MEDWIN PUBLISHERS
Committed to create value for Researchers

Journal of Cosmetology

Role of Tranexamic Acid in Management of Melasma

Tulika Rai*

Assistant Professor, Department of Dermatology and Venereology, I.M.S, B.H.U, India

***Corresponding author:** Tulika Rai, Assistant Professor, Department of Dermatology and Venereology, I.M.S, B.H.U, India, Email: raitulika@gmail.com

Review Article

Volume 1 Issue 1

Received Date: October 20, 2017

Published Date: November 06, 2017

Introduction

Melasma is a common, acquired, circumscribed hypermelanosis of sun-exposed skin. It presents as symmetric, hyper pigmented macules having irregular, serrated, and geographic borders. The most common locations are the cheeks, upper lips, the chin, and the forehead, but other sun-exposed areas may occasionally be involved. Although melasma may affect any race, it is much more common in constitutionally darker skin types (skin types IV to VI) than in lighter skin types. The exact pathophysiology of melasma remains elusive, but multiple factors have been implicated. Studies indicate the possible role of several risk factors such as genetics, sunlight, age, gender, female hormones, pregnancy, thyroid dysfunction, cosmetics, and medications Exacerbation of melasma is universally seen after prolonged sun exposure but the pigmentation fades after periods of avoidance of sun exposure [1]. Current treatments such as hydroquinone (HQ), kojic acid, retinoids, azelaic acid, chemical peels, and lasers demonstrate variable efficacy and side-effect profiles. Tranexamic acid (TXA) delivered orally, topically, and intradermally works via the inhibition of ultraviolet (UV)-induced plasmin activity in keratinocytes.

Tranexamic acid (TXA) is an antifibrinolytic drug. The drug came as a boon in the treatment of menorrhagia in 1968 and acts by blocking the lysine site on plasminogen, thereby inhibiting fibrinolysis [2]. It is highly useful in controlling bleeding in various coagulation defects such as hemophilia, surgeries like cardiopulmonary bypass and arthroplasty [3].

TXA has been tried topically, orally, and intradermally in the management of melasma and has been found to be effective with minimal side-effects. TXA was reported to be useful in the treatment of melasma in 1979 by Nijor in Japan [4]. The drug tackles mostly the vascular component of melasma and is now widely used as an adjuvant with significant results [5].

Pharmacology & Mechanism of Action of TXA

TXA (trans-4-aminomethylcyclohexane carboxylic acid) is a synthetic lysine amino acid derivative which controls and reduces the dissolution of hemostatic fibrin. TXA exerts its antifibrinolytic effects by reversibly blocking lysine binding sites on plasminogen. This prevents plasmin from interacting with lysine residues on the fibrin polymer, leading to subsequent fibrin degradation. The native human plasminogen has 4–5 lysine binding sites. However, their affinity for TXA is low. The high-affinity lysine site of plasminogen is involved in its binding to fibrin. Plasminogen gets displaced from the surface of fibrin once the high-affinity binding site gets saturated with TXA. It is finally excreted unchanged in the urine [6].

It causes inhibition of UV- induced plasmin activity. TXA also prevents the binding of plasminogen to the keratinocytes. Plasmin is a protease that enhances the intracellular release of arachidonic acid (AA) and alpha-melanocyte-stimulating hormone (a-MSH). AA and a-MSH have the property of stimulating melanogenesis by melanocytes. Tranexamic acid being a plasmin inhibitor depletes the keratinocyte pool of AA involved in UV-induced melanogenesis [7].

Following ultraviolet exposure, prostaglandins activate signaling pathways involved in growth, differentiation, and apoptosis of melanocytes. PGE2 is released by keratinocytes following UV radiation (UVR), which stimulates the formation of dendrites in melanocytes and melanocyte tyrosinase activity. TXA inhibits PG production and thus reduces the melanocyte tyrosinase a UVR stimulates the production of angiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF), and interleukin-8. VEGF interacts with VEGF receptors present in epidermal keratinocytes which release metabolites of AA and plasminogen from the proliferated vessels, which enhances melanogenesis. TXA targets the vascular components of the skin [8].

