Randomized, placebo-controlled, double-blind study of oral tranexamic acid in the treatment of moderate-to-severe melasma

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Background: Melasma is a common pigmented disorder that is often difficult to treat. Tranexamic acid (TA) has emerged as a promising treatment for melasma; however, few controlled studies exist.

Objective: To determine the efficacy of oral TA in patients with moderate-to-severe melasma.

Methods: Patients with moderate-to-severe melasma were treated with 250 mg of TA or placebo capsules twice daily for 3 months and sunscreen followed by 3 months of treatment with sunscreen only. The primary outcome measure was the modified Melasma Area and Severity Index (mMASI) score.

Results: A total of 44 patients were enrolled and 39 completed the study. At 3 months, there was a 49% reduction in mMASI score in the TA group versus 18% in the control group. Patients with severe melasma improved more than those with moderate melasma. Three months after treatment was stopped, there was a 26% reduction in mMASI score in the TA group compared with the baseline visit versus a 19% reduction in the placebo arm. No serious adverse events were noted in either group.

Limitations: Single-center study enrolling predominantly Hispanic women.

Conclusions: Oral TA appears to be an effective treatment for moderate-to-severe melasma with minimal side effects. (J Am Acad Dermatol 2018;78:363-9.)

Key words: evidence-based medicine; Hispanic; melanin; melasma; pigmentation; randomized controlled trial; tranexamic acid.
METHODS

This study was approved by the University of Texas Southwestern (UTSW) Medical Center Institutional Review Board; all patients gave written, informed consent. Subjects were recruited through interviews on local English and Spanish language television stations, as well as through flyers posted on the UTSW campus. Eligibility criteria were female sex, age 18 or older, and moderate or severe melasma. Moderate melasma was defined as that with a modified Melasma Area and Severity Index (mMASI) score of 5.8 to 7.9 and severe melasma cases were defined as those with a mMASI score of 8 or higher on the basis of previously defined ranges for melasma severity.8 Exclusion criteria are provided in Table I; they include items listed by the US Food and Drug Administration as contraindications to the use of TA.

Patients were screened by telephone and, if eligible, underwent a screening examination by investigators in the dermatology clinic at UTSW. Eligible patients who agreed to be in the study were enrolled by investigators and randomized to the TA or placebo group stratified by severity (moderate or severe melasma). SAS software (version 9.4, SAS Institute Inc, Cary, NC) was used to generate the 2 randomization lists by using a block factor of 4. All patients were randomized to receive 250 mg of TA or placebo twice daily, and all received sunscreen (Neutrogena Ultra Sheer [Johnson & Johnson, New Brunswick, NJ], sun protection factor 30) with instructions to apply it every morning, with reapplication every 2 hours during daylight hours. The dose of TA was chosen on the basis on a review of published studies using TA for melasma, including a large open study of 561 patients treated in Singapore.7 Both patients and raters were blinded to the treatment arms. The randomization code was held by the study pharmacist and biostatistician, neither of whom saw the patients. A 30-day treatment supply was given at the baseline, 1-month, and 2-month visits.

Demographic information, photographs, mMASI score, and a determination of pigmentation of involved and uninvolved skin with a narrow-band reflectance spectrophotometer (Mexameter, Courage-Khazaka Electronic, Köln, Germany) were obtained at the baseline visit. The degree of pigmentation measured by this instrument is displayed as a number ranging from 0 to 1000, with 0 representing white and 1000 representing black. By measuring the degree of pigmentation of involved and adjacent uninvolved skin, the difference in pigmentation, also called the melanin index, can be obtained. Effective reduction in melasma pigment causes a reduction in melanin index, and complete resolution of melasma should result in a melanin index of 0.

All patients filled out a melasma quality of life (QoL) survey in English or Spanish.9,10 At the 1-month and 2-month visits, patients were photographed and screened for side effects and a pill count was done to determine compliance. At the 3-month visit, photography, pill count, and mMASI and melanin index measurements were performed and all patients completed the melasma QoL survey again. Patients were then instructed to use sunscreen alone for 3 months. Procedures at the final 6-month visit included photography, measurement of mMASI and melanin index, and completion of the melasma QoL questionnaire.

