

EVALUATING THE EFFICACY AND SAFETY OF TRANEXAMIC ACID TO HYDROQUINONE AND TRIPLE COMBINATION CREAM IN THE TREATMENT OF MELASMA

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INFO ARTIKEL	ABSTRACT
Diterima 29 Oktober 2022 Direvisi 14 November 2022 Disetujui 25 November 2022	<i>Background: Melasma is an acquired skin condition characterized by sporadic hyperpigmented macules or patches that affects photo-exposed areas which occur chronically. Melasma seriously impairs a patient's quality of life. Current treatments for melasma include hydroquinone, corticosteroids, retinoids, natural substances, and triple combination creams (TCC), which demonstrate variable efficacy and side-effect profiles. Melasma can now be treated with tranexamic acid (TA), a well-known anti-fibrinolytic drug. Oral, topically applied, and procedural techniques were used to administer TA. Purpose: This review evaluates the efficacy and safety of tranexamic acid to hydroquinone and triple combination cream in the treatment of melasma and suggests steps that need to be taken to mainstream TA use in clinical settings. Review: Among the recent melasma treatments are hydroquinone (HQ), triple combination topicals, and regular use of broad-spectrum sunscreen. .I Because plasmin has been shown to have melanogenic properties, tranexamic acid (TA) is an essential therapy option for melasma due to its anti-plasmin (and consequently anti-fibrinolytic) properties. Recent research has shown that melasma-affected skin has enhanced vascularity and VEGF expression in the epidermis, suggesting yet another method by which TA may treat melasma clinically. Conclusion: The review revealed that a combination of tranexamic acid and hydroquinone has better efficacy in treating melasma rather than hydroquinone alone. Oral tranexamic acid combined with TCC can prevent recurrence and sustain the outcome.</i>
Keywords: Melasma; Tranexamic Acid; Hydroquinone; Triple Combination Therapy.	

Introduction

Melasma is an acquired skin condition characterized by sporadic hyperpigmented macules or patches that affects photo-exposed areas which occur chronically (Espósito et al., 2022);(Zhang et al., 2018). Melasma is a multifactorial disorder in which several factors have been linked to melasma, including genetic predisposition, solar radiation, sex hormones, and oxidative status. The incidence of melasma in first-degree relatives supports the gene hereditary origin of the melasma. According to a study, genes associated with lipid metabolism and VEGFA are downregulated whereas those involved in melanogenesis are upregulated

(Espósito et al., 2022). Direct stimulation of melanogenesis in melanocytes by ultraviolet radiation (UVR). Keratinocytes, mast cells (MC), and fibroblasts are all impacted by UVR, and these cells also control melanogenesis. All of those many conditions lead to enhanced melanosome transfer to keratinocytes and melanosome production in melanocytes (Zhang et al., 2018);(Rajanala et al., 2019).

The clinical manifestation of melasma is hyperpigmented macules and patches which symmetrically oriented. Another varying manifestation can present in patients including blotchy, irregular, arcuate, and polycyclic (Artzi et al., 2021). The pseudo-rete ridges of

the skin might exhibit considerable hyperpigmentation when examined under a dermoscopic examination. When the pigment is epidermal, the hyperpigmentation can be emphasized with a Wood lamp. However, dermal or mixed melasma may induce this accentuation to appear (Ogbechie-Godec & Elbuluk, 2017).

Melasma is classified as dermal, epidermal, or mixed depending on where the melanocytes are located. While the epidermal subtype displays clinically as brown pigment with well-defined edges, the dermal subtype appears more gray-brown and has poorly defined margins. It is referred to be mixed when both epidermal and dermal subtypes coexist (Artzi et al., 2021);(Ogbechie-Godec & Elbuluk, 2017). Based on the pattern of distribution, melasma is further subdivided into the dentofacial (the most prevalent form), malar, and mandibular subtypes (Artzi et al., 2021);(Ogbechie-Godec & Elbuluk, 2017). The forehead, nose, and upper lip are included in the centrofacial pattern. The mandibular pattern is restricted to the jawline and chin, whereas the malar pattern is located on the malar cheeks (Ogbechie-Godec & Elbuluk, 2017).

