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Review Article

A review of oral treatments for melasma

黃褐斑口服治療綜述

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This article aims to evaluate current literature reporting on the efficacy and safety of oral agents in melasma management. An electronic search of publications via PUBMED database was conducted. The search only included clinical trials in the English language until 1 November 2019. This review is limited by small number of high-quality prospective studies each with small patient numbers. Significant heterogeneity in study design concerning study duration, concurrent treatments and outcome measures was present. Irrespective of melasma duration, oral tranexamic acid 500 mg daily appears to be a safe and effective treatment either as monotherapy or as an adjunct treatment.

本文旨在評估現有口服藥物在黃褐斑治療中的有效性和安全性的文獻報告。通過 PUBMED 數據庫對出版物進行了電子搜索，搜索僅包括截至 2019 年 11 月 1 日的英語臨床試驗。本綜述受限於少數高質量前瞻性研究內的患者人數皆很少。研究設計在研究持續時間、同步治療和結果測量方面存在顯著異質性。無論黃褐斑持續時間長短，或作為單一療法還是輔助療法，每天口服 500 毫克氨甲環酸似乎是一種安全而有效的治療方法。

Keywords: Dermatology, melasma, tranexamic acid

關鍵詞：皮膚科、黃褐斑、氨甲環酸

Introduction

Melasma, also known as chloasma, is a commonly acquired hypermelanosis usually involving the face. The prevalence of melasma is approximately 1% in the general population and 9-50% in those with an increased risk for developing the condition.[1] Familial predisposition, ethnicity, darker skin types, pregnancy and varying levels of UV exposure are contributing aetiological factors.[2]

Melasma is a chronic cosmetic disease with a high impact on quality of life.[3] Treatment modalities are multiple, can be complex and are constantly evolving to cater to the unmet needs of patients worldwide.[1] Current available treatments for melasma include topical agents, oral medications, device-based and a combination of treatment methods targeting various phases of its pathogenic process such

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as inflammation, vascularity, photodamage and melanin production and transfer.[1] It has been widely recommended that the management of melasma take a multifaceted approach, with first-line treatments comprising UV protection and topical whitening agents.[4,5]

For half a century now, hydroquinone has been the gold standard in topical agents for the treatment of hyperpigmentary conditions including melasma, backed by robust data proving its efficacy and safety.[6,7] Other topical lightening agents for melasma include azelaic acid, kojic acid, ascorbic acid, retinoids, corticosteroids, niacinamide, liquorice, undecylenoyl phenylalanine, 4-N-butylresorcinol, soybean, arbutin, glucosamine and mequinol.[8] Chemical peels with glycolic acid, Jessner's solution and retinoic acid are common adjuvant therapies but can occasionally result in rebound melasma or post-inflammatory hyperpigmentation (PIH) especially in dark-skinned individuals. In patients with refractory melasma, laser and light therapies are becoming increasingly popular third-line treatment options but suffer similar pigmentary risks as chemical peels. Commonly used device-based therapies for melasma include intense pulsed light (IPL), Q-switched lasers, pico lasers, non-ablative and ablative lasers.[9] Recent years have seen a surging interest in the use of oral agents for melasma. Lauded for convenience, efficacy and safety, such agents include tranexamic acid, *Polypodium leucotomos* extract and various flavonoids.

Tranexamic acid, which was initially found to inhibit bleeding, was later discovered that through the inhibition of the plasmin/plasminogen pathway, firstly it was able to block the melanocyte-keratinocyte interaction, which in turn inhibited epidermal melanocyte tyrosinase activity; and secondly it decreased the production of inflammatory mediators which stimulate melanocyte activity.[10] Tranexamic acid has also been shown to decrease pigmentation caused by UV radiation through blocking UV-induced plasmin activity and arachidonic acid production.[11] Furthermore, tranexamic acid interferes with mast cell activity, which is involved in the degradation of type IV collagen and basement membrane components.[12,13] Lastly, tranexamic acid stops fibroblast growth factor-induced neovascularisation.[14] *Polypodium Leucotomos* extract, when administered orally is known to reduce UV-induced pigmentation through its antioxidant and photoprotective properties.[15,16] Flavonoids, due to their structure, interact with the copper ions of the tyrosinase active site to inhibit the functional capacity of the enzyme.[17,18]

We aim to review and update on these oral agents for melasma.

