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# Tranexamic Acid in Melasma: A Review

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## Abstract

Melasma is a localized, chronic acquired hypermelanosis of the skin. Despite several treatments available, melasma can often be refractory to treatment. Also recurrences are common. Tranexamic acid is a new addition in treatment of melasma and is effective in dosage of 250 mg BD for atleast 4 to 8 weeks. Tranexamic acid acts mainly via the plasminogen activator-plasmin system to prevent UV radiation induced pigmentation in melasma. This article reviews the mechanism of action of tranexamic acid in melasma and current evidence in literature for use of tranexamic acid in melasma.

**Keywords:** Melasma; Tranexamic acid

## Introduction

Melasma is a localized, chronic acquired hypermelanosis of the skin characterised by light to dark brown macules and patches symmetrically involving the sun-exposed areas of the face, neck and occasionally the forearms. This disease is commonly observed in women of reproductive age group, rarely in postmenopausal females and males (10% of cases). Causative factors implicated in the pathogenesis of melasma include genetic susceptibility, ultraviolet (UV) light exposure, pregnancy, sex hormones, contraceptive pills, thyroid disease, cosmetics, phototoxic drugs (e.g., antiseizure medications) [1].

Treatment modalities include use of hypopigmenting agents such as hydroquinone, tretinoin, topical corticosteroids, superficial peeling (lactic acid, glycolic acid, trichloroacetic acid and kojic acid), LASERS (including Q-switched ruby laser, Q-switched Alexandrite laser, erbium: yttrium-aluminum-garnet (Er: YAG) laser, Fraxel laser, and intense pulsed light)

Despite the plethora of treatment modalities tried, melasma poses a great challenge as its treatment can be often unsatisfactory with high recurrence rates.

This article focuses on using Tranexamic acid (TXA) as a novel agent (oral, topical or intralesional), in treatment for melasma. Several studies have found that tranexamic acid (Tranexamic A), a traditional hemostatic drug, has hypopigmentory effect on melasma lesions and also prevents UV-induced pigmentation [2-7].

## Tranexamic Acid, the Molecule and Its Uses

Tranexamic acid (trans-4-aminomethylcyclohexanecarboxylic acid: TXA) is a synthetic lysine analog which has an antifibrinolytic effect through the reversible blockade of lysine-binding sites on plasminogen molecules [8].

TXA has been an approved drug for the treatment of menorrhagia since the 1970s in dosage of 2.0-4.5 g/day during the cycles [9].

Dosages up to 4-4.5 g/day have not been reported to cause any serious adverse effects. Prophylactic oral TXA has been successfully used in hereditary angioedema for duration of 8 to 34 months without any serious adverse effects or abnormal blood fibrinolytic activity [10].

Its usage in the treatment of melasma was first reported in 1979 by Nijo in Japan [11]. It was an accidental discovery in a patient who was treated with tranexamic acid for chronic urticaria. Since then, a few reports have described the administration of TXA for the treatment of melasma. It has been mostly used at a low dosage of 250 mg twice daily in the treatment of melasma, which is only one-sixth of the normal dosage as a hemostatic. It has also been used topically and intradermally in treatment of melasma.

Its contraindications include acquired defective color vision, an active intravascular clotting condition, and hypersensitivity to TXA. It should be also used with caution in patients with cardiovascular disease, cerebrovascular disease, and simultaneous use of coagulating agents. Laboratory tests including prothrombin time (PT), activated partial thomboplastin time (APTT), and other blood-clotting parameters should be performed before starting TXA. The common side effects of TXA are gastrointestinal complaints (nausea, diarrhoea, and abdominal pain).These side effects can be minimised by oral administration after a meal. Other reported side effects include hypomenorrhea which disappears after withdrawal of tranexamic acid. Thromboembolism, myocardial infarction and pulmonary embolism have been reported, too. The actual thrombotic risk is low although factors like old age, very high dose and long duration of TXA and concomitant use of other prothrombotic drugs increase the risk.

