Tranexamic Acid in Melasma: Why and How?

Melasma is a chronic, acquired symmetrical pigmentary disorder characterized by gray-brown macules and patches affecting photodistributed part of the face such as the bridge of the nose, cheek, upper lip, forehead, and mandible. It is seen mostly in women of reproductive age group and has an onset usually after pregnancy. However, in around 10% of the cases, males are also affected. Causative factors that have been implicated in aggravating or precipitating melasma include sex hormones, genetic susceptibility, ultraviolet (UV) light exposure, oral contraceptive pills, cosmetics, and phototoxic drugs.[1] Epidemiologically, melasma is found in all geographical and ethnic groups but occurs more commonly in Asians and Middle Easterners.[2]

Treatment is mostly unsatisfactory. Various modalities include hydroquinone (HQ), tretinoin, and corticosteroid triple combinations, nonsteroidal demelanizing creams, superficial chemical peels (glycolic acid, trichloroacetic acid, kojic acid, and lactic acid), lasers (Q-switched Nd:YAG laser, ruby laser, Alexandrite laser, Er:YAG laser, and Fraxel laser), and intense pulsed light (IPL).

Despite the plethora of treatment modalities, the results of these treatments in melasma are poor. Treatment is often incomplete and there is a high rate of recurrence.

Tranexamic acid (TXA) has been recently recommended for the use in melasma.[3] It can be given as an oral preparation, a topical preparation, or an intralesional agent. It is probably the first oral medication that has proven efficacy in the treatment of melasma. Other oral medications are Polypodium leucotomos which has indirect effect, and glutathione which has unproven efficacy.

Tranexamic Acid

TXA (trans-4-aminomethyl cyclohexane carboxylic acid) is an antifibrinolytic agent which blocks lysine-binding sites on plasminogen molecules.[4]

TXA is not a new molecule. It has been extensively used in the treatment of menorrhagia since the 70s. Dosages up to 2–4 g/day for 4–7 days have been used safely during cycles.[5] TXA has also been used prophylactically in hereditary angioedema in the duration of 8–34 months.[6]

For melasma, it has been used in low doses of 250 mg BD. Contraindications include defective color vision, coagulopathy, hypersensitivity, cardiovascular disease, stroke, and anticoagulant medications. Before starting TXA, it is important to get prothrombin time, activated partial thromboplastin time, and other blood clotting parameters. Common adverse effects include gastrointestinal side effects and reversible hypomenorrhea. Other reported adverse effects include deep vein thrombosis (DVT), myocardial infarction, and pulmonary embolism.[7]

Use of Tranexamic Acid in Melasma

The use of TXA in melasma was first reported by Nijo in 1979.[8] It was an accidental discovery in a patient of melasma who was receiving TXA for chronic urticaria. Sun exposure of the skin leads to synthesis of plasmin activator, which thereby increases plasmin activity in keratinocytes. This plasmin leads to release of arachidonic acid (AA) via phospholipase A2.[9] Prostaglandin E2 synthesis promoted by AA stimulates melanogenesis. Increased plasmin elevates α-melanocyte-stimulating hormone and fibroblast growth factor which are both potent melanocyte stimulators.[7] Plasmin also plays a role in angiogenesis by increasing the release of free vascular endothelial growth factor (VEGF).

Repeated UV damage leads to increased production of mast cell tryptase which weakens and damages the basement membrane, a condition seen in melasma.[10] Contraceptive pills and pregnancy have also shown to increase serum plasminogen activator that can activate the melanogenesis process. Other dermal changes also seen in melasma include disruption of basement membrane, increased blood vessels, and solar elastosis. Number of mast cells may also be increased in the lesional dermis. These dermal factors may be the cause behind the refractory nature of melasma.[10]

TXA prevents UV-induced pigmentation by interfering with the plasminogen binding to the keratinocyte.[7] This reduces free AA and thereby reduces prostaglandins in the melanocytes. It also prevents angiogenesis by blocking the action of plasmin. It also reduces VEGF and endothelin 1 (ET)-1; both may be responsible for increased vascularity in melasma.[11]

Apart from the oral formulation, TXA is also available in 2% emulsion, 3% cream, and 5% solution form. It can also be administered via intradermal injections in the concentration of 4 mg/ml. There are various reports and studies to authenticate safety and usefulness of TXA in melasma. Some of these studies are mentioned here.

