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Oral Tranexamic Acid in Melasma: A Novel Therapeutic Approach

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ABSTRACT

Melasma is a condition characterized by increased pigmentation and blood vessel formation, typically observed in women of childbearing age. The etiology of melasma remains unclear, however, it frequently manifests in sun-exposed regions of the face. Contributing factors encompass genetic predisposition, ultraviolet (UV) radiation exposure, familial background, elevated levels of estrogen/progesterone, and specific pharmaceuticals. Diverse modalities have been employed to address this issue, yielding varying outcomes, yet the results are not encouraging. Tranexamic acid (TXA) is an off-label treatment for melasma that functions as a plasmin inhibitor. TXA can be administered via oral, topical, or intralesional routes. To determine the optimal dose, safety and efficacy of oral tranexamic acid for the treatment of melasma. A comprehensive PubMed/Medline, Google scholar and Cochrane database was searched using the keywords tranexamic acid and melasma. Twenty nine articles were included for this study. Oral TXA in the dose range of 500-1500 mg per day was studied in a variety of randomized controlled trials and have been compared with several traditional treatments. Overall, MASI scores improved and reduction of dermal blood flow was seen on histopathological examination. Oral TXA was found to be the most effective, especially in cases of refractory melasma: however, it causes gastro-intestinal upset and hypomenorrhea in few patients. Due to its pro-thrombotic nature, past history of any thromboembolism and deep vein thrombosis episode or family history must be evaluated before prescribing the patients. Intralesional injections of TXA and microneedling with topical TXA were found to be effective alternatives to oral treatment.

INTRODUCTION

Melasma is a persistent and acquired condition that affects the pigmentation of the skin. It is characterized by the presence of light to dark brown spots and patches on areas of the skin that are exposed to the sun, specifically on the cheeks, nose, forehead and jawline. This condition is predominantly observed in women within the reproductive age group and typically occurs following pregnancy. It primarily affects females, although males are also affected in about 10% of cases. Potential factors that worsen or trigger melasma include sex hormones, exposure to ultraviolet (UV) light, genetic susceptibility, use of oral contraceptive pills, cosmetics and phototoxic drugs[1]. The classification of melasma is based on the depth of melanogenesis and is divided into epidermal, dermal and mixed types[2]. The standard initial treatment choices for melasma involve using topical agents that lighten the skin, such as hydroquinone (2-4%), glycolic acid, kojic acid, 4-n-butylresorcinol, tretinoin and sun-screen. The most potent topical treatment is a cream that combines hydroquinone, tretinoin and corticosteroid, known as triple therapy cream[3]. The second line of treatment involves the use of chemical peels (such as glycolic acid, trichloroacetic acid, kojic acid and lactic acid) and lasers (including Q-switched Nd:YAG, Ruby Laser, Alexandrite laser, Er:YAG laser and Fraxel laser). However, none of them are providing patients with encouraging outcomes. The presence of melasma[4,5] leads to considerable psychological disruption, which in turn negatively affects one's overall quality of life[6]. Tranexamic acid (TXA) has recently been endorsed for the treatment of melasma[7]. Tranexamic acid, also known as TXA, is a synthetic compound derived from the amino acid lysine. It works by blocking the action of plasminogen activator, an enzyme that converts plasminogen into plasmin[8].

What is the mechanism behind melasma? Exposure of the skin to UV light causes an increase in plasmin activity in keratinocytes, which in turn stimulates the production of melanocyte stimulating mediators such as a-melanocyte stimulating hormone (a-MSH) and arachidonic acid. TXA inhibits the activity of plasmin, which is induced by UV, by blocking the lysine-binding sites on plasminogen molecules. Several studies have demonstrated that TXA can effectively inhibit the release of paracrine melanogenic factors, thereby suppressing melanin formation. TXA also has the ability to decrease the appearance of pigmentation by reducing the levels of Vascular Endothelial Derived Growth Factor (VEGF)[7].

TXA is accessible in various formulations such as tablets, injections and topical preparations. TXA tablets are offered in the dosages of 250 mg and 500 mg. An alternative option is the availability of a combination containing 250 mg of a substance along with 50 mg of pine bark extract[8]. The United States Food and Drug Administration (FDA) has granted approval for the use of oral tablets containing TXA to treat cyclic heavy menstrual bleeding. Nevertheless, the application of this treatment for melasma lacks approval from both the US FDA and the Indian regulatory authority, Drug Controller General-India (DCGI)[8].