## Mechanism of action of tranexamic acid in Melasma

UV light exposure plays a key role in the pathogenesis of melasma. Ultraviolet (UV) irradiation induces plasminogen activator synthesis and increases plasmin activity in keratinocytes, which stimulates the release of arachidonic acid (AA) via phospholipase A2 [3]. Free arachidonic acid stimulates melanogenesis via its metabolite, prostaglandin E2 (Figure 1).
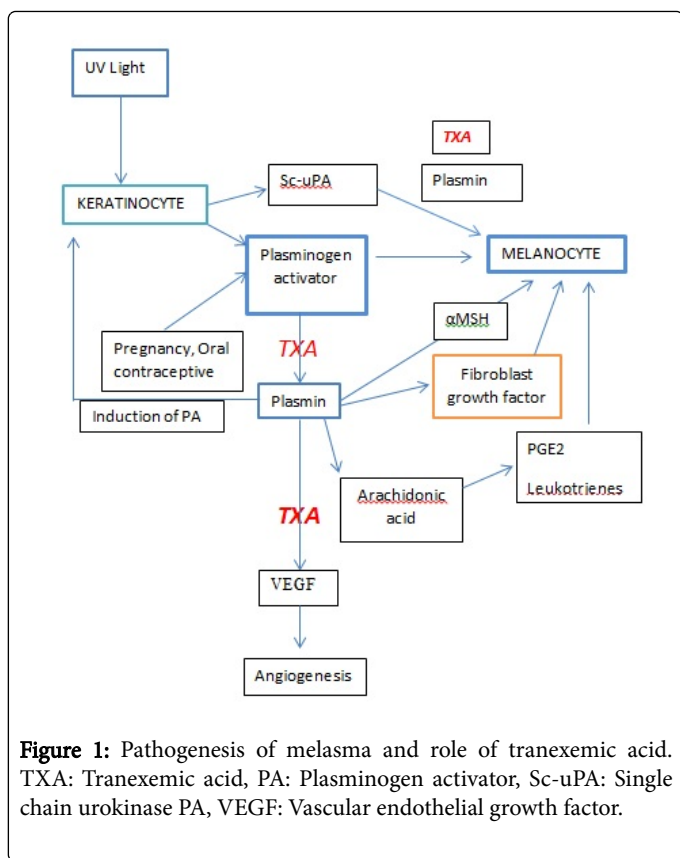
**Figure 1:** Pathogenesis of melasma and role of tranexemic acid. TXA: Tranexemic acid, PA: Plasminogen activator, Sc-uPA: Single chain urokinase PA, VEGF: Vascular endothelial growth factor.

Moreover, the release of AA is increased by plasmin in endothelial cells. Increased plasmin itself elevates α-melanocyte-stimulating hormone, which activates melanin synthesis in melanocyte. Plasmin also plays a role in the release of basic fibroblast growth factor (FGF), which is again a potent melanocyte growth factor. All of these processes result in more melanin production in the skin.

Apart from effect on melanocytes, Plasmin plays an important role in angiogenesis. Plasmin converts extracellular matrix-bound VEGF into freely diffusible forms. TXA, a plasmin inhibitor, suppresses angiogenesis, and also inhibits neovascularization induced by basic fibroblast growth factor (bFGF).

Single chain urokinase PA (Sc-uPA) in keratinocyte induces dose dependent increase in melanocytes, tyrosinase activity, cell perimeter, area, and increased dendrites. Plasmin can significantly increase the amount of Sc-uPA. Sc-uPA can further induce keratinocyte growth, differentiation, and migration. Thus in-vitro studies show that Sc-uPA generated by keratinocytes increases the activity of melanocytes.

Repetitive UV irradiation increases the number of mast cells and mast cell tryptase. Tryptase degrades type IV collagen, thus, increased numbers of mast cells and tryptase might be the cause of weak basement membranes observed in melasma. Mast cells also play an important role in the development of solar elastosis, one of the histological features of melasma. Elastin content in UV exposed skin correlates with mast cell counts.

Another important factor in pathogenesis of melasma, contraceptive pills and pregnancy have been shown to increase serum Plasminogen Activator, which as mentioned above can activate the melanogenesis process.

Histologically, in melasma there is increased epidermal pigmentation; the epidermal melanocytes are more active than in normal skin. On electron microscopy the melanocytes are enlarged, with prominent dendrites more mitochondria, Golgi apparatus, rough endoplasmic reticulum and ribosomes, an indicator of increased melanocytic activity and thereby increased synthesis of eumelanin. Apart from this, various dermal changes are also observed;

1. Disruption and thinning of basement membrane of the lesional skin.

2. Prominent solar elastosis and increased numbers of blood vessels and elevated expression of vascular endothelial growth factor (VEGF).