Statistical plan

The primary objective was to evaluate whether TA plus sunscreen improved melasma in comparison with placebo plus sunscreen on the basis of the mMASI score. Secondary end points were improvement in melanin index and QoL. Adverse effects were also documented.

The statistical design for the primary measure, mMASI, was a repeated measures analysis of variance with analyses of 2 between factors (melasma severity [moderate and severe] and treatment [placebo and TA]) and 1 within factor (time [baseline, 12 weeks, and 24 weeks]). Effect sizes for the placebo group were estimated by using our current database, in which the mean mMASI scores of participants with moderate and severe melasma are 6.5 and 11.5, respectively. For a group of nontreated subjects in this database who used sunscreen alone and returned for a visit at approximately 24 weeks, the average mMASI scores were 5.7 in the group with moderate melasma and 9.0 in the group with severe melasma. In the current study, we assumed the treatment group would have a mean mMASI score similar to that of the placebo group at baseline, whereas its score would be 3 or more points lower.
PASS 12 software was used to perform the sample size estimates. A minimum of 10 participants randomized to each treatment arm by melasma severity group (moderate and severe, 40 cases total) achieved 93% power to test the treatment effect (effect size of .56) and greater than 99% power for both the melasma effect (effect size of 1.34) and the time effect (effect size of 1.23) with use of the F-test and a 5% significance level. The estimated power for the interaction of time by treatment (effect size of .58) was 90% and that for the interaction of time by melasma (effect size of .44) was 68% with use of the F-test and a 5% significance level. A conservative Geisser-Greenhouse corrected F-test was used for any effects or interactions involving the repeated factor of time. Assuming a 16% attrition rate, a total of 44 randomized subjects were needed (11 cases to each treatment arm by melasma severity group). A modified intention-to-treat analysis was used for all randomized patients with more than baseline measures (5 patients dropped out after baseline). The $P$ value for significance was set at less than .05, and SPSS software (version 24, IBM Corp, Armonk, NY) was used to analyze the data.

RESULTS

The study was performed from July 2015 to October 2016 at UTSW in Dallas, Texas. Of the 205 females screened by telephone, 129 met the inclusion/exclusion criteria and were invited for a screening examination. Of the 78 subjects who were screened, 44 satisfied the inclusion/exclusion criteria and were randomized to the 2 treatment groups (Fig 1). Demographics and background characteristics are summarized in Table II. Twenty-one subjects in the TA group (95%) and 18 in the placebo group (82%) were Hispanic white women, 6 with skin phototype (SPT) III, 15 with SPT IV, and 14 with SPT V. The mean age was 43.9 years in the TA group and 44.2 years in the placebo group. Average duration of melasma was 13.4 years in the TA group and 12.3 years in the placebo group. The mMASI scores decreased over time, with the scores of patients taking TA decreasing more than those of patients in the placebo group at 12 weeks. The mMASI scores of patients in both groups increased from 12 to 24 weeks but were found to

Table I. Exclusion criteria

- Pregnant or nursing women
- Current use of hormonal birth control medication or any hormonal therapy
- Use of topical hydroquinone within 3 months of study enrollment
- Use of topical steroids within 1 month of study enrollment
- History of laser or dermabrasion to the face within 9 months of study enrollment
- Regular use of tanning parlors
- Occupation involving primarily outdoor activities
- Current treatment with blood thinning medications
- History of thrombosis or thrombophilia
- History of thromboembolic disease, such as deep vein thrombosis, pulmonary embolism, and/or cerebral thrombosis
- Family history of thromboembolic disease
- History of stroke
- History of >2 spontaneous abortions
- History of kidney dysfunction
- History of cancer
- Smoking
- Significant cardiovascular or respiratory disease (end-stage congestive heart failure or chronic obstructive pulmonary disease)
- History of subarachnoid hemorrhage
- History of acquired disturbances of color vision
be lower than at baseline. Those with severe melasma had higher average mMASI scores than those with moderate melasma at all time points (Fig 2).

