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Short Communication

Topical Tranexamic Acid with Microneedling In Melasma

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Melasma, also known as chloasma or mask of pregnancy, is a common, acquired, hyperpigmentary disorder usually affecting females. It is characterized by irregular, light or dark brown macules in sun-exposed areas symmetrically involving the face, neck and less commonly, the hands and the forearms [1]. Though the exact pathomechanism of melasma is unknown many etiological factors have been implicated in its causation and aggravation [2-4].

It results in cosmetic disfigurement and adversely affects the quality of life. The overwhelming cosmetic impact for many patients leads to tremendous emotional and psychosocial distress and results in seeking treatment. Both medical and procedural therapeutic options are available for its management. Besides the routine use of broad spectrum sunscreens, various topical therapies are used for the treatment of melasma [5]. Chemical peels and lasers have also yielded good results in melasma but carries a risk of post inflammatory hyperpigmentation (PIH) especially in the darker skin types [5,6]. Some systemic therapies have also been tried in the form of vitamin C, glutathione, tranexamic acid and melatonin [7]. Despite the availability of a wide variety of therapeutic options its treatment remains challenging as pigmentation may fade but often recurs.

Melasma being a recurrent and refractory problem requires an appropriate and judicious use of medicines which are effective and can be used for longer time without significant side effects. Various new therapies and medicines are constantly being discovered and tried for the same.

Tranexamic acid in melasma

Tranexamic acid, a synthetic derivative of amino acid lysine is an anti fibrinolytic agent used for treating blood loss during surgery and in various medical conditions. It inhibits the plasminogen activator by reversibly blocking the lysine binding sites on both plasminogen and plasmin, a molecule responsible for degradation of fibrin which is a protein that forms the framework of blood clots. Classically TA has been used systemically (oral and intravenous) at a dose of 0.5–1.5 g three times daily for controlling the blood loss. The commonly reported side effects of TA are nausea, diarrhoea, vomiting and orthostatic hypotension. Rarely, disturbances in colour vision, anaphylactic shock, skin reaction, and acute renal cortical necrosis have also been documented. No harmful fetal effects have been reported. TA has no effect on coagulation parameters and the theoretical thrombotic risk is very low. The risk may be higher if the patient has pre-existing morbidity, old age, is on other prothrombotic drugs (e.g., oral contraceptive pills), or have hereditary protein C and protein S deficiency, use of very high dose and long duration of TA.

Human keratinocytes secrete the urokinase type plasminogen activator, which increases the activity of melanocytes *in vitro*. Tranexamic acid is believed to act in melasma by preventing the activation of melanocytes from ultraviolet (UV) light, hormones and injured keratinocyte through the inhibition of plasminogen activator system present in epidermal basal cells and keratinocytes. It also reduces melanocyte tyrosinase activity by suppressing the production of prostaglandins and has an additional effect on the dermal blood vessels as it decreases the angiogenesis via inhibition of vascular endothelium growth factor (VEGF) (Figure 1). By all these actions it not only improves the melasma, but may also reduce the likelihood of recurrence [8-10].

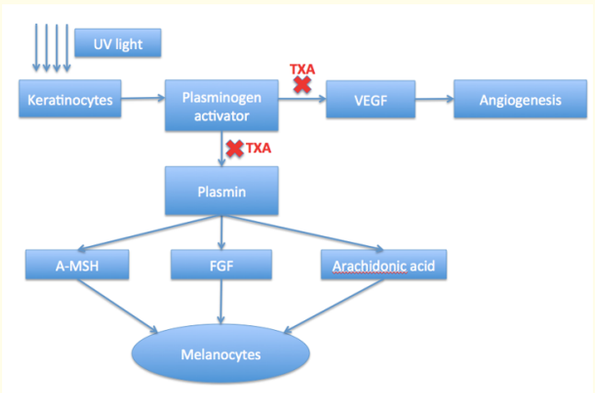

Figure 1: Mechanism of action of Tranexamic acid in melasma. TXA- Tranexamic acid, VEGF- Vascular endothelial growth factor, FGF- Fibroblast growth factor

Orally, the dose used in melasma is much less i.e. 250 mg twice a day and studies have shown fewer adverse effects at such low dose [7]. But in the clinical practice a lot of patients are found to be reluctant in taking oral medications for a longer duration as compared to topical medication. So, Topical TA was tried and have shown a tremendous effects. Maeda K., *et al*. (1998) were the first ones to study the effect of plasmin inhibitor, trans-4-aminomethylcyclohexanecarboxylic acid (Tranexamic acid) (trans-AMCHA), on skin pigmentation induced by UV exposure in Weiser-Maples guinea pigs. The guinea pigs on exposure to UV radiation (840 mJ/cm^2); usually show increasing skin pigmentation from seven days after exposure to 29 days. Post-exposure applications of 2 and 3% solutions of trans-AMCHA to the exposed regions prevented the pigmentation process. The histopathological examination after staining by the Fontana-Masson method showed a significantly reduced melanin content in the basal layer of UV-exposed epidermis where 2 and 3% trans-AMCHA solutions had been applied, compared with the vehicle control [9].