3. Increased number of mast cells in lesional dermis and increased expression of c-kit and stem cell factor have also been reported. Dermal factors are possibly the reasons behind the refractory and recurrent nature of melasma.

Tranexamic acid prevents UV-induced pigmentation by interfering with the structure of plasminogen and preventing the binding of plasminogen to the lysine-binding sites of keratinocytes. The consequences of such event are less free arachidonic acid leading to a reduced ability to produce prostaglandins and thus decreased melanocyte tyrosinase activity and melanogenesis. Tranexamic acid has no effect on non-sun exposed healthy skin. Also, action of TXA on angiogenesis via plasmin could also play a contributory role in its action on melasma. Blocking of the Sc-uPA pathway may be another mechanism through which TXA reduces hyperpigmentation.

Apart from oral administration, Tranexamic acid, has been used as a topical application, intradermal injections (4 mg/ml) and in combination with micro needling. Topical formulations which have been used include 2% emulsion, 3%cream, 5% solution and liposomal formulation. TXA can be combined with other modalities such as Intense pulse light or Nd-YAG Laser

Its positive effect on melasma was first reported in a Japanese study by Nijo in 1979 [11]. Subsequently the effectiveness has been proved in several experimental and in -vivo studies. Maeda and Tomitab suggested that TXA inhibits melanin synthesis in melanocytes by interfering with the interaction of melanocytes and keratinocytes through inhibition of the plasminogen/plasmin system while Zhang et al. showed that TXA can inhibit melanogenesis by interfering with the catalytic reaction of tyrosinase. Moreover, TXA is found to be similar to tyrosine in the part of its structure, which can competitively inhibit the activity of tyrosinase.

Seong et al. used neonatal foreskin cultured melanocytes to demonstrate effects of TXA after UVB irradiation and showed a significant inhibition of multiplication of melanocytes, decreased in tyrosinase activity, tyrosinase-related protein TRP1/2, and melanin content. However, they observed no change in number and length of melanocyte dendrites [12].

Zhu et al. reported that increasing the treatment duration was more effective than increasing the dose of TXA [13]. The duration of therapy has varied in different studies ranging from 6 weeks to a maximum of 6 months. Onset of effect is mostly in 4 weeks. The dosage has also varied from 500 mg /day to 1.5 g/day, but consensus has evolved around 500 mg /day.

Na et al. in their study elucidated the effects of oral and topical TXA on melasma. Patients received oral TXA three times a day along with application of topical TXA twice a day for 8 weeks. The mean lesional

melanin index (MI) scores decreased significantly. Interestingly, the MI scores for the perilesional skin increased. The erythema index scores of lesional and perilesional skin also showed a similar pattern. Histological analysis showed significant reduction of epidermal pigmentation, vessel numbers and mast cell counts. Type IV collagen staining was not observed in all specimens. TXA decreased epidermal pigmentation associated with melasma and also reversed melasma-related dermal changes, such as vessel number and increased numbers of mast cells. This indicates an effect of TXA on all pathogenic mechanisms in melisma [14-25].

Li et al. showed in an experimental study of intradermal TXA on guinea pig skin that melanin content is significantly reduced although melanocytes are not reduced.

Wu et al. used TXA 250 mg twice daily for 6 months in 74 Chinese females aged 21-52 years with acquired symmetrical facial hyperpigmentation (with an option to extend treatment in some severe cases or repeat the treatment for recurrent melasma). Interestingly, in patients with other pigmented lesions, such as freckles and senile lentigo in addition to the melasma, the melasma responded well but these other lesions remained unchanged possibly indicating different pathogenic mechanisms. Improvement started to occur in majority of patients at the end of 4 weeks while in some patients improvement was observed at end of 8 weeks. Overall significant improvement was seen in 94.6 % of patients.