Tyrosinase-related protein (TRP-1) and TRP-2 are important enzymes in the Raper mason pathway of melanogenesis. TXA also decreases the levels of TRP-1 and TRP-2. Activation of the signaling pathway extracellular signal-regulated kinase (ERK) induces microphthalmia-associated transcription factor (MITF) degradation, resulting in reduced melanogenesis. MITF is the key transcription factor regulating these enzymes involved in melanogenesis. TXA stimulates the ERK signaling pathway and downregulates MITF protein level. This reduces inflammation-induced melanogenesis by decreasing tyrosinase protein expression [9].

Oral TXA

A prospective, randomized controlled trial (RCT) study was conducted by Karn et al. in Nepal, in which oral TXA was administered to melasma patients in a dose of 250 mg twice daily for 3 months. The authors concluded that it provides a rapid and sustained improvement in the treatment of melasma [10]. Another descriptive study conducted on 65 melasma patients in Pakistan, the drug was prescribed at the same dose for 6 months. Sixty-three percent had a good response and 23% had an excellent response after 6 months [11]. In many situations, it is used as an adjuvant with other drugs or procedures. The details of the studies are discussed in Table 1 [12,13]. Pradhi T, et al. concluded that oral TXA at a dose of 250 mg twice daily along with fluocinolone containing topical triple combination cream for 8 weeks, produced a significant and faster improvement in melasma, and also saved patients from the adverse effects of long-term use of steroids and hydroquinone [14]. Another study in Hispanic women showed the efficacy of oral TXA in management of melasma [15].

Year	Authors	Type of study	Objectives	Number of patients	Study group	Results	Conclusion
2017	Del Rosario E, et al.	Randomized, placebo-controlled, double-blind study	Efficacy of oral TA in patients with moderate to severe melasma	39	250 mg of TXA or placebo capsules twice daily for 3 months and sunscreen followed by 3 months of treatment with sunscreen only.	At 3 months, there was a 49% reduction in mMASI score in the TA group vs. 18% in the control group.	Oral TXA appears to be an effective treatment for moderate to severe melasma with minimal side effects.
2015	Pradhi T, et al.	Open labeled randomized controlled trial	Oral Tranexamic Acid with Fluocinolone-Based Triple Combination Cream Versus Fluocinolone-Based Triple Combination Cream Alone in Melasma	40	Group A cream only Group B patients oral tranexamic acid 250 mg twice daily and applied a triple combination cream once daily for 8 weeks	Intergroup comparison showed a faster reduction in pigmentation in Group B as compared to Group A and the results were statistically significant at 4 weeks and 8 weeks.	Addition of oral tranexamic acid to fluocinolone-based triple combination cream results in a faster and sustained improvement in the treatment of melasma.
2014	Aamir S, et al	Descriptive cross-sectional study	Evaluation of efficacy and safety of oral TXA in treatment of melasma	65	Patients were given oral TXA 250 mg BD and sunscreen for 6 months	41 patients had good, 15 had excellent and 8 patients had fair improvement.	Oral TXA is safe and effective