After 3 months of treatment with TA, there was a 49% reduction in mMASI score in all patients in the TA arm versus an 18% reduction in the placebo arm (a mean decrease in mMASI score of 4.2 vs 1.4). Compared with the patients with moderate melasma who received placebo, those who received TA had a 45% versus 16% reduction in mMASI score (a decrease in mMASI score of 2.9 vs 1.0), whereas patients with severe melasma had a 51% versus 19% reduction in mMASI score (a decrease of 5.9 vs 1.9). Figs 3-6 present examples of patients treated with TA. Pill counts revealed excellent compliance, with 38 of the 39 patients taking more than 85% of the doses. The single patient who missed 17.7% of the doses was receiving placebo.

At the 6-month visit, there was a 26% reduction in mMASI score in all patients in the TA arm compared with the baseline visit versus a 19% reduction in the placebo arm (mean decrease in mMASI score of 2.2 vs 1.6). Compared with the patients with moderate melasma who received placebo, those who received TA had a 32% vs 13% reduction in mMASI score (a decrease in mMASI score of 2.0 vs 0.8), whereas patients with severe melasma had a 21% vs 24% reduction in mMASI score (a decrease of 2.4 vs 2.4).

Melanin index results were similar to those for the mMASI. The interaction of time by treatment ($P = .0315$) and the main effects of time ($P < .0001$) and melasma group ($P = .0329$) were significant. For both melasma groups, the melanin index decreased from baseline to 12 weeks, with the scores of those patients taking TA decreasing more than those of patients in the placebo group. Melanin index increased in both groups from 12 to 24 weeks except in the group of patients with moderate melasma who took placebo; however, both groups had lower melanin index scores at 24 weeks than at baseline. Those with severe melasma had higher average melanin index scores than those with moderate melasma. There was no significant difference in QoL scores between patients taking TA versus those taking placebo.

Side effects occurred in 63.6% of patients taking TA versus in 36.3% of those taking placebo (Table III). Fisher’s exact $P$ values were greater than .488 for all side effects, indicating no significant differences between the TA and placebo groups. Side effects were predominantly mild and resolved within 1 month despite continued treatment. Only 1 patient discontinued the medication because of moderate myalgia. No thromboembolic events or other serious adverse events were observed in either group.

**DISCUSSION**

Melasma is a common chronic pigmentation disorder seen in all skin types but more frequently in higher SPTs, especially in women of reproductive age. Melasma can be psychologically debilitating and has a significant effect on QoL. $^{10}$ Although there are several treatment options for melasma, including topical depigmenting agents, chemical peels, and laser and energy devices, many patients are recalcitrant to these therapies and more effective treatments are needed. $^{12,13}$

The exact pathogenesis of melasma remains unknown. Studies have implicated several factors that cause melanocytes to become activated and produce excessive melanin in patients with melasma. These factors include sun exposure, hormones, genetic influences, and vascular influences. $^{3-5,14}$ Histologically, lesional skin has increased melanocytes, melanosomes, solar elastosis, $^{15}$ mast cells, $^{16,17}$ blood vessels, vascular endothelial growth
factor, c-kit, and kit ligand. A disrupted and thinner basement has also been reported.

Tranexamic acid, an antifibrinolytic agent, has emerged as a promising treatment for melasma. TA was originally developed for the treatment of menorrhagia and bleeding diathesis. It was found that patients taking TA for these indications in Asia had improvement of melasma. Subsequently, it was found that TA causes decreased tyrosinase activity in melanocytes, possibly because of decreased production of fibroblast growth factor and prostaglandins by blocking the conversion of plasminogen to plasmin.

Although TA has been administered in topical and intradermal forms, the majority of published studies have used oral TA. The most commonly reported side effects are headaches, menstrual irregularity, nausea, and back pain. Even women taking high doses of TA for menorrhagia, usually 3.9 to 4 g/d for 5 days per month, have few adverse effects. There is no evidence to support an increased risk for thromboembolic events at these doses.

The largest study to date using TA for melasma was a retrospective review of 561 patients treated in Singapore. The median duration of treatment was 4 months and 90% of the patients improved. Importantly, adverse events occurred in 40 (7.1%) of patients. Most were transient and mild, but 1 patient developed deep vein thrombosis requiring discontinuation. It was later found that this patient had familial protein S deficiency, a personal history of spontaneous miscarriage, and a family history of thromboembolic phenomenon in 2 siblings.

