treatment options for individuals with melasma. The objective of our systematic review was to review 12 randomized controlled trials and clinical trials on the use and efficacy of TXA with microneedling for melasma. The combination of TXA and microneedling was found to be more effective at improving melasma lesions than either treatment alone; TXA alone was equally effective at reducing melasma lesions vs the standard treatment of hydroquinone.

Melasma (also known as chloasma faciei) is a common chronic skin disorder that results in well-demarcated, hyperpigmented, tan to dark patches that mostly appear in sun-exposed areas such as the face and neck and sometimes the arms. The exact prevalence or incidence is not known but is estimated to be 1% to 50% overall depending on the ethnic population and geographic location.[1,2] Melasma predominantly affects women, but research has shown that approximately 10% to 20% of men are affected by this condition.[3,4] Although melasma can affect patients of all skin types, it primarily affects those with darker skin tones.[5] The groups most often affected are women of Black, Hispanic, Middle Eastern, and Southeast Asian ethnicity. Although the pathogenesis is complex and not fully understood, multiple pathways and etiologies have been theorized to cause melasma. Potential causes include exposure to UV radiation, oral contraceptives, hormonal changes, medications, thyroid dysfunction, genetics, and pregnancy.[6,7] Cytokines and growth factors, including adipokine and angiopoietin, synthesized by sebaceous glands play a role in the pathogenic mechanism of melasma. Cytokines and growth factors are hypothesized to modulate the function of melanocytes.[8] Both melanocytes and sebocytes are controlled by α–melanocyte-stimulating hormone. Therefore, overexpression of α–melanocyte-stimulating hormone will result in overproduction of these 2 cell types, resulting in melasma. Melasma can be classified into 4 subtypes using Wood lamp examination: epidermal, dermal, mixed, or indeterminate.[3] Furthermore, melasma is divided into subgroups based on the location: malar region, mandibular region, and centrofacial patch pattern.[9,10] The involvement of sebaceous glands in the pathogenesis of melasma may explain the predilection for the centrofacial region, which is the most common pattern.

The severity of melasma can be assessed using the melasma area and severity index (MASI), which is calculated by subjective assessment of 3 main factors: (1) facial

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area of involvement; (2) darkness of affected region; and (3) homogeneity, with the extent of melasma indicated by a score ranging from 0 to 48.[11] The modified MASI (mMASI) subsequently was introduced to assist with assessing the severity of melasma and creating distinct ranges for mild, moderate, and severe cases, ranging from 0 (mild) to 24 (severe).[12] Both indices are used in research to assess the improvement of melasma with treatment.

Patients with melasma report a decrease in quality of life, increased emotional stress, and lower self-esteem due to cosmesis.[13] Treatment of melasma can be highly challenging and often is complicated by relapsing. Historically, the treatment of melasma has included the use of chemical lightening agents. Additional treatment options include the use of lasers and complex chemical peels,[9,10] but these interventions may result in adverse outcomes for individuals with darker skin tones. The current gold-standard treatment is topical hydroquinone and broad-spectrum sunscreen. Although hydroquinone is effective in the treatment of melasma, relapse is common. The goal of melasma management is not only to treat acute hyperpigmentation but also to prevent relapse. Other therapies that currently are being explored for the clinically sustained treatment of melasma include tranexamic acid (TXA) (trans-4-[aminomethyl]cyclohexanecarboxylic acid),[9,10] an antifibrinolytic agent routinely used to prevent blood loss during surgery and in the management of menorrhagia. It is a synthetic derivative of lysine and serves as a potent plasmin inhibitor by blocking the lysine-binding sites of plasminogen molecules, thus preventing the conversion of plasminogen to plasmin. It also prevents fibrinolysis and blood loss.

In addition to its hemostatic properties, TXA has been found to have hypopigmentation properties.[14,15] Plasminogen also can be found in human epidermal basal cells and human keratinocytes, and it is postulated that TXA's interaction with these cells explains its hypopigmentation properties. Both UV radiation and hormones activate plasminogen into plasmin, resulting in the activation of tyrosinase and melanogenesis.[14,15] Tranexamic acid is postulated to inhibit the keratinocyte-plasminogen pathway, thus leading to the inhibition of UV-induced and hormone-induced pigmentation. Also, TXA serves as a competitive inhibitor for tyrosinase due to its structural similarity to tyrosine.[15] The combination of these 2 mechanisms contributes to the skin-lightening effects of TXA, making it a potential treatment for melasma.