2013	Cho HH, et al.[12]	Randomized control trial(RCT)	Role of oral TXA in melasma patients treated with IPL and low fluence Q switched Nd-Yag laser	51	Oral TXA during IPL and laser treatments (group A) treated with only IPL and laser (group B)	Modified MASI score right before and after IPL were more reduced in group A. No serious adverse effects were reported up to 8 months of oral TNA medication.	Oral TXA may improve clinical efficacy in light- or laser-based melasma treatment
2013	Shin JU, et al.[13]	RCT	Role of oral TXA in patients treated with low fluence Q sw Nd-Yag laser	48	Combination group-@ sessions of low fluence laser & oral TXA Laser treatment group	Mean mMASI decreased in both groups	Oral TXA is effective option in combination with low fluence Nd-Yag laser
2012	Kanechorn Na Ayuthaya P, et al.	Double-blind randomized controlled clinical trial.	Efficacy of topical 5% tranexamic acid versus vehicle for treatment of melasma.	21	Patients blindly applied topical 5% TXA and its vehicle, to the designated sides of the face twice daily in addition to the assigned sunscreen each morning.	Eighteen out of twenty-three patients (78.2%) showed decrease in the melanin index on either or both sides of the face by the end of 12 weeks. TXA gel was neither superior nor different ($p > 0.05$) compared to its vehicle , erythema was significant on the TXA-applied site ($p < 0.05$)	Although lightening of pigmentation was obtained, the results were not significant between the two regimens
2014	Ebrahimi B, et al.	Double-blind split-face tria	Evaluate the efficacy and safety of topical solution of TXA and compare it with combined solution of hydroquinone and dexamethasone for melasma in Iranian women.	50	Topical solution of 3% TXA on one side of the face, and topical solution of 3% hydroquinone + 0.01% dexamethasone on the other side two times a day.	significant decreasing trend was observed in the MASI score of both groups with no significant difference between them during the study	Topical TXA is as an effective and safe medication for the treatment of melasma.

2015	Banihashemi M, et al.	Split face trial	Compare therapeutic effects of liposomal tranexamic acid and conventional hydroquinone on melasma.	23	Patients blindly applied 5% topical liposomal TA and 4% hydroquinone cream, to the designated sides of the face twice daily in addition to the assigned sunscreen in the morning.	The mean MASI scores significantly reduced in both treated sides ($P < P = 0.001$) after 12 week. A greater decrease was observed with 5% liposomal TA, although this difference was not statistically significant.	Topical liposomal TA can be used as a new, effective, safe, and promising therapeutic agent in melasma.

Table 1: Summary of few recent TXA studies in treatment of melasma

Topical and Intradermal TXA

Epidermal melasma responds better to treatment and hence topical TXA may show some efficacy in this variant, rather than the dermal and mixed melasma variants, which carry a poor prognosis. Topical TXA shows rapid and sustained results with very less adverse effects as far as epidermal melasma is concerned. Few studies comparing topical TXA with vehicle and sunscreen showed significant improvement in MASI scores [16]. Another study comparing topical solution of TXA with combined solution of hydroquinone and dexamethasone for melasma in Iranian women was published in year 2014 [17]. Another study comparing therapeutic effects of liposomal tranexamic acid and conventional hydroquinone on melasma found liposomal TXA to be effective [18].

The dermal and mixed variants of melasma are highly resistant to standard topical treatment. TXA may be administered intradermally in such cases. The microneedling method proves to be efficacious in the intradermal delivery of the drug. In this method, multiple microtrauma are made in the dermis, using a derma roller and this facilitates transport of substances through various transport channels, leaving the epidermis intact. A prospective, randomised, open-label study with a sample size of 60; 30 in each treatment arms was conducted. Thirty patients were administered with localised microinjections of TA in one arm, and other 30 with TA with microneedling. The procedure was done at monthly intervals (0, 4 and 8 weeks) and followed up for three consecutive months. In the microinjection group, there was 35.72% improvement in the MASI score compared to 44.41% in the microneedling group, at the end of third follow-up visit. Six patients (26.09%) in the microinjections group, as compared to 12 patients (41.38%) in the microneedling group, showed more than 50% improvement. The medication is easily available and affordable. Better therapeutic response to treatment in the microneedling group could be attributed to the deeper and uniform delivery of the medication through microchannels created by microneedling [19].

Adverse effects of TXA

TXA is a well-tolerated drug and it is considered safe at the usual dosage. Nausea and diarrhea are the most common side effects. The other systemic side effects observed with low-dose administration include oligomenorrhea, gastric upset, and palpitations [11]. Venous thromboembolism, myocardial infarction, cerebrovascular accidents, and pulmonary embolism have been reported when given in hemostatic doses (up to 1000 mg daily). The contraindications of the drug include acquired defective color vision, active intravascular clotting conditions, and drug hypersensitivity [2]. Though it is used in low doses for a short duration as a systemic depigmenting agent, it is always vital to rule out underlying coagulation defects to prevent untoward adverse events [2]. It is advisable to take a thorough history along with essential investigations pertaining to coagulation defects before giving TXA. Mild discomfort, burning sensation, and erythema were observed when it was used intradermally [19-20].