Methodology

A search via PUBMED database was conducted for articles written in the English language until 1 November 2019, with the medical subject headings of "melasma", "chloasma" and "oral treatment". The search only included clinical trials. All papers identified in the PUBMED search were reviewed, and bibliographies were hand-searched for more papers.

Results

Forty-five articles were identified, with twenty-nine papers excluded as they either did not include oral treatments for melasma, or they were irrelevant to the topic of interest. Sixteen manuscripts were reviewed in this paper. The overwhelming preponderance of data was on the use of oral tranexamic acid for melasma and it is summarised in Table 1. Table 2 summarises other oral agents that have been used in melasma. Results in Tables 1 and 2 report only objective results, with subjective results excluded. Concurrent therapies, adverse reactions and side effects have also been excluded from the tables.

Various scoring systems were used to assess melasma in the studies.

Table 1. Tranexamic acid (TXA) as oral agent for melasma

Study (First author, year)	Study design & duration	Dose	Study outcome
Karn et al. 2012.[23]	6-month prospective, interventional RCT (treatment for 3 months, then 4-weekly reviews for 3 more months)	250 mg BD	MASI **With TXA:** *Baseline:* 11.08±2.91 *8 weeks:* 8.95±2.08 (19.2% reduction) *12 weeks:* 7.84±2.44 (29.2% reduction) **Without TXA:** *Baseline:* 11.60± 3.40 *8 weeks:* 9.9±2.61(14.7% reduction) *12 weeks:* 9.26±3(20.2% reduction)
Wu et al. 2012.[24]	12-month cohort study (treatment for 6 months then follow-up for 6/12)	250 mg BD	Assessor & patient ratings at 6 months Excellent: 10.8% Good: 54% Fair: 31.3% Poor: 4.1% 12 months: 9.5% recurrence of varying degrees
Cho et al. 2013.[25]	8-month retrospective review of medical records	500 mg OD	mMASI **With TXA:** *Baseline:* 11.33±7.07 *8 months:* 6.21±5.04 *Decrease:* 43.8% ± 22.1%; *Baseline & 2-3 weeks after IPL treatment: Decrease:* 30.1% ± 21.1% **Without TXA:** *Baseline:*11.70±6.72 *8 months:* 8.93± 5.89 *Decrease:* 23.6% ± 22.1%; *Baseline & 2-3 weeks after IPL treatment: Decrease:* 13.6% ±14.3%
Na et al. 2013.[26]	8-week prospective open-label study	250 mg TDS	**Melanin Index** *Lesional skin Baseline:* 191.48; *4 weeks:* 186.14 *8 weeks:* 184.82; *Perilesional skin Baseline:* 120.30; *4 weeks:* 126.24 *8 weeks:* 129.70 **Erythema Index** *Lesional skin Baseline:* 272.15; *8 weeks*: 255.00 *Perilesional skin Baseline:* 216.64; *8 weeks:* 231.14
Shin et al. 2013.[27]	8-week prospective RCT	750 mg OD	mMASI (intention-to-treat analysis) **With TXA** *8 weeks*: 2.9 score decrease (8.0±4.3-5.1±3.3); *4 weeks post treatment:* 38.1±22.1% reduction **Without TXA** *8 weeks:* 1.9 score decrease (7.9±3.9-6.0 ±3.2); *4 weeks post treatment:* 21.9±18.5% reduction Melanin Index at 8 weeks (intention-to-treat analysis) **With TXA** 166.5±49.6-157.5±56.9 decrease **Without TXA** 163.1±44.6-158.1±28.7 decrease
Aamir et al. 2014.[28]	12-month prospective, interventional cross-sectional study (6 months treatment then months follow-up)	250 mg BD	Recurrence of any variant at 12 months 87% no recurrence, 12% recurrence
Li et al. 2014.[29]	16-week prospective, open-label study	2 tabs TDS (dose unspecified)	V Value (undefined by authors) *Baseline:* (7.16±0.42)/(6.21±0.54); *4 weeks:* (7.44±0.32)/(6.77±0.37); *8 weeks:* (7.47±0.24)/(6.79±0.31) *;12 weeks:* (7.60±0.22) 0.22)/(7.01±0.28); *16 weeks:* (7.67±0.28)/(7.10±0.36) V Value difference from baseline *4 weeks:* (0.29±0.40)/(0.55±0.50); *8 weeks:* (0.30±0.39)/(0.56±0.47); *12 weeks:* (0.45±0.36)/(0.82±0.51); *16 weeks:* (0.49±0.41)/(0.86±0.57)
Lee et al. 2016.[30]	54-month retrospective review of medical records	250 mg BD	Degree of Improvement Worsened: 0.4%; Unchanged: 10.0%; Improved: 89.7%; Initial time to response was 2 months and the median duration of treatment was 4 months. 27.2% relapse rate.