Furthermore, the use of microneedling is being explored as a treatment option for melasma. Microneedling creates microscopic punctures in the skin using tiny needles, resulting in a wound-healing response and skin resurfacing. The microneedling technique is utilized to create small holes in the skin, with needle depths that can be adjusted from 0.5 to 3.5 mm to target different layers of the dermis and allow for discreet application of TXA.[16] We sought to look at the current literature on the use and effectiveness of microneedling in combination with TXA to treat melasma and prevent relapse.

Methods

A systematic review was performed of PubMed articles indexed for MEDLINE and Embase in November 2021 to compile available articles that studied TXA and microneedling as a treatment for melasma. The PubMed search terms were *(melasma) AND (microneedling* OR 'tranexamic acid' OR TXA or TA)*. The Embase search terms were *(cholasma OR melasma) AND (tranexamic acid OR TXA) AND (microneedling)*(Figure). The search was then limited to "randomized controlled trial" and "clinical trial" in English-language journals. Duplicates were excluded. After thorough evaluation, articles that discussed the use of TXA in combination with treatment options other than microneedling also were excluded.

Results

The literature search yielded a total of 12 articles that assessed the effectiveness of TXA and microneedling for the treatment of melasma (Table).[17-28] Several articles concluded that TXA was equally effective at reducing melasma lesions when compared with the standard treatment of hydroquinone. Some of the reviewed articles also demonstrated the effectiveness of microneedling in improving melasma lesions as a stand-alone treatment. These studies highlighted the enhanced efficacy of the combined treatment of TXA and microneedling compared with their individual uses.[17-28]

Comment

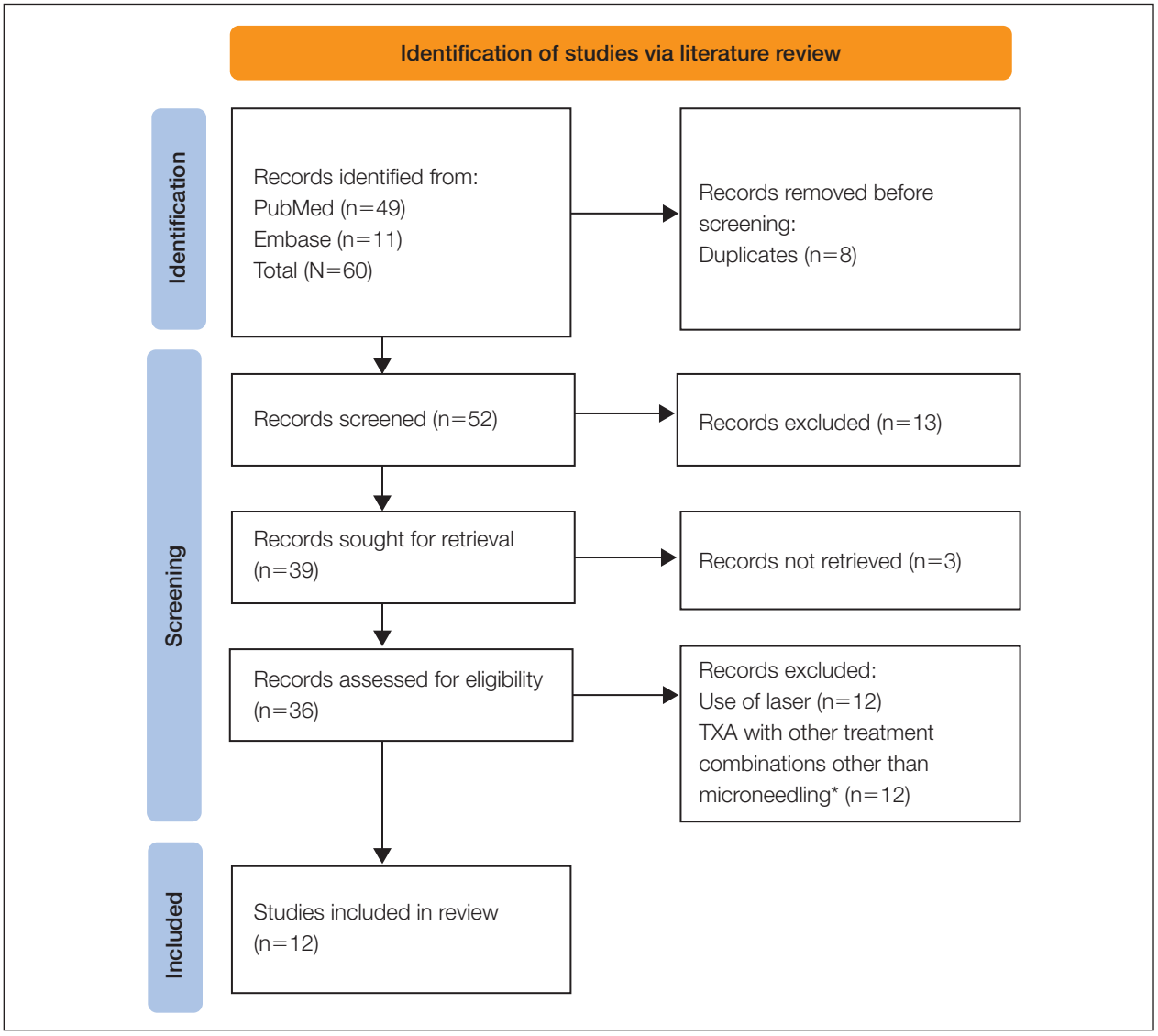
Melasma is a common chronic hyperpigmentation disorder, making its treatment clinically challenging. Many patients experience symptom relapses, and limited effective treatment options make achieving complete clearance difficult, underscoring the need for improved therapeutic approaches. Recently, researchers have explored alternative treatments to address the challenges of melasma management. Tranexamic acid is an antifibrinolytic used to prevent blood loss and has emerged as a potential treatment for melasma. Similarly, microneedling—a technique in which multiple punctures are made in the skin to activate and stimulate wound healing and skin rejuvenation—shows promise for melasma.