Conclusion

Review of literature points out that TXA is a safe and promising drug not only in the treatment of melasma but also in other common pigmentary conditions.

However, larger RCTs with long-term follow-up are needed to fully elucidate the mechanism of action, ideal route of administration, frequency, and duration of administration of TXA. TXA may be used as a depigmenting agent in melasma as the evidence continues to grow in its favour.

References

1. Bandyopadhyay D (2009) Topical treatment of melasma. Indian J Dermatol 54(4): 303-309.

2. George A (2016) Tranexamic acid: An emerging depigmenting agent. Pigment Int 3(2): 66-71.

3. Binz S, McCollester J, Thomas S, Miller J, Pohlman T, et al. CRASH-2 study of tranexamic acid to treat bleeding in trauma patients: A controversy fueled by science and social media. J Blood Transfus 2015.

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

5. Malathi M, Thappa DM (2013) Systemic skin whitening/lightening agents: What is the evidence?. Indian J Dermatol Venereol Leprol 79(6): 842-846.

6. Tse TW, Hui E (2013) Tranexamic acid: An important adjuvant in the treatment of melasma. J Cosmet Dermatol 12(1): 57-66.

7. Calapai G, Gangemi S, Mannucci C, Miniullo PL, Casciaro M, et al. (2015) Systematic review of tranexamic acid adverse reactions. J Pharmacovigil 3: 1-7.

8. Wu S, Shi H, Wu H, Yan S, Guo J, et al. (2012) Treatment of melisma with oral administration of tranexamic acid. Aesthetic Plast Surg 36(4): 964-970.

9. Sonthalia S (2015) Etiopathogenesis of melasma. In: Sarkar R, editor. Melasma: A Monograph. New Delhi: Jaypee 6-14.

10. Kim MS, Bang SH, Kim JH, Shin HJ, Choi JH, et al. (2015) Tranexamic acid diminishes laser induced melanogenesis. Ann Dermatol 27(3): 250-256.

11. Karn D, Kc S, Amatya A, Razouria EA, Timalsina M (2012) Oral tranexamic acid for the treatment of melasma. Kathmandu Univ Med J (KUMJ) 10(40): 40-43.

12. Aamir S, Naseem R (2014) Oral tranexamic acid in treatment of melisma in Pakistani population: A pilot study. J Pak Assoc Dermatol 24(3): 198-203.

13. 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(4): 292-296.

14. Shin JU, Park J, Oh SH, Lee JH (2013) Oral tranexamic acid enhances the efficacy of low fluence 1064 nm quality-switched neodymium-doped yttrium aluminum garnet laser treatment for melasma in Koreans: A randomized, prospective trial. Dermatol Surg 39(3 Pt 1): 435-442.

15. Pradhi T, Pradhan S (2015) Oral tranexamic acid with fluocinolone based triple combination cream versus fluocinolone-based triple combination cream alone in melasma: An open labeled randomized comparative trial. Indian J Dermatol 60(5): 520.

16. Rosario DE, Florez-Pollack S, Zapata L Jr, Hernandez K, Tovar-Garza A, et al. (2017) Randomized, placebo-controlled, double-blind study of oral tranexamic acid in the treatment of moderate to severe melasma. J Am Acad Dermatol pii: S0190-9622(17): 32458-32461.

17. Ayuthaya KNP, 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(3): 150-154.

18. Ebrahimi B, Naeini FF (2014) Topical tranexamic acid as a promising treatment for melasma. J Res Med Sci 19(8): 753-757.

19. Banihashemi M, Zabolinejad N, Jaafari MR, Salehi M, Jabari A (2015) Comparison of therapeutic effects of liposomal Tranexamic Acid and conventional Hydroquinone on melasma. J Cosmet Dermatol 14(3): 174-177.

20. 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(3): 139-143.