Therapy for melasma is available in different routes of administration such as oral, topical, procedural, and combination therapies. These focus on several melasma pathogenesis factors, including photodamage, inflammation, vascularity, and pigmentation. Topical treatment as the first-line treatment of melasma consists of several substances such as hydroquinone, corticosteroid, retinoid, and natural compounds (Artzi et al., 2021); (Ogbechie-Godec & Elbuluk, 2017). Tyrosinase is inhibited by hydroquinone (HQ), preventing the conversion of DOPA to melanin. 4% HQ is the most widely used topical melasma therapy (Artzi et al., 2021);(McKese et al., 2020). Corticosteroids inhibit melanogenesis by non-selectively inhibiting the pigmentation process. When administered alone as monotherapy, corticosteroids are most likely less effective at depigmenting skin. Topical retinoid, tretinoin 0.1%, has a

mechanism of action to induce keratinocyte turnover. Natural compounds like niacinamide, ascorbic acid, and kojic acid have a mechanism of action to decrease pigmentation. Niacinamide prevents the transfer of melanosomes to keratinocytes, which reduces pigmentation. Tyrosinase activity can be inhibited by both ascorbic acid and kojic acid. Reactive oxygen species are thought to be reduced by ascorbic acid, which reduces inflammation in melasma lesions (Ogbechie-Godec & Elbuluk, 2017). Triple combination cream (TCC), which contains HQ 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%, is another option for treating melasma topically. Due to its strong and quick whitening impact, 3-5 TCC is presently regarded as the gold-standard topical therapy for melasma (Cassiano et al., 2022).

Melasma treatment options other than topical methods include oral medication. Arachidonic acid production is decreased by the anti-plasmin drug tranexamic acid (TA), which also lowers melanocyte-stimulating hormone (MSH) levels and pigmentary synthesis. One study suggests that TA may also reduce VEGF and endothelin-1, two substances that may be to blame for the increased vascularity in afflicted lesions. Two complementary medicines are glutathione and Polypodium leucotomos (PL). It has been shown that PL decreases ROS production, lowers UV-induced photodamage, and lessens the T cell-mediated response that increases skin inflammation and pigmentation (Ogbechie-Godec & Elbuluk, 2017);(Forbat et al., 2020).

Typically, procedural treatment is adjunctive therapy of melasma. Chemical peeling can increase keratinocyte turnover and epidermal remodeling. Among the several peels, glycolic acid (GA) has received the greatest research attention for the treatment of melasma. Microneedling is an additional supplementary treatment that uses tiny skin channels to administer topical medications intradermally in small doses. In addition, as compared to traditional resurfacing methods, micro needling skin punctures might encourage

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a beneficial wound-healing process. Using thermal energy, lasers may use certain chromophores in the skin as targets. Non-ablative lasers are preferred over ablative lasers for the treatment of melasma because they tend to induce less inflammation and therefore less post-inflammatory pigment alteration (PIPA) (Ogbechie-Godec & Elbuluk, 2017);(Forbat et al., 2020).