Oral TXA for Melasma—Oral TXA has been shown to reduce melasma lesions. Del Rosario et al[17] recruited 44 women (39 of whom completed the study) with moderate to severe melasma and randomized them into 2 groups: oral TXA and placebo. This study demonstrated a 49% reduction in the mMASI score in all participants taking oral TXA (250 mg twice daily [BID]) compared with an 18% reduction in the control group (placebo capsule BID) after 3 months of treatment. In patients with moderate and severe melasma, 45% and 51% mMASI score reductions were reported in the treatment group, respectively,

vs 16% and 19% score reductions in placebo group, respectively. These researchers concluded that oral TXA may be effective at treating moderate to severe melasma. Although patients with severe melasma had a better response to treatment, their improvement was not sustained compared with patients with moderate melasma after a 3-month posttreatment follow-up.[17]

Microneedling Plus TXA for Melasma—Microneedling alone has been shown to be effective for melasma. El Attar et al[18] conducted a split-face study of microneedling (1.5-mm depth) plus topical TXA (0.5 mL)(right side of the face[treatment arm]) compared with microneedling (1.5-mm depth) plus topical vitamin C (0.5 mL)(left side of the face [control group]) in 20 women with melasma. The sessions were repeated every 2 weeks for a total of 6 sessions. Although researchers found no statistically significant differences between the 2 treatment sides, microneedling plus TXA showed a slight advantage over microneedling plus vitamin C in dermoscopic examination. Both sides showed improvement in pigmented lesions, but vitamin C–treated lesions did not show an improvement in vascularity vs TXA.[18]

Saleh et al[19] further showed that combination treatment with microneedling and TXA may improve clinical outcomes better than microneedling alone. Their study demonstrated a reduction in MASI score that was significantly higher in the combination treatment group compared with the microneedling alone group (P=.001). There was a significant reduction in melanoma antigen recognized by T cells 1 (MART-1)–positive cells in the combination treatment group compared with the microneedling alone group (P=.001). Lastly, combined



Flow diagram of study selection. Asterisk indicates platelet-rich plasma, vitamin C, kojic acid, niacinamide, Kligman's therapy (fluocinolone + hydroquinone + tretinoin), retinoic acid, and cysteamine.

