

Case Report

Treatment-Resistant Melasma Response to Oral Tranexamic Acid

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Abstract

Melasma, a common acquired hyperpigmentation disorder primarily affecting facial skin, poses significant therapeutic challenges due to the limited efficacy and potential side effects of available treatments. Tranexamic Acid (TXA), traditionally used for its hemostatic properties by inhibiting plasminogen activation, has emerged as a promising addition to protocols for treatment-resistant melasma. This study aims to evaluate the efficacy and safety of TXA in combination with Hydroquinone (HQ) and Kojic Acid (KA) in patients with treatment-resistant melasma. We present here a case series of fourteen patients with recurrent melasma refractory to common treatments who achieved successful outcomes with the addition of TXA to their treatment regimen. These patients received 650 mg of TXA in combination with 16% HQ and 6% KA. All patients exhibited a symmetrical reduction in their hyperpigmented patches following treatment and no significant adverse effects were reported. These cases contribute valuable input to the growing body of evidence on the use of TXA for melasma and the combination of treatments and dosing, suggesting its potential as a therapeutic option for this condition. Further research is warranted to explore the mechanisms by which TXA exerts its beneficial effects in melasma and to determine the optimal treatment protocols for achieving effective clinical outcomes.

Keywords: Melasma; Tranexamic Acid

Introduction

Melasma is an acquired hyperpigmentation disorder characterized by asymptomatic light to dark brown patches with symmetrical distribution and irregular borders, primarily affecting the face. It predominantly affects women and individuals with darker skin tones [1]. Factors such as UV light exposure, genetic predisposition and hormonal changes contribute to its pathogenesis [1].

The most common presentation involves centrofacial involvement, including areas such as the forehead, nose and upper lip, while typically excluding the philtrum, cheeks and chin [1,2].

Treating melasma remains challenging due to the limited efficacy and potential side effects of available therapies, as well as the high likelihood of relapse after treatment cessation [2]. The primary approach to melasma treatment involves inhibiting melanocyte proliferation and melanosome formation while enhancing their degradation [2]. Hydroquinone, a tyrosinase inhibitor, has traditionally been the preferred treatment, either alone or in combination with retinoic acid or corticosteroids, known as “triple combination therapy” [2,3]. Triple therapy, typically consisting of hydroquinone 4%, tretinoin 0.1% and dexamethasone 0.1%, has shown the highest efficacy in melasma treatment, although ongoing research focuses on optimizing concentrations and formulations [2]. Other treatment modalities, such as chemical peels, dermabrasion and laser therapy, are associated with irritation and a high likelihood of relapse [2,3].

Given these challenges, there is a need for new therapeutic options. Tranexamic Acid (TXA) has recently emerged as a promising treatment for melasma. Known primarily as a hemostatic agent, TXA functions by inhibiting plasminogen activation through reversible blockade of lysine-binding sites on plasminogen molecules, thereby impeding the conversion of plasminogen to plasmin [2,4]. Although the precise mechanism of TXA in melasma treatment remains unclear, it is hypothesized that TXA may

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hinder melanin synthesis by disrupting the interaction between keratinocytes and melanocytes and reducing the vascularity implicated in melasma pathogenesis [4].

This case report aims to contribute to the existing literature by documenting fourteen cases of treatment-resistant melasma that have achieved statistically significant successful outcomes through the addition of TXA to their existing protocols, often including HQ and KA. We detail the past treatment protocols that were ineffective for these patients and outline the screening protocols used for the prescription of TXA. We highlight two patients of the cohort in detail.

Case Report

All fourteen patients selected for this series were treated between 2019 and 2024. Each were asked about their personal and family medical history with special attention paid to past histories of pregnancy, birth control use, smoking, clotting disorders, NSAID use, breast cancer, medications, dermatological conditions, allergies and previous treatments they had attempted. All had failed on HQ at lower levels of concentration from 12% to 20%. No patients had a personal or family history of clotting disorders except for patient #2 who had a mother with a clotting disorder.

Most of the fourteen patients were placed on 650 mg of oral TXA along with 16% HQ and 6% KA cream, except for one being on a combination of 16% HQ and Pracasil instead (patient #12). Two patients were eventually increased to 975 mg of oral TXA (patients #2 and #7), another two had their HQ increased to 18% (patients #11 and #13) and one patient was also given tretinoin 0.1% (patient #4). No side effects were reported by these patients except for patient 5 who had a sensitivity to kojic acid (Table 1).