Table II. Patient demographics

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo</th>
<th>TA</th>
<th>Independent samples t test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Height, in</td>
<td>20</td>
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<tr>
<td>Weight, lb</td>
<td>20</td>
<td>154.60</td>
<td>26.38</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>20</td>
<td>28.11</td>
<td>3.91</td>
</tr>
<tr>
<td>Duration of melasma, y</td>
<td>22</td>
<td>12.30</td>
<td>6.14</td>
</tr>
<tr>
<td>Melanin index</td>
<td>22</td>
<td>47.15</td>
<td>16.90</td>
</tr>
<tr>
<td>Total mMASI score</td>
<td>22</td>
<td>8.24</td>
<td>2.44</td>
</tr>
<tr>
<td>Quality of life score</td>
<td>22</td>
<td>40.23</td>
<td>17.60</td>
</tr>
</tbody>
</table>

BMI, Body mass index; df, degree of freedom; mMASI, modified Melasma Area and Severity Index; SD, standard deviation.

Fig 2. Improvement in modified melasma area and severity index (mMASI) scores in patients with moderate and severe melasma treated with tranexamic acid (TA) versus placebo.

Fig 3. Moderate melasma: baseline.
a 51% reduction in mMASI score after 3 months in the TA plus HQ group versus a 33% reduction in the control group. When the patients were examined 3 months later (after use of TA had stopped), the relapse rate was not significantly different between the 2 groups (30% vs 26% in the treatment vs control group, respectively). Side effects were similar in both groups but treatment satisfaction was higher in the intervention group. Most of the patients in this study had SPT III and mild-to-moderate melasma.

Our study enrolled patients with moderate-to-severe melasma, the type of patients who often seek the help of dermatologists for recalcitrant disease. We found a significant overall decrease in melasma severity (mMASI score) of 49% in moderate and severe melasma at 3 months in patients taking TA capsules in comparison to an 18% decrease in melasma severity in patients taking placebo. There was a concomitant reduction in melanin index as well.

Three months after TA therapy had been discontinued, the beneficial effects of this medication were sustained in those with moderate melasma.

### Table III. Adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Tranexamic acid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal discomfort</td>
<td>5 (22.7%)</td>
<td>3 (13.6%)</td>
</tr>
<tr>
<td>Change in menstrual period</td>
<td>4 (18.2%)</td>
<td>3 (13.6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (13.6%)</td>
<td>5 (22.7%)</td>
</tr>
<tr>
<td>Myalgias</td>
<td>2 (9.1%)</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (9.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>1 (4.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Blurry vision</td>
<td>1 (4.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>
However, most of the improvement in those with severe melasma was lost after 3 months of using sunscreen alone. A longer course of therapy may be needed in patients with severe melasma, and further investigation into this possibility is warranted.

Interestingly, we found no significant difference in QoL between patients taking TA and those taking placebo, despite significant reduction in both mMASI and melanin index scores. This could be due to high expectations by our patients for treatments for melasma, in which complete clearance is the preferred goal. Because our patients did not use a topical depigmenting cream, it is possible that the addition of a topical tyrosinase inhibitor, such as HQ or triple-combination cream could improve results. Future studies investigating this hypothesis are warranted.

Oral TA was well tolerated in the vast majority of patients. Importantly, as in the vast majority of studies examining use of TA for melasma, no thromboembolic events occurred. Limitations of our study include the lack of male subjects and enrollment of predominantly Hispanic patients. In addition, the follow-up period after treatment was only 3 months.

In summary, oral TA at a dose of 250 mg twice daily for 3 months significantly improved moderate-to-severe melasma. Severe melasma responded better than moderate melanin; however, those with severe melasma did not sustain their improvement compared with those with moderate melasma after TA was discontinued. The use of sunscreen alone improved melasma, in which complete clearance is the preferred goal. Because our patients did not use a topical depigmenting cream, it is possible that the addition of a topical tyrosinase inhibitor, such as HQ or triple-combination cream could improve results. Future studies investigating this hypothesis are warranted.

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REFERENCES

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