Summary of Reviewed Research Articles on TXA and Microneedling for Melasma

Reference (year)	Country	Sample size	Treatment groups	Outcomes
Oral TXA				
Del Rosario et al[17] (2018)	United States	44 enrolled; 39 completed study	Participants randomized to 1 of 2 groups: oral TXA 250-mg capsules BID + sunscreen; placebo capsules BID + sunscreen for 30 d; 30-d oral TXA treatment supply given at baseline, 1-mo, and 2-mo visits	49% reduction in mMASI score in TXA group vs 18% reduction in control group after 3 mo of TXA treatment; 26% reduction in mMASI score in TXA group compared with baseline vs 19% reduction in placebo compared with baseline at 3 mo posttreatment
Microneedling plus TXA				
El Attar et al[18] (2022)	Egypt	20	Right side of face: topical 0.5 mL TXA (500 mg in 5 mL) after microneedling (1.5-mm depth); left side of face: topical 0.5 mL vitamin C after microneedling	Right side: hemi-MASI score (which assesses melasma severity on 1 side of the face) decreased with a mean (SD) change of 53.76% (25.45%) before and after treatment; left side: hemi-MASI mean (SD) reduction of 45.94% (23.20%); physician evaluation: right side showed better improvement of melasma lesions vs left side, with no statistically significant differences between the 2 sides (P=.346); dermoscopy: both sides showed improvement of pigmented lesions, but the side treated with vitamin C did not show an improvement in vascular findings in all patients vs TXA
Saleh et al[19] (2019)	Egypt	42	Group I: microneedling and TXA (ampoules, 100 mg/1 mL), 6 sessions with 2-wk interval between sessions; group II, microneedling alone, 6 sessions with 2-wk interval between sessions; microneedling with electric pen, 12 needles, adjustable needle length of 1.5 mm	MASI score significantly decreased in both groups; reduction in score was statistically higher in group I vs group II (P=.001); mean percentage reduction of MASI scores were 62.1% (group I) and 22.5% (group II), with a statistically significant difference between groups (P=.001); difference in clinical improvement between groups was statistically significant (P=.001); no statistically significant difference between group I and group II in melasma histologic pattern (P=.753); IHC staining showed a significant decrease in monoclonal mouse MART-1 cells between group I and group II after treatment (P=.001); percentage reduction in number of MART-1–positive cells was significantly higher in group I (60.8%) vs group II (37.5%)(P=.001)
Xu et al[20] (2017)	China	28	Left side of face: microneedles (pen penetrates skin with frequency of 3000×/min), then TXA solution 0.5% once per week for 12 wk; right side of face: sham device and TXA solution 0.5% once per week for 12 wk	Mean (SD) MI decreased significantly in both groups (microneedling + TXA: 240.25 [36.05][P=.00]; TXA: 272.5 [37.54][P=.01]), with MI significantly less on left side vs right side (P=.002); biophysical properties showed no difference between 2 sides; physician evaluation revealed better results at wk 12 with combined therapy vs TXA only; participant satisfaction was statistically significant between both sides (microneedling + TXA: 2.75 [0.84]; TXA: 1.61 [0.57][P=.00])

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TABLE. (continued)