The MASI scores for these patients were given by analyzing the original clinical scans taken upon presentation and the scans taken at the most recent follow up appointments utilizing Visia skin analysis. Examples can be seen in Fig. 1,2. Due to the significant variance in the consistency of treatment length, appointment regularity, stopping and starting treatment during season changes, surgeries and vacations, we were unable to provide a reliable or meaningful measure of length of treatment to MASI score improvement. Clinically, excellent results were commonly noticeable by both clinician and patient within 1-2 months of treatment.

Patient #	Age	Pre, Peri or Menopause	Years of Melasma Burden	Failed Treatments	TXA Regimen	MASI before TXA	MASI using TXA (most recent)
1	51	Peri	3	HQ 8-12%, IPL	HQ 16%/KA 6% Cr, TXA 650 mg qd	10.8	1.2
2	49	Pre	6	HQ 8-12%/KA 6% Cr	HQ 16%/KA 6% Cr, 975 TXA qd	6	1.2
3	39	Pre	15	OTC products	HQ 16%/KA 6% Cr, TXA 650 mg qd	25.2	2.4
4	52	Peri	10	HQ 12%/KA 6% Cr, YAG laser, IPL, tretinoin	HQ 16%/KA 6% Cr TXA 650 mg qd, tretinoin 0.1%	20.1	9
5	61	Menopause	8	HQ 4-16%/KA 6% Cr, tretinoin, Gemini, IPL	HQ 16%/KA 6% Cr, TXA 650 mg qd	21.3	1.2
6	43	Pre	4	OTC products	HQ 16%/KA 6% Cr, TXA 650 mg qd	13.2	0
7	54	Pre	15	HQ 18% & Retin A, Halo laser.	HQ 16%/KA 6% Cr, 975 TXA qd	30	0
8	37	Pre	6	HQ 8-16%/KA 6% Cr, Retinol, IPL	HQ 16%/KA 6% Cr, TXA 650 mg qd	12.3	0.6

9	47	Pre	Unknown	Unknown	HQ 16%/KA 6% Cr, TXA 650 mg qd	18	5.7
10	45	Pre	9	HQ 12%/KA 4% Cr, tretinoin 0.1%, Obaji	HQ 16%/KA 6% Cr, TXA 650 mg qd	12	1.2
11	46	Pre	Unknown	HQ 16%/KA 6 Cr, IPL, OTC products	HQ 16%/KA 6% Cr TXA 650 mg qd, Then increased to HQ 18%	15.9	9
12	58	Menopause	11	HQ 8-20%/KA 6% Cr, Fraxel, IPL	HQ 16%/Pracasil, TXA 650 mg qd	19.8	8.4
13	40	Pre	1	Unknown	HQ 18%, TXA 650 mg qd	16.2	5.4
14	62	Menopause	Unknown	HQ 16%/KA 6% Cr	HQ 16%/KA 6% Cr, TXA 650 mg qd	21.3	3.5

Table 1: Summary of patient demographics, failed treatments, TXA regimen and MASI scores before and after treatment.

The details of two patients in particular are discussed in the sections below:

Patient 4

A 52-year-old female with a history of resistant melasma began treatment with oral Tranexamic Acid (TXA) in April 2021. She was prescribed a regimen of TXA 650 mg once daily, in combination with 16% HQ, 6% KA cream and tretinoin 0.1%. Her medical history included Gastroesophageal Reflux Disease (GERD), migraines, hypothyroidism, rosacea, hypertension and an elbow replacement. She also had a history of a facelift. Her current medications were omeprazole, levothyroxine and lisinopril. She reported no allergies, no history of nicotine use and consumed alcohol 2-3 times per week. There was no known personal or family history of bleeding or clotting disorders, Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) or breast cancer. She had two pregnancies and was in the perimenopausal stage.

The patient's melasma was first documented approximately ten years prior to her presentation. Upon presentation, she exhibited hyperpigmentation on her forehead, nose and cheeks. Her MASI score at this time was measured at 20.1. Prior treatments included HQ 12%, KA 6%, YAG laser, foto-facial and tretinoin, none of which provided lasting improvement. At her follow-up appointment in October 2022, she reported excellent results with minimal residual hyperpigmentation on the lateral cheeks bilaterally. Her MASI score at this time was measured at 9.0. No significant side effects were reported throughout her treatment.



Figure 1: A 52-year-old female with a history of resistant melasma began treatment with oral Tranexamic Acid (TXA).

