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Tranexamic Acid in the Treatment of Melasma: A Comprehensive Review of Topical, Intradermal, and Oral Administration

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ABSTRACT

A malfunction in human melanogenesis called melasma causes the epidermis to become hyperpigmented in certain regions of the body gradually. It significantly affects physical appearance, results in psychological and physiological distress, and diminishes those impacted individuals' quality of living. In order to restrict blood loss, tranexamic acid (TA), a plasmin inhibitor, is used for stopping unusual fibrinolysis. It works by permanently inhibiting lysine binding sites on plasminogen molecules, which prohibits plasminogen activator (PA) from converting plasminogen to plasmin. It seems sense that tranexamic acid might have an impact on keratinocyte association and function because plasminogen is additionally found in human epidermis basal cells and owing to the fact that PA has been shown to be produced by cultivated human keratinocytes. A comprehensive review of the literature demonstrates that although TA is administered by topical, oral, and intradermal injection as well as utilized as an adjuvant therapy Added to the laser therapy to treat melasma, its effectiveness has not been sufficiently proved. To fully understand the function of TA in the management of melasma, additional investigation is required.

KEYWORDS: tranexamic acid; hyperpigmentation; melisma.

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INTRODUCTION

Mostly affecting women in their 20s to 40s, melasma is an acquired pigment condition characterized by enhanced melanogenesis and vascularization. It manifests as light-to-dark brown spots and macules on sun-exposed facial regions. Although the exact etiopathogenesis is unknown, hormone imbalances, drugs, UV exposure, and family history have all been linked to the condition [1]. Depending on the level of melanogenesis, there are three different forms of melasma: epidermal, dermal, and mixed [2]. The Melasma Area and Severity Index (MASI) and modified Melasma Area and Severity Index (mMASI) have been verified and used as a usual outcome assessment of melasma effectiveness in therapy. accurate techniques for assessing melasma severity [3].This technique takes into account the homogeneity, darkness, and dimension of melasma in four distinct facial regions.

Melasma treatment is challenging, and relapse is typical. The majority of therapies seek to reduce either the depth of melanocyte migration and melanogenesis. Topical lightening medications such as retinoids,mequino, azelaic acid, kojic acid, and hydroquinone are some of the conventional initial treatments for melasma. The most successful topical treatment is triple therapy cream, which combines hydroquinone, tretinoin, and corticosteroid [4]. Chemical peels and laser therapy are examples of further second-line treatments. Dermatologists frequently employ a variety of therapies, each with varied degrees of effectiveness. All melasma treatment regimens will contain sunblock because sun protection is an essential component of melasma therapy.

One potential therapy for this challenging illness is tranexamic acid (TA). It had previously been employed to treat bleeding disorders and is a synthetic lysine precursor that prohibits plasmin from operating. Because UV radiation promotes plasmin activity in keratinocytes, it may result in a rise in melanocytic-stimulating mediators which includes α-melanocyte stimulating hormone and arachidonic acid.

plasmin plays an essential part in melasma. This UV-induced plasmin activity can be inhibited by TA.

TA has been extensively studied as a therapy for pigment conditions as well as to its conventional application in disorders of hemorrhage. Studies have also demonstrated that TA may stop the production of paracrine melanogenic substances, as usually function to activate melanocytes, hence reducing the production of melanin. TA also reduces endothelin-1-induced angiogenesis and Vascular Endothelial Derived Growth Factor (VEGF), which lessens the appearance of pigmentation. TA is a topical in nature, transepidermal, intradermal, and oral treatment for melisma [5]. This review aims to describe the various TA methods of administration and their effectiveness in comparison to conventional treatments.

INTRADERMAL AND TOPICAL TRANEXAMIC ACID

The effectiveness of topical tranexamic acid for treating melasmahave evaluated by numerous research. 5 out of 6, among these research required relatively minor sample sizes ranging from 13 to 50 participants, notable variations in Melasma Area and Severity Index (MASI) scores have been studied after and before therapy. Assessment of the severity and extent of melisma is done by MASI score. It suggest that topical TA treatment had a positive impact on improving the MASI scores and reducing melasma in the treated individuals. [6].

Many treatment regimens and topical formulations have been used in studies evaluating the effectiveness of (TA) for melasma treatment. These include:

a. 3% TA cream applied for three months.
b. 5% TA gel applied for three months.
c. 3% TA solution utilized for three months.
d. 5% TA liposome applied for three months..
e. 2% TA formulation used for three months..