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Table 1. Tranexamic acid (TXA) as oral agent for melasma (cont'd)

Study (First author, year)	Study design & duration	Dose	Study outcome
Lajevardi et al. 2017.[31]	6-month parallel-group, double-blind, RCT (3 months treatment followed by 3 months follow-up)	250 mg TDS	MASI **With TXA:** *Baseline:* 14.4±8.4; *1 month:* 35% reduction from baseline; *3 months:* 51% reduction from baseline; *6 months:* relapse rate of 30% ***Without* TXA:** *Baseline:* 10.7±6.2; *1 month:* 21% reduction from baseline; *3 months:* 33% reduction from baseline; *6 months:* relapse rate of 26%
Sharma et al. 2017.[32]	12-week prospective RCT	250 mg BD	MASI **With oral TXA:** *Baseline:* 12.25±4.44; Week 4: 21.29±17.24% reduction; Week 8: 53.32±16.50% reduction; Week 12: 77.96±9.39% reduction **With intradermal TXA:** *Baseline:* 11.29±6.07; Week 4: 18.27±15.34% reduction; Week 8: 51.32± 17.20% reduction; Week 12: 79.00±9.64% reduction
Del Rosario et al. 2018.[33]	6-month prospective RCT (intervention for 3 months, then off intervention for 3 months)	250 mg BD	mMASI **With TXA** *3 months:* 49% reduction - *Moderate melasma:* 45% reduction; *Severe melasma:* 51% reduction *6 months:* 26% reduction - *Moderate melasma*: 32% reduction; *Severe melasma:* 21% reduction **With placebo** *3 months:* 18% reduction - *Moderate melasma:* 16% reduction; *Severe melasma:* 19% reduction *6 months:* 19% reduction - *Moderate melasma:* 13% reduction; *Severe melasma:* 24% reduction Melanin Index (MI) *Baseline to 12 weeks:* Greater reduction in Group TXA; *24 weeks:* Lower scores than baseline in both groups
Khurana et al. 2019.[34]	6-month prospective, randomised, open label study (treatment for 3 months followed by follow-up for 3 months)	250 mg BD	MASI **With oral TXA** *Baseline:* 7.48±3.73; *6 months:* 3.18±1.93% *improved:* 57.48; *% of patients with worsening of lesions at the 6-month follow-up from baseline:* 6.25 **With intralesional TXA** *Baseline:* 4.11±2.69; *6 months:* 2.32±2.56% *improved:* 43.55; *% of patients with worsening of lesions at the 6-month follow-up from baseline:* 9.37 % Grading of Treatment Response **With oral TXA** >50% improvement: All patients (100%); >75% improvement: 8 patients (25%) **With intralesional TXA** >50% improvement: 17 patients (53%) >75% improvement: 3 patients (9%)