Aims and objective:

- To determine the optimal dose of oral tranexamic acid for the treatment of melasma
- To asses safety profile and efficacy of oral tranexamic acid in melasma

MATERIALS AND METHODS

A comprehensive literature review was searched using the electronic online data base from PubMed/Medline, Google Scholar and Cochrane Database. The key words which were searched was "melasma"," oral tranexamic acid", "trial" and "study" in the title. References from relevant articles were also included for review. Prospective studies, retrospective analysis, clinical trials, review articles, systematic reviews, meta-analysis, case series and case reports were considered for this review. Indian studies as well as other countries were included for analysis. After screening of all the articles, evidence from clinical studies with oral TXA was summarized and the draft was documented.

RESULTS

We have retrieved 25 clinical studies published from 2012 to 2023 and summarized the results in two sections; prospective studies and retrospective studies.

Evidence from prospective studies: Minni *et al*.[4] conducted a comparative analysis to assess the effectiveness of oral TXA in combination with a topical fluocinolone-based combination cream, as compared to using the topical fluocinolone-based combination cream alone. After a duration of 12 weeks, a significant enhancement was observed in 65.6% of patients in the initial group, while only 27.1% of patients in the other group showed improvement. Recurrence at 24 weeks in the first group was much lower than another group (18.03% vs 64.4% respectively)[4].

Sahu, *et al*. conducted a comparative analysis of the effectiveness of oral tranexamic acid (TXA) at a dosage of 250 mg twice daily with topical TXA and a modified Kligman's regimen over a period of 8 weeks, in conjunction with the use of sun-screen. Modified

Kligman's regimen was slightly more efficacious than oral TXA[9]. In 2012, Wu *et al*. conducted a study on the use of oral TXA in treating melasma. The participants were given a dosage of 250 mg twice daily for a duration of 6 months and were followed up for an additional 6 months. Out of a total of 74 women, 95.9% demonstrated a favorable to outstanding response by the conclusion of the 6-month period. Some patients experienced gastrointestinal discomfort and hypomenorrhea as adverse events. After discontinuing treatment, a recurrence of melasma was observed in 9.5% of patients[10].

In 2018, Harini Bala and colleagues reported that Oral TXA has proven to be effective for treating melasma in Asian skin, even when administered in low doses of 500 mg per day for a short duration of 8-12 weeks. Moreover, it is a secure therapeutic alternative that is simple to administer and has minimal and inconsequential side effects[11].

Cho *et al*. conducted a comparative analysis of the effectiveness of Intense Pulse Light (IPL) and Q-switched Nd:YAG laser, both with and without Tranexamic Acid (TXA), for treating melasma. The dosage of TXA administered was 500 mg per day. Oral tranexamic acid (TXA) effectively decreased the modified melasma area severity index (mMASI) in both groups[12]. In 2012, Karn, *et al*. conducted a randomized controlled trial involving a sample size of 260 patients. The patients were divided into two groups, each consisting of 130 patients. The first group received standard treatment along with oral administration of TXA 250 mg twice daily for a duration of 3 months, whereas the second group was solely treated with routine topical measures. The evaluation was conducted using the Melasma Assessment Severity Index (MASI). The researchers determined that the inclusion of oral tranexamic acid leads to prompt and consistent enhancement in the management of melasma[13]. In a separate small study conducted at a single center, the effectiveness of a treatment for melasma was evaluated using four different methods. The results showed that 50% of the patients in group A experienced improvement in their condition, while only 5.9% of the patients in group B showed improvement. The difference in improvement between the two groups was statistically significant ($p<0.005$). There were no significant adverse effects reported during the administration of oral TXA therapy[14].