Its TA is effective in reducing MASI scores and reducing dyschromia (abnormal skin pigmentation). Using various treatment and formulations durations can lead to positive consequences in terms of brightening melasma pigmentation and improving the severity of the case as assessed by MASI scores. [3].

There was typically a lack of significant changes between the placebo (vehicle) and different (TA) formulations .A routine of dexamethasone and topical HA, and intradermal injections of TA suggest that the effectiveness of topical TA is analogous to usage of hydroquinone topically [7].

Another study involved 18 women who were divided into two groups: one group received weekly intradermal TA injections, and the other group received twice-daily topical TA. Although the improvement was greater with those perceiving intradermal and there were no significant differences in the two groups' objective improvements according to the measurements. further research need to investigate the effectiveness of intradermal. [7].

The MASI scores dropped after 8 and 12 weeks, according to a study on one hundred women who experienced weekly intradermal TA microinjections for 12 weeks. [8]. Similar results were obtained from analyzing sixty women who got every week of TA intradermally, used silymarin lotion, or underwent peeling by glycolic acid [9]. although MASI improved in all groups, the intradermal TA group improved the minimum in contrast to the other groupings.

In an additional investigation, 37 patients participated in a randomised split-face trial where the application of local HA and intradermal TA were compared. Each side of the face was treated for three months with nightly hydroquinone or every month doses of TA intradermally. After a month of treatment, TA showed superior outcomes. But after twenty weeks of treatment, there were no discernible changes in the overall modifications between the two groups.[10].

Their split-face, controlled experiment contrasting intradermal TA with hydroquinone cream included a total of 49 participants. There was no noticeable difference between the treatments after twenty-four weeks of twice-daily hydroquinone or every two weeks TA injections in the decreased MASI scores. It will require more double-blinded, controlled experiments to thoroughly assess the effectiveness of intradermal TA. [11].

ORAL TRANEXAMIC ACID

On the other hand, oral TA has started to demonstrate greater potential in the management of melasma. Nine studies were finished between 2011 and 2016. Despite the absence of placebo groups in any of these investigations, some of them claimed that oral TA was efficient according to patient reviews or higher MASI scores [3]. More clinical investigation has been finished since 2016 total. One of them, which is absent from a control group, discovered that oral TA increased MASI scores by 69%. However, within two months of quitting the oral TA, 72% of patients suffered a return of melasma. This happened inspite the usage of combined topical skin brightening solutions.

A study that used a placebo-controlled experiment found that utilizing oral TA for three months resulted in higher MASI scores (49%) compared to using a control (18%). Again, after ninety day of stopping the treatment and using sunscreen instead, improvements in individuals with severe melasma were reversed. [12].

Another study that used a placebo-controlled experiment discovered that oral TA was linked to a fifty percent improvement at twelve week as opposed to a 5.9% improvement in the group that received a placebo. Although a placebo group has been used in some recent trials, more thorough research is still required. Following the end of oral

TA, many of these trials noted a resurgence of dyschromia. [4].

In general, oral TA was tolerated well by patients, with gastrointestinal issues being the most frequent side effects. [12].

More severe adverse effects such DVT, acute renal cortex necrosis, acute MI, and PE were infrequent because of the low dose of oral TA used. It would be advised to perform a detailed patient history and relevant laboratory monitoring methods to check for coagulation hazards, which may include factor V Leiden, coagulation times, protein C, protein S, and antiphospholipid antibody. [12].

SAFETY AND SIDE EFFECTS

This type of therapy must be advised as a systemic medicine owing to its plasmin inhibitory mechanism of action while with precaution. [14]. Therefore, healthcare professionals must check all patients for color blindness, cerebral hemorrhage, traumatic events, and history of thromboembolic events as well as active thrombotic illness [14].

Gastrointestinal issues are oral TA's most frequent negative effects. Menstrual abnormalities were an adverse effect in oral TA studies as well. DVT, abrupt renal cortical necrosis, acute myocardial infarction, and PE are some of the more severe adverse effects. Given the lesser TA doses utilized in melasma patients, these are uncommon. Before beginning this medication, it is essential to perform a baseline a complete history of the patient evaluation and the appropriate laboratory screening procedures can be used to look for clotting risk factors. Additionally, healthcare professionals should exercise caution while providing oral TA in light of the COVID-19 pandemic. Using this drug may make the SARS-CoV-2 virus more likely to advance and cause respiratory failure, microthrombic events, and hypercoagulability. [15].

