Prescribing practices of tranexamic acid for melasma: Delphi consensus from the Pigmentary Disorders Society

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Abstract

Introduction: There is ambiguity regarding usage of tranexamic acid for melasma in India, be it in its pre-administration evaluation, administration route, dosing or monitoring. Hence, we conducted this study to understand various tranexamic-acid prescribing patterns and provide practical guidelines.

Materials and methods: A Google-form-based questionnaire (25-questions) was prepared based on the key areas identified by experts from the Pigmentary Disorders Society, India and circulated to practicing dermatologists across the country. In rounds 2 and 3, the questionnaire was re-presented to the same group of experts and their opinions were sought. The results of the practitioners' survey were denoted graphically alongside, to guide them. Consensus was deemed when at least 80% of respondents chose an option.

Results: The members agreed that history pertaining to risk factors for thromboembolism, cardiovascular and menstrual disorders should be sought in patients being started on oral tranexamic-acid. Baseline coagulation profile should be ordered in all patients prior to tranexamic-acid and more exhaustive investigations such as complete blood count, liver function test, protein C and S in patients with high risk of thromboembolism. The preferred oral dose was 250 mg orally twice daily, which can be used alone or in combination with topical hydroquinone, kojic acid and sunscreen. Repeated dosing of tranexamic-acid may be required for those relapsing with melasma following initial tranexamic-acid discontinuation. Coagulation profile should ideally be repeated at three monthly intervals during follow-up, especially in patients with clinically higher risk of thromboembolism. Treatment can be stopped abruptly post improvement and no tapering is required.

Limitation: This study is limited by the fact that open-ended questions were limited to the first general survey round.

Conclusion: Oral tranexamic-acid provides a valuable treatment option for melasma. Frequent courses of therapy may be required to sustain results and a vigilant watch is recommended for hypercoagulable states during the course of therapy.

Key words: Delphi; India; melasma; tranexamic acid

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Plain Language Summary

Tranexamic acid is a molecule that may be used in oral, injectable and cream formulations for the treatment of melasma. However, there is ambiguity in the right dose, duration of therapy and its place in the therapeutic armamentarium. Thus, we conducted a study, in which we asked dermatologists from across the country about their prescribing practices, experiences and observations with the use of this molecule. We presented these findings to a group of experts dealing with melasma and other disorders of hyperpigmentation and asked their opinion on the use of tranexamic acid. We considered a consensus to have been reached if more than 80% of experts had an agreeable opinion. Those opinions, which did not reach a consensus, were re-presented to the experts in another round. At the end of this round, experts agreed that: a history and work up of coagulation disorders must be obtained prior to therapy. Tranexamic acid tablets were the preferred route and formulation of administration, and this can be combined with other de-pigmenting creams and sunscreens. Repeat dosing may be required to prevent relapse and have a sustained response.

Introduction

Melasma is a common dermatosis of hyperpigmentation, which causes considerable psychological burden and morbidity.[1] Although number of therapeutic modalities have been tried, lately tranexamic acid has become an important treatment option in melasma. The use of tranexamic acid in melasma was an accidental discovery by Nijo *et al*. in 1979 in a patient with urticaria.[2] Further, the identification of the vascular component in melasma pathogenesis led to its rapid and widespread usage.[3] However, there is a lack of guidelines on its usage, and its pattern of utility varies far and wide.[4] There is also a doubt on its utility as a stand-alone agent vis-à-vis as an adjuvant with other therapies.[5] The molecule has been formulated in oral, topical and intradermal preparations, although all may not be as popular or effective.[6] This was an attempt by the Pigmentary Disorders Society of India to explore the prescribing patterns of tranexamic acid for melasma in India; and arrive at a consensus among experts about its usage.

Materials and Methods

A physical meeting of a group of experts in the field of melasma was held by the Pigmentary Disorders Society in the month of May 2022 at New Delhi. The members identified key research areas pertaining to the usage of tranexamic acid in melasma. Then a multiple-choice questionnaire, wherein more than one option could be selected, was formulated with the help of Google forms (Google Inc, California, USA). The Google forms also had an option to suggest any additional area that participants felt was important.

First round

The 25 questions framed by the experts were circulated among practicing dermatologists across India. The only inclusion criterion was that they must have had either a post-graduate degree or diploma in dermatology, and there was no restriction on the age of participants or the type of practice. The questionnaire was open from July to August 2022. Their individual opinions and experiences were collected, analysed and depicted in the form of bar graphs.

Second and third rounds

The Delphi technique involves sending repeated rounds of questionnaires to a panel of experts and stakeholders, in order to reach a consensus. The anonymous responses provided by each are tallied and presented at subsequent rounds so as to guide decision making. An advantage of this technique is that equal weightage is given to all participating members.