Table 2. Other oral agents for melasma

Study (First author, year)	Study design & duration	Dose	Study outcome
Ni et al. 2002.[36]	1-month prospective cohort study	25 mg of Pycnogenol (French maritime pine bark) TDS	Melasma area (mm^2) Baseline: 68.65±44.06; Day 30: 42.79±35.59; Decrease: 25.8±20.39 Pigmentary intensity (unit) Baseline: 2.10±0.71; Day 30: 1.63±0.61; Decrease: 0.47±0.51 3-point semi-quantitative scale (melasma area & pigmentary intensity collectively) 2: markedly improved (23.33%); 1: effective (56.67%); 0: ineffective (20.00%)
Yamakoshi et al. 2004.[37]	1-year prospective open design study	67 mg of GSE (54 mg of proantho-cyanidin) TDS. There was a mandatory one-month break mid-way in the study. SE = Grape-seed extract	L (lightening) value of melasma using reflectance spectrophotometer (measured monthly) Baseline: 57.84±2.48; 6 months: 59.25±2.31; 12 months: 58.70±2.52 MI (calculated monthly) Baseline: 0.025±0.005; 6 months: 0.019±0.004; 12 months: 0.021±0.005 Size (length & width) using electronic callipers (measured monthly) Baseline: L 4.42±0.82 mm W 4.44±0.93 mm; 6 months: L 4.10±0.71 mm W4.07±0.77 mm; 12 months: L 4.26±0.6 mm W 4.17±0.78 mm
Handog et al. 2009.[35]	8-week prospective RCT comparing oral procyanidin with vitamins A, C, E versus placebo	24 mg procyanidin, 6 mg of Vit A precursor, 60 mg Vit C, and 15 IU of Vit E. BD.	MI Measured at baseline, week 4 and week 8. Decreased significantly across all **with procyanidin** group participants at weeks 4 and 8. Exact figures unspecified. MASI Measured at baseline, week 4 and week 8. Decreased significantly in both groups. Exact figures unspecified.
Ahmed et al. 2013.[38]	12-week prospective RCT comparing *Polypodium leucotomos* extract versus placebo	240 mg TDS	Melanin Index **With *Polypodium leucotomos* extract** Baseline: 43; Week 6: 35; Week 12: 30.62 (28.8% improvement from baseline) **With Placebo** Baseline: 53; Week 6: 47.5; Week 12: 45.68 (13.8% improvement from baseline) MASI **With *Polypodium leucotomos* extract** Baseline: 14.4; Week 6: 11.0; Week 12: 11.0 **With Placebo** Baseline: 13.2; Week 6: 10.8; Week 12: 10.2

The Melasma Area and Severity Index (MASI) scoring system, as developed by Kimbrough-Green et al, is the most common outcome measure adopted in clinical trials.[19] This tool accounts for subjective evaluations of four regions of the face: forehead (30%), right malar region (30%), left malar region (30%) and chin (10%), and considers aspects of area of involvement (A), darkness (D) and homogeneity (H). The area of involvement in each of the four regions is given a score from 0 to 6 (0= no involvement; 1=<10%; 2=10%-29%; 3= 30%-49%; 4=50%-69%; 5=70%-89%; and 6=90%-100%), whilst darkness and homogeneity are both scored from 0 to 4 (0=absent; 1=slight; 2=mild; 3=marked; and 4=maximum) for each corresponding region. The MASI score, ranging from 0 to 48, is then calculated using the following algorithm: $[0.3(D+H)]_{A(forehead)} + [0.3(D+H)]_{A(left\ malar)} + [0.3(D+H)_{A(right\ malar)} + [0.10(D+H)]_{A(chin).}$[20]

The MASI scoring system was assessed for its reliability and validity by Pandya et al and revealed difficulties in assessing individual components of the algorithm, particularly in homogeneity and the chin. As part of the validation process of MASI using ANOVA models, Pandya et al proposed the mMASI scoring system with the exclusion of the homogeneity component to produce a more consistent scoring system. Evaluation of the chin was retained as it is essential to assessment of the face and with only 10% representation of the total score, it was deemed to cause little change to the score. The mMASI score ranging from 0 to 24, was proposed to be calculated as follows: $[0.3D]_{A(forehead)} + [0.3D]_{A(left\ malar)} + [0.3D)_{A(right\ malar)} + [0.10D]_{A(chin).}$[20]

A narrow-band reflectance spectrophotometer is used to measure the Melanin Index (MI) and Erythema Index (EI). The spectrophotometer reflects light onto the subjects' skin and a Red-Green-Blue sensor assesses the intensities of each light reflected back, which is then used to calculate the MI and EI scores as follows:[21]

$$MI = 100 \times \log \frac{1}{I_{red}}$$ [22]

$$EI = 100 \times \log \frac{I_{red}}{I_{green}}$$ [22]

Studies in this paper that adopted the MI and EI outcome measurements used either the Mexameter® or the Minolta CM-2600d spectrophotometers.

Lightening (L*) value, which assesses the skin's darkness (0) or lightness value (100) was adopted in one study using the Minolta CM-2600d spectrophotometer.