INTRALESIONAL TRANEXAMIC ACID INJECTIONS

Small needles are used to inject TA into the dermis at a dosage of 4 mg/ml with injections spaced 1 cm apart. This procedure is known as mesotherapy, or intralesional injections of TA. 4 mg/ml is the most typical concentration for intralesional therapy. Melasma can be effectively treated with the use of intralesional TA. Direct delivery of the target drug and equipment availability are advantages of intralesional TA, whereas its drawbacks include a small surface area, a longer injection time, and a need for a competent hand. (Table 1) [16].

Dosage form	dosing	benefit	Disadvantage	Side effects
oral	Tablet available as 650mg thus may need to be spilt into 325mg tablets twice daily	can cure severe melisma that has not responded to previous treatments	overall adverse effects Thromboembolic event risk and the requirement for screening for hypercoagulable conditions	Abdominal aches, bloating, tinnitus, and headaches are frequent.
topical	5% cream 2% cream	better tolerated than alternative topical treatments	Possibly ineffective in severe melasma sometimes takes many weeks for the results to appear	Non
Micro needling	TXA solution at 4 mg/ml 1.5 mm needle depth with a dermapen or dermaroller for 5% TXA and 10% TXA.	Product is evenly distributed and penetrates the dermis. Noninvasive has additional skin advantages like minimizing the look of scars and fine lines and wrinkles minimal time for healing	Requires special tool and associated cost	Burning Itching
Intralesional	4 mg/ml TXA solution	deep epidermal penetration of a concentrated medication without systemic absorption	Requires skilled hand	Bruising Hypopigmentation

SAFETY AND SIDE EFFECTS

Tranexamic acid injection side effects include erythema, hypopigmentation, and discomfort and burning at the injection sites [16] Intralesional TA caused the emergence of a vitiligo like macule on the lip in one case, and 3 every month intra lesional 5 mg/ml TA injected in the face caused the appearance of hypopigmented asymptomatic macules over the arms and wrist in the other case. Some repigmentation happened after the TA injections were stopped. [17].

MICRONEEDLING WITH TRANEXAMIC ACID

Local formulations can penetrate deep in the skin thanks to microneedling, which also stimulates the creation of collagen and the secretion of growth factors. Microwounds are typically created at a depth of 1.5 mm in the skin. Many different tools can be used for microneedling. Dermarollers allow the device to roll across the skin without having to remove it, whereas dermapens only allow the needles to puncture the epidermis where a device is placed. Entire face is often rolled over by clinicians multiple times in various directions. TA microneedling frequently uses 4 mg/ml TA. Topical TA can be applied evenly and more deeply into the dermis thanks to microneedling. This technique has the advantage of being a reasonably rapid and non-invasive way to apply TA to the skin. [18].

SAFETY AND SIDE EFFECTS

For most patients, discomfort, itchiness and erythema from microneedling with TA last for roughly 1-2 days. [18].

CONCLUSION

Melasma is a mutual skin problem that is hard to cure and has a high risk of recurrence. TA is a medication available in topical, intralesional, and oral forms that is used off-label to treat refractory melasma. With thorough screening, oral medication is an efficient and secure treatment for melasma. Intralesional injections and microneedling with topical TA ,exhibit equivalent effectiveness to oral therapy whereas limiting general adverse effects, despite the fact that some patients may be reluctant to begin an oral medication. Both approaches have comparable efficacies and few side effects when it comes to minimizing the appearance of melasma. Despite being minimally invasive, relatively painless, and requiring the purchase of a particular tool, microneedling may cause increased itchiness and discomfort

On the other hand, intralesional injections require expert injectors, more specialized equipment, and may cause more pain than microneedling as well as potential hypopigmentation. The least effective TA treatment was topical TA therapy. However, this technique of treatment for melasma has few negative effects and can be used in conjunction with other cosmeceuticals. In individuals who might not tolerate HQ, clinicians should think about administering topical TA. For refractory or severe melasma, intralesional TA injections or oral TA may be used in addition to laser or light therapy or as a substitute. It is significant to highlight that many of the trials didn't contain additional monitoring, making it challenging to determine the treatments' long-term efficient and safe. Furthermore, there is no established dosage for TA, and it is challenging to compare studies because they all used unique dosages and concentrations. Additional placebo-controlled, randomized are necessary to assess the long-term safety and effectiveness of each approach.

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