In the second and third rounds, the questions from round one were re-circulated to experts. Alongside each question, the bar charts depicting the opinions of practitioners were presented to guide the decision of experts. The questionnaires for each round can be found in Supplementary Table 1.

Results

Round one

A total of 425 participants across the country answered the first round of the study questionnaires. The common opinion (359, >80%) has been presented in Table 1. Slightly more than half (223, 52.5%) of the participants felt that oral tranexamic acid was second only to hydroquinone in the armamentarium against melasma. More than 80% felt that oral tranexamic acid should be used in combination with sunscreen. In decreasing order, the barriers to the prescription of oral tranexamic acid were an unfavorable risk profile (156, 36.7%), possibility of medicolegal complication (101, 23.8%), difficulty in counseling patients (92, 21.6%) and investigations adding to the cost of therapy (69, 16.2%). Sixty four percent felt that dermatoscopic examination helped to determine their choice of therapy. History pertaining to the intake of oral contraceptive pills, oral anticoagulants and history of cardiovascular disease was thought to be essential by 70–80% of the respondents. A majority (282, 66.4%) felt that exhaustive baseline investigations prior to oral therapy are required only in high-risk cases.

Table 1: Summarizing the common opinion among the respondents of the first round of the study

Choice of therapy in melasma depends on • Extent and severity of melasma • Previous therapies taken
History regarding risk factors for thromboembolism to be taken before starting oral tranexamic acid in melasma patients
Oral tranexamic acid should preferably be used in combination with sunscreen in treating melasma
Preferred dosing of oral tranexamic acid in melasma is 250 mg twice a day
Relapse is seen in melasma patients after stopping tranexamic acid therapy

The general prescription of oral tranexamic acid was for 3 months (193, 45.4%) to 6 months (239, 56.2%). More than half (228, 53.6%) of the participants would repeat a course of oral tranexamic acid in practice. The commonest side effects seen with this formulation were oligomenorrhoea (152, 35.8%), abdominal cramps (78, 18.4%) and headache (71, 16.7%). Twenty five to fifty percent reduction in melasma severity had been observed in 176 (41.6%) patients with oral therapy.

Forty eight percent (204) felt the order of preference of formulations was oral, followed by topical formulation and intradermal. The most common adverse effect observed with topical and intradermal formulation of tranexamic acid was irritation/erythema (163, 38.4%), pain (78, 18.4%) and rebound by perpigmentation (72, 16.9%).

Other than melasma, tranexamic acid was commonly used by practitioners to treat post inflammatory hyperpigmentation (86, 20.2%), lichen planus pigmentosus (72, 16.9%), Reihl's melanosis (68, 16%) and periorbital hyperpigmentation (54, 12.7%).

Rounds two and three

Sixteen experts from across the country participated in the second and third rounds of this study. Their average age was 45.8 ± 9.7 years, 12 (75%) saw 10–30 patients of melasma in a week and 60% of them worked in teaching institutes or government hospitals. The experts, on an average, had 17.6 ± 9.1 years of experience post-graduation, and had been prescribing tranexamic acid for melasma for an average of 31.6 ± 24.3 months.

The consensus reached among the experts has been tabulated in Table 2. More than 80% felt that oral tranexamic acid can be combined with sunscreen, hydroquinone and kojic acid. Half of the participants felt that oral tranexamic acid can be given to all patients of melasma, who do not have any contraindications. An oral dose of 250 mg twice a day was preferred by 11 (68.8%). The prescription duration should be for 6 months as per 9 participants (56.2%), others advocated a shorter duration of treatment. Eleven (69%) participants felt that courses of oral tranexamic acid should be repeated often. Three quarters of the participants suggested an interval of 6 months prior to repeat therapy. Among the agents that could be combined with oral tranexamic acid—triple combination, azelaic acid and antioxidants reached 60–70% of the consensus.

Table 2: Summary of statements reached among experts

Summary of statements on which >80% agreement was reached among experts
History to be taken before starting oral tranexamic acid in melasma patients: • Risk factors for thromboembolism • History of cardiovascular disease/coronary artery disease • Menstrual disorders
Oral formulation of tranexamic acid is preferred over topical and intradermal routes of administration for treating melasma
Oral tranexamic acid be used in combination with • Sunscreen • Hydroquinone • Kojic acid
Coagulation profile should be ordered before starting oral tranexamic acid in patients of melasma
All baseline investigations (hemogram, liver function tests, renal function tests) prior to oral tranexamic acid initiation is required in selected patients with high risk only
Coagulation profile should be repeated at three monthly intervals during follow-up visits in melasma patients being treated with oral tranexamic acid
Oral tranexamic acid in melasma patients may be stopped right away in practice, without need for tapering
Statements which had 60–80% agreement among the experts
Oral tranexamic acid should be used in combination with • Triple combination • Azelaic acid • Antioxidants
Complete hemogram should be ordered before starting oral tranexamic acid in melasma
Preferred dosing of oral tranexamic acid for melasma is 250 mg twice a day
Courses of tranexamic acid need to be repeated often to treat melasma
Tranexamic acid should be repeated after an interval of 6 months

Discussion

Given the wide variation in literature and clinical practice, we undertook this study to understand the prescribing patterns of tranexamic acid in India. We then questioned the experts on the said gray areas and elicited their opinions, while providing them with a glimpse of the current trends in practice.