H H Cho et al. in their study evaluated the usefulness of oral TXA as an adjuvant to the treatment of melasma using laser and light-based devices in Fitzpatrick type III and IV skin. Along with Oral TXA 500 mg/day patient simultaneously received intense pulsed light (IPL) and three or four times of low fluence Q-switched (QS) Nd:YAG laser treatments. Oral TXA 500 mg/day was found to improve clinical efficacy in light- or laser-based melasma treatment especially during the period of relative high sun exposure without serious adverse effects. However Kato et al. reported that oral TXA of 750 mg/day did not effectively cut down the risk of hyperpigmentation after Q-switched ruby laser on senile lentigo patients. It has been shown that the TXA is as effective as the cumulative effect of hydroquinone and dexamethasone in treatment of melasma while it is safer than the gold standard of melasma treatment, hydroquinone [26].

A pilot study by Lee et al. among Korean women in 2006, to evaluate the efficacy of intralesional tranexamic acid injection in melasma treatment, showed a decrease of 42.74% in MASI score after 12 weeks of treatment. Similar results were also seen in a study done by evaluating the efficacy and safety of TXA in treatment of melasma, comparing Group A: the use of localized microinjection [intradermal injections of TXA (4 mg/ml) weekly] versus Group B: 3 % TXA topical therapy. The mean dose of TXA injected in patients was 1.5 mg, which is lower than the usual dose used for antifibrinolytic effect, and the concentration of topical cream to 3% has minimal systemic absorption. There was a statistically significant reduction in MASI after 12 weeks in both groups, with no statistically significant difference between them [27].

## Conclusion

Thus oral TXA at 250 mg twice daily dosing for 6 months is a promising modality in the treatment of melasma. Tranexamic acid is possibly the only treatment for melasma that can prevent the activation of melanocyte by sunlight, hormonal influence, and injured keratinocyte (after UV exposure, chemical peeling, IPL, laser) through the inhibition of the PA activation system [28]. It can not only reduce the development of melasma, but also reduce the possibility of recurrence after other treatment modalities. TNA can be used as stand-alone therapy or as an adjuvant to other treatment modalities.

Although several studies have been documented, large scale randomised controlled studies and long term follow-up studies are required in future. Further studies are required to find out the frequency of usage, long-term benefits, and effect of combination therapy with other medications and methods of melasma treatment to evaluate the additive effect of TNA. Also large studies in all ethnic groups including Caucasians and Africans are required as studies have been done mostly in the Asians. A clinical trial with a control group and utilizing skin histopathology and immunochemistry would be an ideal set up to make a more conclusive study. Also, research on the ideal duration of TXA intake to affect improvement in melasma with no recurrence is desirable; this will enable the detection of long-term effects of TXA. Lastly more studies are required to determine ideal dosage/duration of topical and intradermal TXA.

## References

1. Grimes PE (1995) Melasma. Etiologic and therapeutic considerations. Arch Dermatol 131: 1453-1457.

2. Lee JH, Park JG, Lim SH, Kim JY, Ahn KY, et al. (2006) Localized intradermal microinjection of tranexamic acid for treatment of melasma in Asian patients: a preliminary clinical trial. Dermatol Surg 32: 626-631.

3. Maeda K, Naganuma M (1998) Topical trans-4-aminomethyl cyclohexanecarboxylic acid prevents ultraviolet radiation-induced pigmentation. J Photochem Photobiol B 47: 136-141.

4. Kondou S, Okada Y, Tomita Y (2007) Clinical study of effect of tranexamic acid emulsion on melasma and freckles. Skin Res 6: 309-315.

5. Cho HH, Choi M, Cho S, Lee JH (2013) Role of oral tranexamic acid in melasma patients treated with IPL and low fluence QS Nd:YAG laser. J Dermatolog Treat 24: 292-296.

6. Na JI, Choi SY, Yang SH, Choi HR, Kang HY, et al. (2013) Effect of tranexamic acid on melasma: a clinical trial with histological evaluation. J Eur Acad Dermatol Venereol 27: 1035-1039.

7. Wu S, Shi H, Wu H, Yan S, Guo J, et al. (2012) Treatment of melasma with oral administration of tranexamic acid. Aesthetic Plast Surg 36: 964-970.

8. Dunn CJ, Goa KL (1999) Tranexamic acid: a review of its use in surgery and other indications. Drugs 57: 1005-1032.

9. Wellington K, Wagstaff AJ (2003) Tranexamic acid: a review of its use in the management of menorrhagia. Drugs 63: 1417-1433.