Melasma can now be treated with tranexamic acid (TA), a well-known anti-fibrinolytic drug. TA was incidentally discovered and reported by N. Sadako attempted to apply TA to treat severe urticaria in 1979 (Perper et al., 2017);(Parikh & Naik, 2021);(Zhang et al., 2018). Tranexamic acid is used as a hemostatic drug to treat aberrant fibrinolysis and stop massive bleeding. It is a chemical lysine precursor that inhibits plasminogen activator (PA) activation by interfering with its lysine-binding sites in reversible ways. As a result, PA cannot convert plasminogen into plasmin, which is how it achieves its impact. It promotes the inhibition of tyrosinase activity by suppressing the plasminogen/plasmin system, which prevents contact between keratinocytes and melanocytes. TA also reduces the function of mast cells and blocks fibroblast growth factors (Cassiano et al., 2022);(Perper et al., 2017);(Fraone & Bartoletti, n.d.). Tranexamic acid is available in three different drugs administration including oral, topical, and procedural (intradermal microinjection) (Fraone & Bartoletti, n.d.);(Zhang et al., 2018). The most common adverse effects of TA are spinal discomfort, irregular menstruation, muscle ache, headaches, urticaria, and cramping in the abdomen. TA is contraindicated in cases of renal impairment, cancer, cardiovascular or respiratory illness, ongoing anticoagulant medication, a personal or family history of thromboembolic disease, and pregnancy. TA should be avoided by those who have clotting issues or a background of thromboembolism, and people who are using hormonal contraceptives or other pro-

coagulants (Cassiano et al., 2022). This review evaluates the efficacy and safety of tranexamic acid to hydroquinone and triple combination cream in the treatment of melasma and suggests steps that need to be taken to mainstream TA use in clinical settings.

Research Methods

Current treatments for melasma include hydroquinones, corticosteroids, retinoids, natural ingredients, and triple combination creams (TCC), which show variable efficacy and side effect profiles. Melasma can now be treated with tranexamic acid (TA), a well-known antifibrinolytic drug. Oral techniques, topical applications, and procedures are used to manage TA.

Results and Discussion

Melasma is an acquired skin condition characterized by sporadic hyperpigmented macules or patches that affects photo-exposed areas which occur chronically (Espósito et al., 2022);(Zhang et al., 2018). Melasma seriously impairs a patient's quality of life, leading to psychological distress in many people, including frustration, embarrassment, and depression (Zhu et al., 2022). Although the specific pathogenesis of melasma is unknown. It has been hypothesized that several factors have a role including genetic predisposition, solar radiation, sex hormones, and oxidative status. According to research, genes associated with lipid metabolism and VEGFA are downregulated whereas those involved in melanogenesis are upregulated. Direct stimulation of melanogenesis in melanocytes by ultraviolet radiation (UVR). Keratinocytes, mast cells (MC), and fibroblasts are all impacted by UVR, and these cells also control melanogenesis (Espósito et al., 2022);(Rajanalala et al., 2019).

Among the recent melasma treatments are hydroquinone (HQ), triple combination topicals, and the regular use of broad-spectrum sunscreen (Espósito et al., 2022).

Because plasmin has been shown to have melanogenic properties, tranexamic acid (TA) is an essential therapy option for melasma due to its anti-plasmin (and consequently anti-fibrinolytic) properties. Recent research has shown that melasma-affected skin has enhanced vascularity and VEGF expression in the epidermis, suggesting yet another method by which TA may treat melasma clinically (Pandya et al., 2011). It is also believed that TA competitively inhibits tyrosinase, which would exacerbate the skin-lightening effect (McKeseey et al., 2020). TA has become a novel therapeutic option for melasma and has demonstrated encouraging outcomes with all routes of administration including topical, oral or systemic, and intradermal (Fraone

& Bartoletti, n.d.);(Zhang et al., 2018).

Based on our literature review we compared the effectiveness and safety of TA versus hydroquinone (HQ) and triple combination cream (TCC).

Tranexamic Acid Versus Hydroquinone Cream

Eight studies compared tranexamic acid, in different routes of administration, with hydroquinone cream. All the studies used different HQ concentrations making the review quite challenging. Four of the seventh studies compared hydroquinone cream with oral TA, 1 study compared topical TA, and three of them evaluated TA intradermally. Several of them compared hydroquinone with TA as an adjuvant, and others compared hydroquinone with TA as a single agent.