Zhu, *et al*. determined that all four oral doses of TXA (500 mg, 750 mg, 1,000 mg or 1,500 mg) were equally effective, as there were no notable variations in the MASI or melanin index across the different doses[15]. A separate investigation conducted by Na JI *et al*. examined the results of combining oral and topical TXA over a period of 8 weeks, including a histopathological examination. The researchers observed a notable reduction in the average scores of lesional melanin index (MI), as well as a decrease in epidermal pigmentation. Additionally, they observed a reversal of melasma-related dermal changes, including a decrease in vessel number and a reduction in the number of mast cells[16]. Shin, *et al* examined the impact of two sessions of low-fluence 1064-nm quality-switched neodymium-doped yttrium aluminum garnet (QSNY) laser, with and without oral tranexamic acid (TXA), over a period of 8 weeks. The study concludes that both groups experienced a substantial decrease in mMASI score after 4 weeks of the second treatment. Therefore, they deduced that oral tranexamic acid (TA) could be a secure and effective treatment choice for melasma when used in conjunction with low-fluence Q-switched neodymium-doped yttrium aluminum garnet (QSNY) laser therapy[17].

In a separate investigation, Agamia et al. conducted a comparative analysis of the effectiveness of Q-switched Nd YAG laser (1064-nm) with and without oral TXA. The study involved two groups, each consisting of 60 patients. The evaluation of responses was conducted based on clinical criteria, which involved the utilization of the Modified Melasma Area and Severity Index (mMASI) and dermoscopy. Statistically significant difference was found between the studied groups regarding the change of mMASI ($p = .036$) by using dermoscopy. The researchers determined that the addition of oral TXA improves its clinical effectiveness and reduces the occurrence of adverse effects[18].

Behrangi, *et al*. documented their findings on the use of microinjections of TXA compared to oral TXA 250 mg taken three times a day, along with Q-switched 1064 laser treatment every 2 weeks. This treatment approach was used in both groups as a standard therapeutic method. The study documented a noteworthy decrease in MASI score in both groups. Therefore, they concluded that tranexamic acid is an efficient and secure remedy for melasma, regardless of how it is administered[19] Khurana *et al*. found that oral tranexamic acid (TXA) resulted in a higher MASI score compared to microinjections. Additionally, the recurrence rate was also higher with microinjections[20].

Hadidi *et al*. conducted a study to assess the effectiveness of oral tranexamic acid (TXA) at a dosage of 250 mg twice a day, compared to various dilutions of tranexamic acid microinjections administered intradermally (at concentrations of 100mg/ml and 4mg/ml), in treating melasma. There was no significant difference observed in the changes of mMASI, melanin index and erythema index among the three groups

after a 2-month therapy period ($p<0.05$)[21]. Poostiyan et al. conducted a study comparing TXA microinjection and TXA mesoneedling in melasma. They found that the results in both groups were similar, but patient satisfaction was significantly higher with TXA mesoneedling[22]. Shihab, *et al* conducted a study in which fifty subjects were enrolled. In Group A, there was a significant decrease of 55% in mMASI after 3 months, from a mean of 8.96 (SD 2.45)-4.0 (SD 1.6). In comparison, Group B only experienced a reduction of 10.9%, from a mean of 8.53 (SD 2.04)-7.6 (SD 2.0). The study findings indicate that the combined use of oral TXA and topical hydroquinone is superior to the use of topical hydroquinone alone[23]. In a separate prospective study conducted by Malik *et al*. involving 100 participants, the combination of oral and topical 3% TXA yielded significantly superior results compared to oral TXA with 20% azelaic acid ($p<0.05$)[24] Akl *et al*. conducted a study to examine the impact of oral TXA combined with liposomal azelaic acid 20% cream compared to oral TXA combined with hydroquinone 4% cream. Liposomal azelaic acid demonstrated a statistically significant improvement compared to hydroquinone 4% cream ($p<0.05$)[25].

Elkamshoushi, *et al* conducted a study comparing the effectiveness of oral TXA 250 mg taken twice daily for three months alone, with a combination of either topical hydroquinone 4% or low-fluence 1064 nm Q-switched Nd: YAG laser in treating melasma. There was a notable decrease in telangiectasia in all groups. However, relatively early and better cosmetic outcomes were observed with combination of hydroquinone 4% and oral TXA[26]. Padhi and Pradhan conducted a study comparing the effectiveness of topical therapy with oral TXA in combination with fluocinolone acetonide 0.01%, tretinoin 0.05% and hydroquinone 2% cream. The treatment was administered for a duration of 8 weeks. This study demonstrated a notably accelerated decrease in pigmentation when using oral TXA in conjunction with triple combination therapy[27].