Reference (year)	Country	Sample size	Treatment groups	Outcomes
Microneedling plus TXA (continued)				
Kaur et al[21] (2020)	Unspecified, but population described as North Indian	40	Microneedling with TXA solution 10% (0.5–1 mL) on 1 side of face (treatment side); microneedling with distilled water on other side (control side); 8 wk, with procedure done at 2-wk intervals	65.92% improvement in mean mMASI scores on treatment side vs 20.75% improvement on control side at 8 wk
Ebrahim et al[22] (2020)	Egypt	56	Right side of face: TXA 0.5 mL (4 mg/mL) with microneedling (needle length, 1.5 mm; diameter, 0.25 mm; penetration depth of needle, 0.25–1 mm); left side of face: 4 mg/mL TXA with intradermal injection (1-mL insulin syringe with 30-gauge needle; injection of 0.1 mL per point at 1-cm intervals on the melasma area); every 2 wk for 12 wk	74.8% reduction in mMASI score with intradermal injections of TXA and 73.6% reduction with microneedling application of TXA at 12 wk
Saki et al[23] (2018)	Iran	31	Monthly intradermal TXA injection (20 mg/mL) on 1 side of the face; 2% topical HQ 1×/night on other side of the face for 3 mo	TXA was superior to HQ in reducing mean (SD) melanin value at the first follow-up vs baseline (27 [21.7] for TXA vs 16.7 [21.1] for HQ [P=.013]); no difference was observed between the 2 treatments for reduction in melanin value between first and second follow-up, second and third follow-up, and overall melanin reduction; no statistically significant difference observed for erythema on sides (P=.085 for TXA side and P=.5 for HQ side)
Sharma et al[24] (2017)	India	80	Group A: oral TXA 250 mg BID for 12 wk; group B: intradermal (10-mm intervals using insulin syringe 28-gauge needle) microinjection of TXA 4 mg/mL every 4 wk	Statistically significant decrease in mean MASI score [SD] from baseline to wk 12 for group A (from 12.25 [4.44] to 2.78 [1.57]) and for group B (11.29 [6.07] to 2.37 [1.75]); no statistically significant differences in mean MASI percentage reduction [SD] in both groups at wk 4 (group A=21.29% [17.24%]; group B=18.27% [15.64%]), wk 8 (group A=53.32% [16.50%]; group B=51.32% [17.20%]), and wk 12 (group A=77.96% [9.39%]; group B=79.00% [9.64%])
Cassiano et al[25] (2020)	Brazil	64	Participants were divided into 4 groups—M group: 2 sessions of microneedling alone and oral placebo BID for 60 d; T group: oral TXA (250 mg) BID for 60 d; MT group: 2 sessions of microneedling and oral TXA (250 mg) BID for 60 d; CT group: control group (no microneedling and oral placebo BID for 60 d); microneedling needles were 1.5 mm; intervention phase was 60 d, followed by a 60-d maintenance phase (through day 120)	Day 30: microneedling + TXA group and TXA-only groups showed early improvements vs control group (P<.03); day 60: all treatment groups outperformed control group (P<.05); no difference between treatment groups (M group, T group, MT group) at 60 d (P>.1); day 120: no difference between microneedling alone and microneedling + TXA (P=.47)

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TABLE. (continued)

Reference (year)	Country	Sample size	Treatment groups	Outcomes
HQ				
Shamsi Meymandi et al[26] (2020)	Iran	60	Group A: microneedling (6 fine needles with length of 1.5 mm and width of 0.25 mm, penetrated skin to 0.1–1.3 mm) + topical TXA 4% (maximum dose of 8 mg) monthly; group B: topical HQ 4% nightly; mMASI score at baseline, 4 wk, 8 wk, and 12 wk was evaluated	Mean (SD) mMASI score in group A decreased from 12.89 (5.16) at baseline to 6.84 (4.31) at 12 wk ($P<.01$); mean (SD) mMASI score in group B decreased from 13.56 (4.88) at baseline to 7.16 (4.38) at 12 wk ($P<.01$); no statistical difference between the 2 groups; physician and patient assessments were not statistically significant between the 2 groups
Xing et al[27] (2020)	China	50	Group A: topical 1.8% liposomal TXA BID; group B: microneedling (stamp-mode electric microneedling, 100 needles on 12.25 mm^2 chip (every needle has a diameter <80 nm and depth of 100 mm) + topical TXA 5%; group C: HQ cream 2% every night (conventional treatment); treatment period was 12 wk	Mean (SD) MI of all treatment groups significantly improved from baseline to end point (12 wk)(group A: 203.14 [10.27] to 178.33 [11.41][$P<.01$]; group B: 261.13 [7.89] to 221.17 [18.83][$P<.001$]; group C: 214.85 [10.19] to 176.48 [9.57][$P<.001$])
Zaky et al[28] (2021)	Egypt	50 (27 completed the study)	Patients were randomly assigned to 1 of 2 groups in a split-face study design—group A: topical HQ 4% nightly on 1 side of the face; group B: microneedling (36 needles with length of 1.5 mm) + topical TXA 4% (100 mg/mL, maximum dose of 8 mg per session) every other week on 1 side of the face; treatment period was 8 wk	Mean (SD) mMASI score for group A decreased from 6.604 (4.02) at baseline to 3.032 (1.19) after 8 wk of treatment and for group B decreased from 6.348 (3.84) at baseline to 3.712 (1.19) after 8 wk of treatment; mean (SD) percentage decrease was 54.8% (19.4%) for group A and 57.4% (23.4%) for group B; mean reduction in mMASI was statistically significant for both groups ($P<.001$); group B showed slightly lower mean mMASI score than group A, but no statistical significance between both sides ($P=.405$); patient satisfaction showed no statistically significant differences between both treatments ($P=.629$); 2 blinded physician assessments showed no statistically significant differences in improvement between both sides (blinded physician 1, $P=.252$; blinded physician 2, $P=.327$)