Discussion

This review included twelve studies (ten prospective, two retrospective) on oral TXA comprising of 1380 participants.[23-34] The largest pool of 561 participants came from a retrospective review by Lee et al.[30] Participants were mainly Asians, but also included cases of Hispanic and Middle Eastern ethnicity. A few studies examined the characteristics of the melasma in subjects;[23,28,32,34,35] not unexpectedly, the predominant pattern was epidermal followed by mixed and then dermal. Supplementation of 500 mg oral TXA to mainstream therapies such as hydroquinone, intense pulsed light and Q-switched Nd:YAG laser doubled the effectiveness in treating melasma, as suggested in one retrospective study and two prospective randomised controlled trials. Notwithstanding the disparity in daily dosages adopted (three studies looked at 750 mg while nine looked at 500 mg), all papers reported significant improvements from baseline across all outcome measures. The longest duration of oral tranexamic acid was studied by Aamir.[28] Adverse effects were uncommon but the most frequently reported were menstrual (irregularities were observed in no higher than 18.2% of subjects in any paper) and gastrointestinal disturbances (highest observed

incidence was 22.7% in a 6-month prospective open-label study).[33] We try to ascertain the lowest effective dose by comparisons within individual outcome measures.

Four studies reported with the MASI scoring system.[31-34] Comparison between efficacy outcomes at the third month were conflicting over the two doses.[23,31,32] At six months, participants on 750 mg/day demonstrated a greater relapse rate than those on 500 mg/day, perhaps contributed by Fitzpatrick skin type, melasma duration and distribution (relapse rates of 30% and 6.25% respectively).[31,34] It is important to note that the former study was double-blinded whereas the latter was open-label. Interestingly, two studies that compared oral and intralesional tranexamic acid demonstrated superiority in MASI improvements at weeks 4, 8 and 24 with oral treatment.[32,34]

Three studies used the mMASI scoring system.[25,27,33] Score reductions were 2.9 at two months with 750 mg/day,[27] and 5.12 at eight months,[25] and 4.2 at three months with 500 mg/day.[33] As studies looked at different timeframes from baseline, it was difficult to decisively conclude on the more efficacious dosage. Three studies reported with the MI scoring system.[26,27,33] At the two-month mark, MI scores reduced by 6.66,[26] and 9 ($p=0.23$)[27] with 750 mg/day. The 500 mg/d group saw greater MI score reductions than placebo although values were unspecified.[33]

Five studies reported mean melasma duration, with four reporting ranges between three and six years and one study reporting a duration of 13 years. Participants demonstrated significant improvements at 3 and 6 months, suggesting that a longer melasma duration did not have any impeding effect on drug efficacy.

Four studies investigating non-TXA oral agents (*Polypodium leucotomos* extract, the proanthocyanidins family including the French maritime pine bark and Vitamins A, C and E) were identified.[35-38] The efficacy of the oral agents was assessed by looking at outcome measures such as MASI, MI and melasma area, pigmentary intensity and L values; clinical evaluations and patient self-assessments. Only two were placebo controlled. Although an overall trend towards improvement with active intervention was observed, patient self-assessments in the controlled studies failed to report significant improvements. In the three studies on proanthocyanidins family, dosages and outcome measures adopted varied widely rendering it difficult to make any meaningful conclusion on the efficacy of this class of supplement in treatment of melasma.[35-37]

Limitations

This review is primarily limited by the small number of high-quality prospective studies, each with small patient numbers. Except for the study by Del Rosario, all the prospective tranexamic acid studies were not controlled with placebo, and only included patients without previous interventions. Indirect head-to-head comparisons made in the discussion must be interpreted with a high degree of caution due to significant heterogeneity of study designs. Wide variations were noted in study duration and outcome measures. Data on concurrent treatments suffered from lack of clarity in dosing regimens and consistency in dosing. Caucasians and Afro-Caribbeans were excluded from all studies. Therapeutic compliance to interventional and adjuvant therapies was not evaluated in any study.

Conclusion

Oral tranexamic acid at 500 mg/day is shown in this review to be a safe and effective treatment for melasma. As the therapy has been shown to be highly promising, large-scale multicentre double-blind placebo-controlled studies on oral tranexamic acid for melasma in all ethnicities using validated objective (mMASI) and patient-centred (MelasQOL)

scoring systems, preferably with long-term (beyond six months) extension studies on the safety and maintenance of efficacy of oral tranexamic acid should be considered.

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