Evidence from retrospective studies: The retrospective analysis conducted by Lee, *et al*. revealed improvement in 503 patients, accounting for 89.7% of the total. Individuals without any familial predisposition to melasma exhibited a more favorable response. Adverse events were observed in 7.1% of the patients. One patient, who had familial protein deficiency, was reported to have deep vein thrombosis[28]. Oral tranexamic acid (TXA) has been found to significantly improve melasma in 81.25% of vitiligo patients when applied to the face, resulting in moderate to excellent outcomes. Tan *et al*.[29] conducted a study on refractory melasma, involving a sample size of 25 individuals. The participants were treated with Oral TXA (Tranexamic Acid) at a dosage of 250 mg twice daily, in addition to their existing combination topical therapy. They observed a notable enhancement in MASI scores following the treatment in comparison to the initial measurements.

In 2022, Simpson *et al*.[30] published a study stating that oral TXA is a secure and efficient therapeutic alternative for individuals with persistent melasma. Out of the 42 patients, only seven encountered side effects such as headache, nausea, gastrointestinal disturbance, leg numbness, reduced menstrual flow and increased menstrual flow. Patients who encountered adverse reactions were relieved of their symptoms upon discontinuing the medication. There were no observed long-term adverse effects in any patient[31]. The aforementioned findings were corroborated by a recently published meta-analysis conducted by Feng *et al*., which reported the efficacy of oral TXA in treating melasma with a well-tolerated response[32].

DISCUSSION

Multiple clinical studies with diverse study designs and conducted in various countries were assessed to examine the impact of oral TXA on melasma. The majority of the studies obtained were prospective, while only five were retrospective. The typical recommended doses of TXA in various studies range from 250 mg administered twice daily or three times daily. The standard dosage typically prescribed is 250 mg administered twice daily. TXA has been employed either as a standalone treatment or as an adjunctive therapy in patients suffering from melasma. Efficacy in treating moderate to severe melasma has been demonstrated. The user's text is enclosed in tags. The study conducted by Zhu et al. demonstrated that there was no statistically significant variation in effectiveness when administering TXA doses ranging from 500-1500 mg[15]. The efficacy of oral tranexamic acid (TXA) has been investigated in combination with a topical cream containing fluocinolone. Other treatments that have been studied include sunscreen, intense pulse light (IPL) therapy, laser therapy, topical TXA, topical azelaic acid, topical hydroquinone (HQ) and a liposomal formulation of azelaic acid at a concentration of 20%.The number 25 and The therapy duration ranged from 4 weeks to 6 months.

Various clinical studies have demonstrated the clinical advantages of treating melasma, which is further corroborated by histopathological examination[16]. A study has also shown a decrease in blood flow in the skin of areas affected by melasma[33]. Indian studies[20,27]. show promising potential on par

with international research. The duration of treatment varied in each study and recurrence has been reported following the cessation of therapy. The findings of retrospective studies are consistent with a limited number of randomized clinical trials[28,29,30]. The adverse event profile observed in various clinical studies does not give rise to significant concerns. A small number of patients experienced gastrointestinal adverse events and hypomenorrhea.

Adverse events and contraindications associated with the oral administration of tranexamic acid (TXA) Adverse events related to the digestive system and reduced menstrual flow are commonly reported side effects of TXA[10]. Discontinue oral TXA if patients experience visual or ocular symptoms or a severe allergic reaction.The number 34 is enclosed in square brackets. Patients who have demonstrated hypersensitivity reactions to TXA, women who are currently taking oral contraceptive pills and individuals with a past history, family history, risk factors, or active thromboembolic disease or Deep Vein thrombosis should avoid the use of TXA[34].

TXA is not authorized for the treatment of melasma by the US Food and Drug Administration (USFDA) or the Drug Controller General of India (DCGI). Hence, clinicians must communicate this information to the patient and acquire explicit verbal consent prior to employing it for melasma treatment.

CONCLUSION

Melasma is an acquired, common, difficult-to-treat skin condition with high recurrence rates. Oral TXA at the dose of 250 mg twice daily is found to be a promising therapeutic modality for the treatment of melasma. It can be used both as a monotherapy and in conjunction with other modalities. But, further randomized and placebo controlled trials are required to standardize the dose, duration, long term safety and efficacy of oral TXA in melasma.

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