Table 1
Tranexamic Acid compared to Topical Hydroquinone

Year	Author	Study design	Sample Size	Intervention Group	Duration	Side Effect	Conclusion
2016	(Lajevardi et al., 2017)	A single-blinded, randomized controlled trial	100	Group A: 250 mg of TA oral thrice a day + 4% of HQ cream Group B: 4% of HQ cream	3 months	10.5% of patients, all of whom were in group A, had gastrointestinal issues and irregular periods.	Although oral TA can increase the effectiveness of hydroquinone 4% cream in the treatment of melasma, the high rate of recurrence raises the possibility that therapeutic effects may be transient and calls for more research.
2019	(Benhiba et al., 2020)	Randomized Clinical Trial	30	Group A: oral TA 250 mg twice daily + 2% HQ cream nightly Group B: 2% HQ cream nightly	12 weeks	NA	Oral TA can increase the efficacy of 2% hydroquinone cream in the treatment of melasma, although it has a high recurrence

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Year	Author	Study design	Sample Size	Intervention Group	Duration	Side Effect	Conclusion
							rate.
2021	(RIAZ et al., n.d.).	Clinical trial	80	Group A: topical 4% hydroquinone Group B: capsule TA 250 mg twice a day + topical 4% hydroquinone	6 months	Hydroquinone had mild side effects including local erythema and a burning sensation.	Hydroquinone 4% topical treatment paired with oral tranexamic acid is more effective than topical 4% hydroquinone alone for epidermal melasma.
2018	(Tehranchinia et al., 2018)	Randomized split-face clinical trial	55	TA intradermal 100 mg/ml every 4 weeks + 4% HQ cream on the right or left side and topical 4% HQ alone every night on the other side	12 weeks	In the TA+ HQ group: erythema (47.3%) and pruritus at the injection site (10.9%). In the HQ group: erythema occurred in 50.9% of cases and pruritus in 12.7%.	The efficiency of the topical treatment can be increased by adding intradermal tranexamic acid to typical hydroquinone cream therapy.
2017	(Samreen et al., 2017).	Randomized Clinical Trial	140	Group A: topical 2% hydroquinone Group B: oral TA 500 mg once daily	8 weeks	2 patients presented with nausea, vomiting, and diarrhea, which were self-limiting	When compared to topical hydroquinone 2% cream, oral tranexamic acid 500 mg offered a superior response and safer safety profile.
2019	(Marpaung et al., 2021)	Double-blind, randomized clinical trial	60	Group A: 3% TA cream Group B: 4% HQ cream	8 weeks	Only two patients in the HQ group had erythema.	In epidermal-type melasma, 3% TA cream and 4% of HQ cream are efficient in lowering the MSI score and Melanin Index (MI). The MSI score and MI in the 3% TA group were lower by the eighth week

Year	Author	Study design	Sample Size	Intervention Group	Duration	Side Effect	Conclusion
							than in the 4% HQ group.
2017	(Saki et al., 2018)	Randomized split-faced Controlled Trial	37	TA intradermal injection on the right or left side and topical HQ every night on the other side	3 months	No harmful response was noticed on the HQ side. On the TA side: Two people had acne, and one experienced burning pain during injection.	The melanin level was reduced more effectively during the first four weeks by monthly TA injection than by daily HQ. However, after 20 weeks, there was no difference in the total changes between the two methods.
2022	(Taha & Sheer, 2022)	Comparative clinical trial	31	Group A: intradermal TA 500 mg/5 ml every 2 weeks + 4% HQ cream every night	8 weeks	in group A, 2 patients had redness, and 1 patient with irritation. Meanwhile, in group B, 1 had redness, and 1 patient presented with irritation	In the treatment of melasma, topical hydroquinone alone is less effective than topical hydroquinone coupled with intradermal injection of TA. Both forms of treatment are equally safe and effective.