There are many studies of topical uses of TA in various concentrations for melasma. Studies by Kondou., *et al*, Ebrahimi., *et al*, Kim., *et al*. with topical 2%, 3% and 2% TA emulsion respectively showed significant improvement at the end of the study and no significant side effect was recognized [10-12]. Whereas a study by Ayuthaya., *et al*. with topical 5% TA did not show any significant benefit but caused more irritation to the applied area [13].

Topical tranexamic acid have shown some local side effects of itching, burning and erythema which may hinder the long term use and also lead to reduction in patient compliance [8,14].

Tranexamic acid has also been used with transdermal drug delivery methods like intralesional microinjections and microneedling. In Intralesional microinjections, tranexamic acid is injected directly into the dermis whereas in microneedling, a device known as dermaroller is used to deliver tranexamic directly into the dermis.

Microneedling in melasma

Microneedling is a relatively new minimally invasive procedure involving superficial and controlled puncturing of the skin by rolling with miniature fine needles. Traditionally used as a collagen induction therapy for facial scars and skin rejuvenation, it is also widely used now as a transdermal delivery system for therapeutic drugs and vaccines. As compared to intralesional injections, it is relatively painless and provides a uniform administration of drug. It enhances the delivery of various drugs across the skin barrier as it bypasses the stratum corneum and deposits the drug directly up to the vascularised dermis. It has also been shown to cause significant widening of the follicular infundibulum by 47%, which may partly explain the increased penetration of the medication across the skin barrier. Various drugs have been used in melasma along with Microneedling like vitamin-C, glutathione, tranexamic acid etc [15].

Microneedling has also been used alone for melasma. This was based on the observation of improvement in melasma in patients who underwent microneedling for acne scars [16]. Lima., *et al*. was the first to investigate the clinical, quality of life, colorimetric and histological improvement in facial melasma with the addition of microneedling to the classic treatment showing the effect of microneedling in recalcitrant melasma. As it promotes fibroblast proliferation and upper dermal collagenesis, microneedling can restore upper dermal and basal membrane damage in melasma, disfavouring the contact of melanocytes with dermal released melanogenic stimuli as endothelin, stem cell factor and hepatocyte growth factor. Additionally, a thicker epidermis can promote additional protection against UV damage [15,16].

This effect of microneedling is contrary to the fact that such procedures like microneedling, lasers and chemical peels causing microtrauma are expected to lead to resultant PIH with a background of a hypermelanosis. The exact physiogenesis process behind the skin lightening remains unclear. It has to be used cautiously in the patients of Fitzpatrick skin type- IV and V along with religious use of sunscreen to prevent the consequential PIH.

Microneedling with tranexamic acid in melasma

Various studies of Microneedling with tranexamic acid have shown remarkable results in the past without significant side effects. A randomised, open label, comparative study of TA microinjections and TA with microneedling by Budamakuntla., *et al*. in patients of melasma where treatments were done 3 times at monthly intervals (0, 4 and 8 weeks) by 4mg/ml TA & followed up for a further 3 months showed 35.72% improvement in the MASI score in the microinjection group compared to 44.41% in the microneedling group. No recurrence was seen on follow up.8 Another randomized, self-controlled, split face study by Yang., *et al.* was done where one side of face was treated with topical TA 0.5% along with functional microarray of microneedles and other half was control, treated with a sham device plus topical TA at 4 weekly interval (0, 4, 8 and 12 weeks) showed that pretreatment with a functional microarray of microneedles significantly increase the effectiveness of topical TA in treating melasma, and the combined therapy is safe and painless, without obvious side effects. Transepidermal water loss, roughness, skin hydration, skin elasticity, and erythema index showed no significant differences between 2 sides [17].

A study of 100 patients conducted by Sharma., *et al*. comparing the therapeutic efficacy of 250 mg twice daily oral TA vs local infiltration of TA of 4mg/ml given at 4 weekly intervals (0, 4, 8 and

12 weeks) showed both treatment methods were equally effective, with an average reduction of MASI at 12 weeks of 77.96 ± 9.39 in group A and 79.00 ± 9.64 in group B [18]. This study claims topical intradermal TA to be as effective as oral TA.

Topical TA is much safer and freer from systemic adverse effects of oral TA, still a few studies have shown local side effects. Other physical therapies, like microneedling when used along with conventional TA therapy had an added effect and also leads to improvement in the skin texture and results in better patient satisfaction. Adding microneedling along with TA helps to reduce the frequency of TA application and hence the persistant local side effects due to topical treatment.

There is no consensus on the optimum route, dose and timing of the treatment with topical TA in melasma. When used along with microneedling, the frequency of the treatment depends on the size of the dermaroller used i.e the needle size. The effect could be maintained by repeating the procedure once in 3 months or 6 months along with strict photo protection in the form of physical sunscreen.

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