Patient 5

A 61-year-old female presented with melasma that had been resistant to previous treatments. She began treatment with oral Tranexamic Acid (TXA) in August 2022, at a dosage of 650 mg once daily, along with 16% HQ and 6% KA cream. Her medical history included hypertension, depression, hypothyroidism, keloids and Aspirin-Exacerbated Respiratory Disease (AERD), also known as Samter's triad. Her current medications were lisinopril, pravastatin, citalopram, levothyroxine, Celebrex (as needed), Xyzal, Symbicort, Spiriva and Vitamin D. She reported allergies to latex, kojic acid and NSAIDs. She did not use nicotine, consumed alcohol occasionally and used NSAIDs as needed. There was no personal or family history of bleeding or clotting disorders, Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) or breast cancer. She had six pregnancies, with four resulting in miscarriage. The patient was in the postmenopausal stage.

The earliest documentation of her melasma was in February 2014, indicating an 8-year history of the condition. She presented with symmetric hyperpigmented patches on her cheeks and her MASI score at this time was measured at 20.3. Previous treatments included varying concentrations of HQ (4%, 8%, 10%, 12% and 16% twice daily), 6% KA, tretinoin, Gemini laser therapy and cautery. These treatments led to temporary improvements followed by flares and recurrences, with the patient being sensitive to KA.

At her first follow-up in October 2022, she reported a 90% improvement and expressed high satisfaction with the results. By the next follow-up in April 2023, she continued to show excellent results, with sustained improvement and no significant side effects reported throughout the treatment. Her MASI score at this time was measured at 1.2.



Figure 2: First follow-up and reported a 90% improvement and expressed high satisfaction with the results.

Discussion

Findings

These case reports highlight the potential efficacy of oral TXA as an adjunct treatment for patients with melasma unresponsive to traditional therapies. All patients experienced marked improvements in their condition with a significant mean MASI score reduction of 13.8 (p -value=0.000003335). These results are best considered as support for continued and more detailed research regarding the use of oral TXA for treatment-resistant melasma, due to the paucity of data we were able to provide regarding the treatment to MASI score improvement timeline. Our findings suggest that TXA may be a valuable addition to melasma treatment, particularly for treatment-resistant cases. Notably, the majority of patients in the study previously failed to see results with high-concentration HQ and KA but showed substantial improvement when oral TXA was incorporated, emphasizing its role as an effective adjuvant therapy. No side effects from the treatment regimen were noted from any patients with the exception of one patient who noted a sensitivity to the KA.

Further investigation is warranted to assess the long-term benefits and safety of TXA in a larger patient population.

Mechanisms and Administration of TXA

TXA, a plasmin inhibitor, can be administered orally, via intralesional injection, through microneedling or topically to treat melasma [2]. While concerns about the pro-coagulant properties of TXA and the potential for thromboembolic events exist, recent research offers reassurance.

Safety and Side Effects

A meta-analysis by Jung, et al., involving 667 patients across 11 studies, found no thromboembolic events among patients receiving low-dose oral TXA [2]. The most common side effect was oligomenorrhea, with other reported effects including

abdominal cramps, palpitations, urticarial rash with angioedema and headache [2]. Despite the low incidence of adverse effects, caution is advised, especially in patients with a history of thromboembolic events or those using oral contraceptives [5]. Intralesional injection and microneedling with TXA reduce systemic side effects, though pain and erythema at the injection site are common and intralesional injection may cause hypopigmentation [2]. Topical TXA has fewer side effects but may cause erythema, irritation, xerosis and scaling [2]. Notably, a comparison study demonstrated that irritation was more common with hydroquinone than with topical TXA [2].

Efficacy Assessment

TXA has demonstrated effectiveness in melasma treatment, with reductions in Melasma Area Severity Index (MASI) scores observed in various studies. A meta-analysis by Jung, et al., reported an average MASI score reduction of 1.60, with oral TXA showing the greatest effect, followed by injectable and topical TXA [2]. TXA, as an adjunct to traditional therapies, further reduced MASI scores, highlighting its potential utility in managing refractory cases [2].

Lack of Standardization

The absence of standardized dosing and treatment guidelines for TXA in melasma treatment poses challenges. A meta-analysis suggested an optimal oral TXA dosage of 750 mg/day for 12 weeks, but variations in dosage and duration across studies complicate comparisons [6,7]. Further large-scale, randomized controlled trials are needed to establish standardized protocols and long-term safety profiles. Comparative studies between triple therapy and TXA, as well as research on optimal treatment durations to prevent relapse, are essential to advance melasma management.

Conflict of Interests

The authors declare they do not have conflicts of interest.

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