Three studies used oral TA combined with hydroquinone compared with using only hydroquinone was conducted by (Lajevardi et al., 2017). (RIAZ et al., n.d.);(Benhiba et al., 2020); (Lajevardi et al., 2017). used 250 mg TA three times per day orally and 4% HQ cream, (Benhiba et al., 2020).observed 250 mg TA twice daily and 2% HQ cream, whilst (RIAZ et al., n.d.). used 250 mg of tranexamic acid twice a day and 4% HQ cream. Despite different dosage and concentration used in those studies, nonetheless, the result is similar. The results showed that topical hydroquinone alone is not as effective as HQ cream combined with oral tranexamic acid (Lajevardi et al.,

2017);(Benhiba et al., 2020).

A study by (Lajevardi et al., 2017) report side effects including gastrointestinal issues and irregular menstruation in 10.5% patients where all were from the group given oral TA. Partial recurrence of melasma was seen over the three-month follow-up period in both groups, as shown by a rise in mean MASI scores. In the TA + HQ group, MASI scores climbed by 4.3 + 4.2 points and by 2.7 + 8.8 points in the HQ group, respectively, reflecting relapse rates of 30% and 26% (Lajevardi et al., 2017). The 30% recurrence rate in the intervention group in this study may have been caused by the shorter length of therapy in the trial. As a result, longer-

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term research may be suggested while side effects are thoroughly monitored

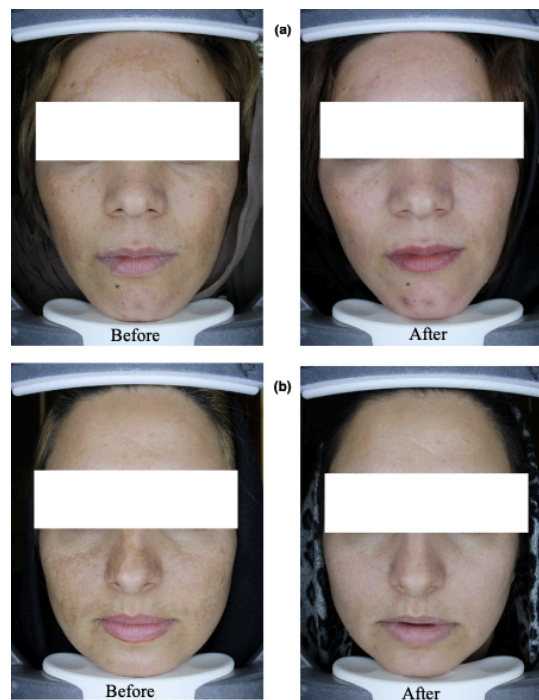


Figure 1. Melasma patients in TA+HQ group, before (baseline) and after (3 months in treatment). a) 33-year-old, b) 37-year-old (Lajevardi et al., 2017).

A study by (Samreen et al., 2017), compared oral tranexamic acid alone with HQ cream. According to a study, oral tranexamic acid 500 mg showed a higher safety profile and response when compared to topical hydroquinone 2% cream. The oral usage of TA was shown to have minor and insignificant side effects. A tiny percentage have diarrhea, nausea, and vomiting, although these symptoms were self-limiting (Samreen et al., 2017). Four studies were evaluated periodically using MASI score. When compared to area measurements, the melasma severity scale, and Mexameter scores, the MASI and mMASI ratings have been proven to be valid and reliable both within and across raters (Ogbechie-Godec & Elbuluk, 2017);(Pandya et al., 2011). Based on these four trials, we can conclude that oral tranexamic acid has a high level of safety and effectiveness when used to treat melasma. It is possible to utilize oral tranexamic acid on its own with a high level of safety and effectiveness. However, when used

in conjunction with hydroquinone, it produces greater outcomes than hydroquinone alone (Lajevardi et al., 2017);(Samreen et al., 2017).

A topical TA was another one that was studied (Marpaung et al., 2021), did a double-blind RCT study in epidermal melasma patients to compare three percent of TA with 4% of hydroquinone cream. The patients were grouped into two categories, receiving 3% TA cream group and 4% HQ cream group. Side effect of TA cream were not found, but erythema was found in two of 30 patients which given 4% HQ cream. The baseline mMASI scores for the two groups were identical. The two groups had different mMASI scores at weeks 4 and 8, with the TA 3% group having a lower mMASI score and melanin index than the HQ 4% group. However, 4% HQ cream and 3% TA cream are equally beneficial in lowering the MASI score and MI in melasma of the epidermal type.