10. Agostoni A, Marasini B, Cicardi M, Martignoni G, Uziel L, et al. (1978) Hepatic function and fibrinolysis in patients with hereditary angioedema undergoing long-term treatment with tranexamic acid. Allergy 33: 216-221.

11. Nijo T (1979) Treatment of melasma with tranexamic acid. Clin Res 13: 3129-3131.

12. Hernández-Barrera R, Torres-Alvarez B, Castanedo-Cazares JP, Oros-Ovalle C, Moncada B (2008) Solar elastosis and presence of mast cells as key features in the pathogenesis of melasma. Clin Exp Dermatol 33: 305-308.

13. Kim EH, Kim YC, Lee ES, Kang HY (2007) The vascular characteristics of melasma. J Dermatol Sci 46: 111-116.

14. Maeda K, Tomitab Y (2007) Mechanism of the inhibitory effect of tranexamic acid on melanogenesis in cultured human melanocytes in the presence of keratinocyte-conditioned medium. J Health Sci 53: 389-396.

15. Zhang X, Yang X, Yang H, Yang Y (2003) Study of inhibitory effect of acidum tranexamicum on melanin synthesis. Chin J Dermatovenereol Integr Tradit West Med 2: 227-229.

16. Ebrahimi B, Naeini FF (2014) Topical tranexamic acid as a promising treatment for melasma. J Res Med Sci 19: 753-757.

17.   Kanechorn Na Ayuthaya P, Niumphradit N, Manosroi A, Nakakes A (2012) Topical 5% tranexamic acid for the treatment of melasma in Asians: a double-blind randomized controlled clinical trial. J Cosmet Laser Ther 14: 150-154.

18.   Manosroi A, Podjanasoonthon K, Manosroi J (2002) Development of novel topical tranexamic acid liposome formulations. Int J Pharm 235: 61-70.

19.   Budamakuntla L, Loganathan E, Suresh DH, Shanmugam S, Suryanarayan S, et al. (2013) A Randomised, Open-label, Comparative Study of Tranexamic Acid Microinjections and Tranexamic Acid with Microneedling in Patients with Melasma. J Cutan Aesthet Surg 6: 139-143.

20.   Seong JS, Sung HC, Wan IC, Ro SW, Kim MN et al. (2007) Effect of Trans-4-Aminomethylcyclohexanecarboxylic acid on the proliferation and melanization in cultured normal human melanocytes. Ann Dermatol 19: 60-67.

21.   Zhu HJ, Yang XH (2001) The clinical study of acidum tranexamicum on melasma. Pharm Prog 3: 178-181.

22.   Li Y, Sun Q, He Z, Fu L, He C, et al. (2014) Treatment of melasma with oral administration of compound tranexamic acid: a preliminary clinical trial. J Eur Acad Dermatol Venereol 28: 393-394.

23.   Li D, Shi Y, Li M, Liu J, Feng X (2010) Tranexamic acid can treat ultraviolet radiation-induced pigmentation in guinea pigs. Eur J Dermatol 20: 289-292.

24.   Cho HH, Choi M, Cho S, Lee JH (2013) Role of oral tranexamic acid in melasma patients treated with IPL and low fluence QS Nd:YAG laser. J Dermatolog Treat 24: 292-296.

25.   Kato H, Araki J, Eto H, Doi K, Hirai R, et al. (2011) A prospective randomized controlled study of oral tranexamic acid for preventing postinflammatory hyperpigmentation after Q-switched Ruby laser. Derm Surg 37: 605-610.

26.   Ebrahimi B, Naeini FF (2014) Topical tranexamic acid as a promising treatment for melasma. J Res Med Sci 19: 753-757.

27.   Steiner D, Feola C, Bialeski N, Antiori ACP, Flavia Alvim Sant'Anna Addor FA et al. (2009) Study evaluating the efficacy of topical and injected tranexamic acid in treatment of melisma. Surgical & Cosmetic Dermatology 1: 174-177.

28.   Tse TW, Hui E (2013) Tranexamic acid: an important adjuvant in the treatment of melasma. J Cosmet Dermatol 12: 57-66.