In a study by Seo *et al*., a significant inhibition of multiplication of melanocytes was seen following TXA application to neonatal foreskin-cultured melanocytes before UVB irradiation. They also observed decreased tyrosinase activity, decreased tyrosine-related protein 1 and 2 expression, and decreased melanin content. However, no change in number of all length of dendrites of melanocyte was seen.[12] A study by Hongjin and Xihui reported that the treatment duration was more important parameter than the dose of TXA.[13] Hence,

the consensus arrived at a dose of 500 mg a day instead of 1.5 g/day used for menstrual disorders.

Histological analysis by Na *et al*. showed a significant reduction in epidermal melanin pigmentation, vessel numbers, and mast cell counts.[14] A significant reduction in lesional melanin index was also seen. Lee *et al*. showed a significant reduction in melasma area severity index (MASI) score at 8 and 12 weeks as compared to baseline following weekly intradermal injection of TXA (4 mg/ml).[15] Injections were given 1 cm apart, and 0.05 ml of TXA was injected at each site.

Wu *et al*. showed a significant improvement in 96% of the 74 women who received TXA tablets in the dose of 250 mg twice daily for 6 months for melasma. 5.4% of the study population had some sort of gastrointestinal discomfort and 8.1% developed hypomenorrhea. No serious complications were encountered. They also noted that women with multiple pigmented lesions along with melasma, such as freckles and lentigines, showed improvement only in melasma and not in any other lesion. This indicated different pathogenetic actions of TXA in melasma. Improvement started to appear at 4–8 weeks.[3]

Cho *et al*. compared the efficacy of IPL and Q-switched Nd: YAG laser treatment for melasma with and without oral TXA. They found oral TXA at 500 mg/day to improve the clinical efficacy of lasers and IPL in melasma. This is especially true during the relatively high sun exposure months.[16]

In a study by Kim *et al*., 2% topical TXA was applied in 23 melasma patients for 12 weeks. Significant improvement in modified MASI score was observed in 22 of 23 participants. Fontana-Masson staining showed a significant reduction in melanin content of epidermis. ET-1 was also found to be downregulated.[11] In a large study by Lee *et al*. in 2016, oral TXA was given to 561 patients of melasma. 89.7% showed improvement while 10% did not show any improvement. Among those cases who responded, improvement was seen in 2 months. A relapse rate of 27.2% was seen. One patient developed DVT and required discontinuation of therapy. She was later found to be a case of familial protein S deficiency.[7]

A recent split face study by Saki *et al*. comparing monthly intradermal TXA and daily 2% HQ cream showed a significant reduction in melanin value in each side. Monthly TXA showed better improvement at the end of 4 weeks, but the results were comparable at the end of 20 weeks.[17]

In another recent study by Atefi *et al*. comparing the 5% TXA cream and 2% HQ cream in two groups of people, they found significant improvement in MASI scores in both groups but no significant difference between the groups. A higher level of patient satisfaction was seen in TXA group (33.3% vs. 6.7% in HQ group). HQ group also suffered higher incidence of adverse effects such as skin irritation and erythema (10% vs. no major side effect in TXA group).[18]

We feel that TXA with microneedling using 2-mm dermaroller gives significant improvement in melasma. Treatment session is repeated monthly for 4 months. In our practice, we use a higher dose of TXA, i.e. 40 mg/ml. An important point missed by various studies is the frequency of maintenance sessions. In other words, how frequently the sessions have to be repeated to maintain the improvement. If the sessions required are too frequent, for example monthly, then it becomes too inconvenient for the patient. In our protocol, maintenance sittings are required every 6 months. This time gap is long enough for the patient to follow and thus prevent recurrence of melasma.

Conclusion

Oral TXA at the dose of 250 mg twice daily is found to be a promising modality for the treatment of melasma. It is the only agent that acts by inhibiting UV light-induced melanocyte activation, hormone-induced melanocyte proliferation, VEGF-induced neovascularization, and mast cell-induced basement membrane damage.[19] It can be used both as a standalone therapy and in conjunction with other modalities. It can improve the results achieved by lasers and IPL.[16]

Considering effects of TXA at various levels of melanogenesis in melasma, it has a definite place in the treatment of this frustrating condition. Further studies are required to standardize the dose and duration of oral TXA in melasma. Large studies need to be done in various ethnic groups. In addition, studies need to be done for the ideal dose, concentration, and frequency of intradermal TXA injections. In conclusion, TXA has proven to be an essential tool in the armamentarium against melasma.

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