In addition to oral and topical, there are also studies comparing hydroquinone with TA

in an intradermal form (Taha & Sheer, 2022);(Tehranchinia et al., 2018). conducted study that compare a combination of intradermal with 4% HQ cream every night and 4% HQ cream only. (Taha & Sheer, 2022) used TA in 500 mg/5 ml every 2 weeks for 8 weeks while (Tehranchinia et al., 2018) used 100 mg/ml in every 4 weeks for 12 weeks. Both groups in two studies were asked to apply sunscreen of SPF 50 during the treatment period. Side effect in both groups (intervention and control group) of two studies showed insignificant statistically difference, both had erythema and pruritus in certain patients.

During the follow-up period, mean MASI score in intervention group showed significant improvement. Thus, therapeutic outcome in intervention group (TA + HQ group) were significantly better than HQ group. In conclusion, the intradermal injection of TA combined with topical hydroquinone has more effectiveness than hydroquinone cream alone in the treatment of melasma (Taha & Sheer, 2022);(Tehranchinia et al., 2018). Figures 2 and 3 show, respectively, the clinical profile of melasma patients in the study performed by (Taha & Sheer, 2022);(Tehranchinia et al., 2018).

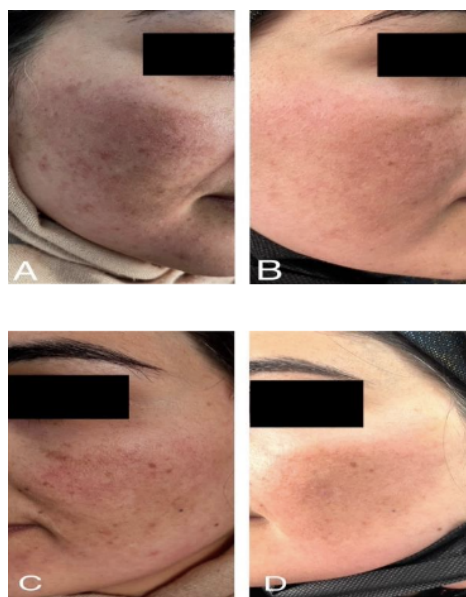


Figure 2. Right side before treatment, b) after 8 weeks of intradermal TA+HQ. c) Left side of face before treatment, d) after treatment with TA intradermally + HQ. (Minni & Poojary, 2020).



Figure 3. Melasma patient treated with (a) 4% of HQ cream, before treatment (left) and after 16 weeks of treatment (right); (b) TA intradermal + 4% hydroquinone cream (Tehranchinia et al., 2018).

Another study about intradermal TA was performed by (Saki et al., 2018). The study was randomized split-face controlled trial which compared intradermal tranexamic acid, not in a

combination therapy, and hydroquinone alone. TA was given 20 mg/ml concentration intradermally to left or right side of the face every month for 2 months and 2% HQ cream on the other side. Patients were instructed to use

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SPF 50 sunscreen. On the HQ side, there were no indications of a negative reaction, while three patients reported negative effects after TA injections; one of them felt burning during the treatment, and the other two had acne. This study discovered that in order to reduce the melanin value during the initial four weeks, monthly TA injection was superior to daily HQ. However, after 20 weeks, there was no difference in the total changes between the two

groups ([Saki et al., 2018](#)).

According to three studies about intradermal TA compared to HQ cream. Intradermal TA alone after 20 weeks exhibited insignificant results when compared to HQ cream alone, while the combination of intradermal TA and HQ cream has significant outcome.