Abbreviations: BID, twice daily; EI, erythema index; HQ, hydroquinone; IHC, immunohistochemical; MART-1, melanoma antigen recognized by T cells 1; MASI, melasma area and severity index; MI, melanin index; mMASI, modified Melasma Area and Severity Index; TXA, tranexamic acid.

therapy improved melasma patches better than microneedling alone.[19]

Xu et al[20] conducted a split-face study (N=28) exploring the effectiveness of transdermal application of topical TXA using a microarray pen with microneedles (vibration at 3000×/min) plus topical TXA on one side of the face, while the other side received only topical TXA as a control. After 12 weeks of treatment, combination therapy with microneedling and TXA decreased brown spot scores, lowered melanin index (MI) values, improved blinded physician assessment, and improved patient satisfaction vs TXA therapy alone.[20]

Kaur et al[21] conducted a split-face, randomized, controlled trial of microneedling (1-mm depth) with TXA solution 10% vs microneedling (1-mm depth) with distilled water alone for 8 weeks (N=40). They graded participant responses to treatment using reductions in mMASI scores[12] at every 2 weeks of follow-up (no response, minimal or poor response=0%–25%; partial or fair response=26%–50%; good response=51%–75%; and excellent response=>75%). They reported an overall reduction in mMASI scores for both the treatment side and the control side in all participants, s howing a 65.92% improvement in mean mMASI scores on the treatment side vs 20.75% improvement on the control side at week 8. Both sides showed statistically significant reductions in mean mMASI scores ($P<.05$). Clinically, 40% (16/40) of participants showed an excellent response to combined treatment compared with 0% (0/40) to microneedling alone. Overall, patient satisfaction was similar across both groups. This study demonstrated that microneedling alone improves melasma, but a combination of microneedling plus TXA showed a better clinical reduction in melasma. However, the researchers did not follow up with participants posttreatment, so it remains unclear if the improved clinical outcomes were sustained long-term.[21]

Ebrahim et al[22] reported that the combination of 0.5 mL TXA (4 mg/mL) and microneedling (0.25- to 1-mm depth) was effective for melasma. Although there was improvement within microneedling and TXA, the study also showed that intradermal injection of TXA was significant in reducing mean mMASI scores and improving melasma ($P<.001$). The reduction in mMASI scores for the group receiving intradermal injections of TXA (left side; 74.8% reduction in mean mMASI score) vs the group receiving microneedling application of TXA (right side; 73.6% reduction in mean mMASI score) was not statistically significant. These findings suggest that the mode of TXA application may not be critical in determining clinical responses to TXA treatment. Although there was no reported statistically significant difference in clinical outcomes between the 2 treatments, patient satisfaction was higher on the microneedling side. Only 8 of 50 participants (16%) experienced recurrence 3 months posttreatment.[22]

Saki et al[23] compared the efficacy of topical hydroquinone (2%) to intradermal TXA injections in treating melasma. They found intradermal TXA injections to be a clinically effective mode of treatment.[23]