Prior studies with histological evaluation of melasma patients treated with tranexamic acid have shown a reduction in the vascular density post treatment.[7] A dilemma in the minds of many is whether to prescribe tranexamic acid exclusively for those with a significant vascular component to their melasma or to all patients. However, tranexamic acid also inhibits melanin synthesis via the plasminogen/plasmin and autophagy pathways.[8] Thus, it may be effective even in those without significant telangiectasia prior to therapy, thus, half of the experts felt that it could be given to all patients without any contraindications. Thirty eight percent opined that it can be used in those with a vascular component, whereas 13% opined that it can be used in all cases.

The idea of giving a systemic agent that alters the coagulation pathway for the treatment of a cosmetic indication may hinder its routine prescription. However, earlier studies have shown that the risk of thrombosis is low in patients on tranexamic acid therapy, at doses used for melasma, and is likely to occur in those with a high risk for thrombosis such as hypercoagulability, prior pulmonary embolism and immobilization.[9] Both practitioners and experts in our study deemed eliciting this history important, prior to the initiation of therapy. In addition, experts felt the need to include menstrual history

so as not to adversely affect those with already scant menstrual bleeding.[10] Experts also felt that a coagulation work up was necessary at the baseline and subsequent follow up, to be repeated at three monthly intervals, while the patient is on therapy.

A network meta-analysis had identified 250 mg thrice a day dosing of oral tranexamic acid for 12 weeks, as optimal in the therapy of melasma.[11] However, practitioners from across the country preferred a dose of 250 mg twice a day. In a randomised double blinded monocentric controlled clinical trial in Brazil, it was observed that 250 mg twice daily, oral tranexamic acid had improved the melasma severity in 50% of the patients.[12] A similar response rate was observed by practitioners. Three quarters of experts (12) felt that oral tranexamic acid can be repeated every 6 months. This frequency probably provides an optimal balance between good compliance to treatment and maintenance of efficacy.[13]

In a retrospective study among women in California who were prescribed 650 mg tranexamic acid twice a day for melasma, it was seen that headache (2.4%), malaise, gastrointestinal upset (4.8%) and menstrual irregularities (4.8%), were the most common side effects. This is similar to the trends observed by dermatologists in our country at lower doses.[14]

Topical tranexamic acid was next in popularity to the oral formulation. The most common adverse effects seen with topical tranexamic acid by practitioners were erythema and irritation. Although this may be true, a review of the literature revealed that topical tranexamic acid had a lower rate of irritation compared with topical hydroquinone, and thus may be a safe therapeutic option.[15]

Prior studies have shown that a combination of oral tranexamic acid and triple combination cream could achieve a faster and sustained improvement in melasma.[16] Similarly, its combination with platelet-rich plasma had been found to achieve a better reduction in the mMASI score and patient satisfaction score, as compared to being used alone.[17] Our experts also concurred that a combination of triple combination and oral tranexamic acid was effective. The experts also opined that sunscreens provide an added benefit in the therapy of melasma, when combined with tranexamic acid. Literature reveals 3% topical tranexamic acid is better compared to 20% azelaic acid as a combination agent with oral tranexamic acid.[18] However, no consensus could be reached regarding the co-utilization of both topical and oral formulation of tranexamic acid.

This study is limited by the fact that open-ended questions were limited to the first general survey round.

Conclusion

The aim of this Delphi consensus was to analyse the trends in the prescription of tranexamic acid for melasma patients in India, and seek the consensus opinion among experts in gray areas. tranexamic acid may provide a valuable therapeutic option in melisma that can be combined with topical agents. According to this consensus, the preferred oral dose of tranexamic acid is 250 mg orally twice daily, to be taken for a period of 6 months. Although dermoscopic examination may help identify the vascular component, it isn't a must to initiate therapy. The therapy may need to be repeated to sustain the response. Until further evidence emerges, a coagulation profile is recommended both before and trimonthly during the treatment with oral tranexamic acid, especially in high-risk patients.

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Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

MeSH terms

melasma, tranexamic acid, pigmentary disorders society, delphi.

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