Tranexamic Acid Versus Triple Combination Cream

Table 2
Tranexamic Acid compared to Triple Combination Cream

Year	Author	Study Design	Sample Size	Intervention Group	Duration	Side Effect	Conclusion
2020	(Minni & Poojary, 2020)	Randomized Clinical Trial	130	Group A received a triple combination cream (TCC) once daily, as well as oral tranexamic acid 250 mg and ranitidine 150 mg twice a day.	24 weeks	The most frequent side effects during therapy in groups A and B were erythema and burning, showing that fTCC was mostly to responsible for both symptoms.	For a rapid, more lasting recovery and to avoid recurrence, oral tranexamic acid should be administered in conjunction with f-TCC. It is unquestionably a benefit to the arsenal of melasma treatment tools.
2021	(SHAHZAD et al., n.d.)	Randomized Comparative Trial	110	Group I: Intradermal TA 4 mg/ml every 15 days Group II: fbTCC (hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%) every night for three hours.	2 months	Group I had no clinically significant side effect Hypertrichosis, acneiform, erythema, and hypopigmentation were detected by Group II.	MASI scores in groups I and II both significantly decreased from baseline (15.4) to 2.4 and 5.6, respectively. Because there were no clinically significant adverse effects discovered following this therapy and because the MASI score was

							significantly reduced, intradermal TA was both safe and effective in the treatment of melasma.
2021	(Basit et al., 2021)	Randomized Controlled Trial	60	Group A: TCC cream + oral TA Group B: TCC cream	8 weeks	NA	Oral tranexamic acid was added to a topical triple regimen, however this did not appreciably lower the MASI score. As an adjunct to topical combination treatment, it could be useful.
2022	(Martinez-Rico et al., 2022)	Randomized Clinical Trial	44	Group A: 325 mg of TA orally twice a day with fTCC cream. Group B: 325 mg of TA orally twice daily	8 weeks	There were no major negative effects identified.	Oral TA and f-TCC are more effective when combined than when used alone for the treatment of severe melasma.

We reviewed four studies comparing tranexamic acid and triple combination cream. One study used TA administered intradermally, and three studies were oral TA. (Shahzad et al., n.d.) conducted randomized comparative trial in 110 patients which divided into two groups. First group was given TA 4mg/ml intradermally every 15 days, and the other group received f-TCC (fluocinolone acetonide 0.01%, tretinoin 0.05%, hydroquinone 4%) which applied at night on melasma lesions for 3 hours per day. Baseline MASI score in group I and group II were 15.4. Side effects were not present in group I, while several patients in group II experienced hypertrichosis, erythema, acneiform lesions, and hypopigmentation. During follow-up, MASI score in two groups decreased to 2.4 and 5.6, respectively. The

decrease in the MASI score indicates that intradermal TA has a higher effectiveness than fTCC alone. Since there were no significant adverse effects discovered following this treatment and because the MASI score was significantly reduced, the use of intradermal TA in the treatment of melasma was effective and safe (Shahzad et al., n.d.).

(Minni & Poojary, 2020) performed randomized clinical trial study in 130 patient which were categorized into two groups. Intervention group (group A) was given 250 mg of TA oral twice daily and applied a fTCC (0.01% of fluocinolone acetonide 0.01%, 0.05% tretinoin, and 2% of hydroquinone) once daily, whilst control group (group B) accepted placebo tablets (contain multivitamin and calcium lactate) and applied fTCC only. The

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baseline mMASI score from each group was 10.45 and 9.16, respectively. Measurement mean mMASI score in group A at the end of 4th, 8th and 12th week were 6.16, 4.32, 2.26, respectively. Similarly, in group B, mMASI score fell to 7.11, 5.39, and 4.09, respectively. Both groups had topical fTCC side effects. None of the patients receiving oral TA experienced any systemic side effects. Erythema was the most frequent adverse effect seen after therapy, followed by burning sensation in both groups, indicating that fTCC

was predominantly responsible for both conditions. Recurrence of melasma at 24th week in group A was 11 patients (18.03%) and 38 patients (64.4%) in group B. This indicates that oral TA helps reduce recurrence of melasma (Minni & Poojary, 2020).