Sharma et al[24] explored the efficacy and safety of oral TXA by randomly assigning 100 Indian patients (20 of whom withdrew before study completion) with melasma into 2 groups: group A received TXA 250 mg twice daily, and group B received intradermal microinjections of TXA (4 mg/mL) every 4 weeks. The MASI scores were assessed at 4-week intervals for a total of 12 weeks. There was a decrease in MASI scores in both groups, and there was no statistically significant difference in mean percentage reduction in MASI scores between the 2 routes of drug administration, further suggesting the effectiveness of TXA independent of administration route. Two patients in group A relapsed at 24 weeks, and there were no relapses in group B, which may suggest a minimal superiority of TXA plus microneedling at providing more sustainable results compared with oral TXA alone. A notable limitation of this study was a high dropout rate as well as lack of long-term follow-up with participants, limiting the generalizability of the conclusions.[24]

Cassiano et al[25] assigned 64 women with melasma to 1 of 3 treatment groups or a control group to compare the effectiveness of microneedling (M group: 1.5 mm; 2 sessions), oral TXA (T group: 250 mg/d twice daily for 60 days), and a combination of microneedling (2 sessions) and oral TXA (MT group: 250 mg/d twice daily for 60 days)with placebo for clinically reducing melasma lesions. The intervention period was 60 days followed by a 60-day maintenance phase for a total study period of 120 days. The researchers evaluated mMASI scores, quality of life, and difference in colorimetric luminosity. All treatment groups showed a reduction in mMASI scores at both 30 days and 60 days, indicating improved melasma severity. The MT and T groups had more significant improvement at 30 days compared with the control group ($P<.03$), suggesting that microneedling plus TXA and TXA alone promote faster improvement in melasma lesions. By 60 days, the M, T, and MT groups outperformed the control group, with no significant differences between the M, T, and MT groups. However, at the 120-day maintenance follow-up, the T group did not maintain its improvement compared with the control group. The M and MT groups showed no significance difference in effectiveness at 120 days, suggesting that microneedling may promote less frequent relapse and sustained remission compared to TXA alone.[25]

Hydroquinone for Melasma—Additional studies on the use of TXA treatments show that TXA may be an equally effective alternative to the standard use of hydroquinone treatment. Shamsi Meymandi et al[26] did not find a statistically significant difference in treatment with TXA plus microneedling vs the standard regimen of hydroquinone. More importantly, patient and physician satisfaction assessments were similar between the 2 groups.

Compared to hydroquinone, nightly treatment is not necessary with microneedling and TXA.[26]

Xing et al[27] supported these conclusions with their study. They compared 3 study arms for a duration of 12 weeks: group A received topical 1.8% liposomal TXA BID, group B received stamp-mode electric microneedling with 5% TXA weekly, and group C applied 2% hydroquinone cream nightly. The study concluded that all 3 groups showed a significant reduction in mean MI by the end of the study, but a better MI improvement was observed in groups B and C (both $P<.001$) compared with group A ($P<.01$).[27]

Zaky et al[28] showed that both hydroquinone and combination treatment of TXA plus microneedling are effective at improving melasma lesions. Further studies are needed to definitively conclude if combination treatment is more efficacious than hydroquinone; if the combination is more effective, it provides a treatment option for patients with melasma who may not be good candidates for hydroquinone treatment.

Study Limitations—One limitation in all the studies evaluated is the sample size. Because they all had small sample sizes, it is difficult to definitively conclude that the combination TXA and microneedling is an effective and appropriate treatment for patients with melasma. Furthermore, the quality of these studies was mostly dependent on subjectivity of the mMASI scores. Future large randomized controlled trials with a diverse participant population are needed to assess the effectiveness of TXA and microneedling in melasma treatment.

Another limitation is that many of the studies did not follow the patients longitudinally, which did not allow for an evaluation of whether patients had a relapse of melasma. Due to the chronic nature of melasma and frequent disease recurrence, future longitudinal studies are needed to monitor for disease recurrence.

Conclusion

Tranexamic acid and microneedling are potential treatment options for patients with melasma, and combination therapy appears more effective than either TXA or microneedling alone at providing sustained improvement of melasma lesions. Combination therapy appears safe and well tolerated, but its effect on reducing long-term disease recurrence is yet to be established.

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