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Review Article

# The Efficacy and Safety of Oral Tranexamic Acid (TXA) in the Treatment of Melasma

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## Abstract

Melasma is a disfiguring skin disease that is often challenging to treat. Treatments options including topical remedies, laser therapies and systemic medications vary widely in efficacy and tend to display safety concerns. Systemic tranexamic acid has been widely feared in practice as a treatment option, despite growing evidence in literature of its high efficacy and safety in the management of melasma. In this article, we discuss the efficacy and safety of oral tranexamic acid in the treatment of melasma.

**Keywords:** Melasma; Chloasma; Tranexamic Acid; Hydroquinone; Tretinoin

## Introduction

Melasma, also known as chloasma, is an acquired pigmentary disorder of the skin predominantly affecting women, up to a third of child-bearing age [1]. Typically presenting on sun-exposed areas such as the face, melasma is characterized by light brown to blue-grey coloured, irregular, reticulated macules that cause visible disfigurement and hence can affect an individual's self-esteem and quality of life [2]. Key factors that play a role in the pathogenesis of melasma include genetic predisposition, chronic ultraviolet exposure, and female hormone stimulation [3]. Treatment of melasma can be very challenging due to the high relapse rate. Growing evidence suggests that melasma is a disease of melanocytes but also due to surrounding photoaged, damaged skin. Hence, therapeutic options often target the activity of melanocytes, surrounding inflammation and damaged tissue due to photoaging. Combination topical therapies such as hydroquinone, tretinoin, and corticosteroids have been the mainstay treatment for melasma with better efficacy than monotherapy [4]. However, complications secondary to topical agents, especially hydroquinone, have been reported and include post-inflammatory hyperpigmentation, irritant dermatitis, allergic contact dermatitis, and nail bleaching. Systemic treatment with tranexamic acid (TA) has been one of the novel therapies for managing melasma due to its multimodal mechanism of action [3]. Safety concerns of TXA inducing thromboembolism have limited its use in the routine management of melasma. This article reviews the literature to assess the safety and efficacy of TXA in the management of melasma.

### Tranexamic acid: Mechanism of action

Tranexamic Acid (TXA) is a synthetic derivative of the amino acid lysine and harbours antifibrinolytic properties by competitively blocking lysine binding sites on plasminogen molecules, and effectively inhibiting the activation of plasmin [5]. Consequentially, fibrin degradation is halted and that contributes to lessening of bleeding in conditions such as menorrhagia. Blood coagulation and its cascade however remain unaffected. Key to melasma, TXA

has been shown to have properties that inhibit ultraviolet-induced melanogenesis and surrounding neovascularization by disrupting plasmin activity [6]. Na., *et al*. [7] conducted a study of 22 women with melasma and an 8-week course of oral TXA. They demonstrated key histological changes including decreased epidermal pigmentation, mast cell numbers, and numbers of vessels or vascularization. These findings suggest a multimodal function of TXA in the management of melasma, targeting epidermal and dermal factors of melasma such as vascularization and mast cell involvement.

## Tranexamic acid: Safety

The safety profile of TA and the risks of adverse effects, especially thromboembolism, have continuously limited its systemic use. According to the electronic medicines compendium (2018), the risk of thromboembolism from systemic TXA use is categorized as rare, which is defined as possibly occurring in at least one in 10,000 to less than one in 1000. Other rare adverse effects include allergic skin reactions and visual disturbances. Meadi., *et al*. [8] reviewed 63,896 Danish women who had taken a course of oral TXA with a median filled prescription of 15g per user. When comparing oral TXA use versus non-use, they reported that the adjusted incidence rate ratios of venous thromboembolism and arterial thrombosis are 4.0 and 1.3 respectively. Crucially, the number needed to harm per five days of treatment with TXA was 78,549, which they concluded was an acceptably high figure. A meta-analysis by Zhang., *et al*. [9] assessed 21 studies that looked at the safety profile of oral TXA in the treatment of melasma. The majority of reported side effects were gastrointestinal symptoms such as heartburn, nausea, and abdominal discomfort. There were some reports of oligomenorrhoea, allergic skin reactions, headache, hypopigmentation and anxiety. No cases of thromboembolism were reported, however. A retrospective study by Lee., *et al*. [10] looked at 561 patients who took oral TXA for the management of melasma. They reported transient adverse effects in 7.1% with the exception of a single case of deep vein thrombosis that was later diagnosed with familial protein S deficiency.

## Tranexamic acid: Efficacy in melasma

The use of tranexamic acid to treat melasma was accidentally discovered by Nijo Sadako whilst studying its effect on treating chronic urticaria in the 1970's [11]. Zhang., *et al*. [9] conducted a key meta-analysis of 21 studies, involving 1563 adults randomized in trials of single or adjuvant TXA for the treatment of melasma. There was statistically significant reductions in Melasma Area and Severity Index (MASI) and Melanin Index (MI) scores. Five of the included studies looked at the effects of oral TXA alone on melasma and showed statistically significant reductions in MASI scores. The daily systemic doses of TXA across all the studies included ranged from 500mg to 700mg. A systematic review by Kaur [12] reviewed 14 studies that studied oral TXA's role in melasma with or without topical adjuncts. Despite using variable TXA doses and course durations, the studies do suggest that oral TXA can be effective in reducing melasma either as single therapy or with topical adjuncts. As an example**,** a 46-year-old female patient was seen in our local community dermatology clinic with 3 years history of mid-facial bilateral hyperpigmented macules consistent with melasma. She normally takes zolmitriptan and propranolol for migraine and levothyroxine for hypothyroidism. She does not have a personal or family history of venous thromboembolism. Figure 1 (left) shows the hyperpigmented macules on both cheeks and also involving the forehead. She tried topical Azelaic acid 20% and Retinoic acid with no noticeable improvement. We prescribed her a 3-month course of TXA 250mg BD. Upon follow up and completion of the course, macules were no longer visible on examination, as evidenced on figure 1 (right). There were no reported side effects or complications [13].

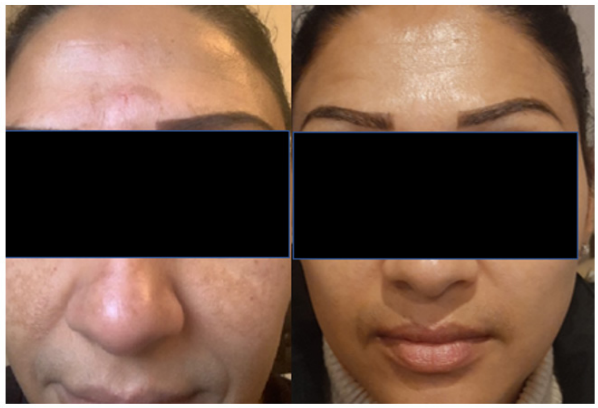

**Figure 1:** Left: Melasma in patient prior to treatment. Right: Patient after 3-month course of oral TXA.

## Conclusion

Tranexamic acid is an effective agent in the treatment of melasma, either as stand-alone or adjunct therapy. Serious adverse

effects, such as venous thromboembolism, associated with the systemic use of TXA are rare. With appropriate counselling and careful history taking, TXA can be prescribed safely in the management of melasma.

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