The clinical picture of melasma patients in the study conducted by (Minni & Poojary, 2020) is in Figures 4 and 5. Figure 4 showed a patient in group A, and the patient in Figure 5 is one of the patients in group B.

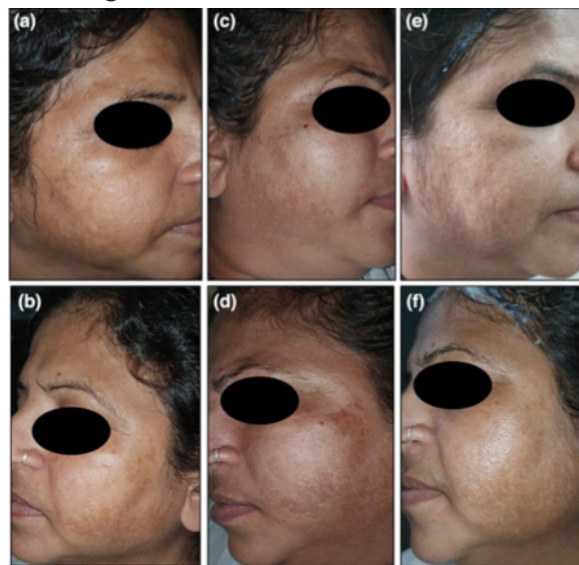


Figure 4. Improvement picture in patient received 250 mg of TA twice a day + fTCC. (a,b) baseline: mMASI = 15.6; (c, d) 4th week: 7.5 (51.9%), (e, f) 8th week: 5.1 (67.3%) (Minni & Poojary, 2020).



Figure 5. Improvement picture in patient treated with placebo + fTCC. a) baseline: mMASI = 3.6; (b) 4th week: 1.8 (50%); (c) 12th week: 1.2 (67%); (d) 24th week 24: 1.2 (67%) (Minni & Poojary, 2020).

The study conducted by (Basit et al., 2021) was randomized control trial study which enrolled 63 patients. The patients were classified into group A and group B. Group A had oral TA + TCC (fluocinolone acetonide 0.01%, tretinoin 0.05%, and 4% of hydroquinone) and group B was given TCC only. The mean decrease of MASI score in group A and group B was 6.4933 ± 4.38358 and 5.7833 ± 5.04251 , respectively. p-value was 0.56 which mean the difference was insignificant statistically. TCC was a control in this study. Therefore, the comparative findings are insignificant, due to the fact that TCC's potential is more efficient than oral TA. In this instance, oral TA is better combined with TCC (Basit et al., 2021).

Opposite (Martinez-Rico et al., 2022)

studied the efficacy and safety of oral tranexamic acid as a single therapy and in a combination with TCC for treating melasma. This study involved 44 patients and was divided into two groups. Group A was given 325 mg of oral TA twice a day plus f-TCC, and f-TCC only for group B. Evaluations were made at baseline and Weeks 4, 8, 12, and 16, which include measurement of MelasQoL, mMASI score, and melanin index (MI). The highest results on the melanin index level were consistent with the application of the combination therapy. f-TCC and oral TA perform better together than they do separately. The greatest improvement in MASI scores was associated with the use of combination therapy modalities. The two groups' MelasQoL ratings did not substantially vary from one another (Martinez-Rico et al., 2022).

CONCLUSION

A combination of tranexamic acid, in either route of administration, and hydroquinone has better efficacy in treating melasma rather than hydroquinone alone. Furthermore, additional TA and HQ alone both have essentially equal side effects. Despite the combination of oral TA and TCC had less significant results when compared to TCC alone. However, this combination can prevent recurrence and sustain the outcome. Tranexamic acid given intradermally is effective and safe based on MASI score and minimal adverse effects. Our analysis of the literature indicates that tranexamic acid should be taken into consideration as a potential treatment for melasma because it does diminish the condition while having minimal adverse effects.

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