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Comparing the efficacy of topical hydroquinone 2% versus intradermal tranexamic acid microinjections in treating melasma: a split-face controlled trial

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ABSTRACT

Introduction: Melasma is a benign, acquired and chronic hypermelanosis. Topical hydroquinone (HQ) is a conventional choice to treat melasma. Tranexamic acid (TA) is a relatively new brightening agent that interferes with keratinocyte–melanocyte interactions. The aim of the present study was to compare the efficacy and safety of TA intradermal injections with HQ in treating melasma.

Materials and methods: In this split-face controlled trial, 37 patients were randomized to receive three monthly sessions of TA intradermal injections either on the right or the left side of their face and topical HQ once a night for three months on the other side. Melanin and erythema were measured for each side of the face at the baseline and at the end of each month.

Results: A reduction in melanin value was observed for TA and HQ separately (p value <.001). Monthly TA injection was better than daily HQ in reducing the melanin value during the first four weeks (p value = .013); but after 20 weeks, the overall changes was not different between the two groups (p value = .17).

Conclusion: Monthly TA intradermal injections can be an effective treatment for melasma. Further studies are required to support our results.

Introduction

Melasma (chloasma) is a benign, highly prevalent, acquired, and chronic hypermelanosis characterized by symmetrical light to dark brown macules and patches. It is due to epidermal melanocytes hyperactivity, on different areas of the face, like the forehead, malar area and the chin. Most patients with melanoma are either Asian or Hispanic. It is more common in women during reproductive age with Fitzpatrick skin types III to V, and they account for 90% of all melasma cases (1–10). Although there are still many questions about the etiology of melasma; however, sun exposure, genetic susceptibility, hormonal therapies, pregnancy, cosmetics, photosensitizing drugs and antiseizure medications are considered as possible causes and the first three aforementioned triggering factors play major roles (1,4,5,8,11,12).

Different treatment modalities, with variable rates of safety and success have been utilized in treating melasma. Topical agents and broad-spectrum sunscreens, chemical peels and laser are in front lines of therapy. Topical hydroquinone (HQ) is a conventional choice for hyperpigmentary disorders, which interferes with melanogenesis by inhibiting tyrosinase enzyme, modulating the conversion of DOPA (dihydroxyphenylalanine) to melanin. However, a triple topical combination containing HQ, retinoic acid, and steroid is preferred over HQ monotherapy. HQ side effects include contact dermatitis (both allergic and irritant), post-inflammatory hyperpigmentation (PIH), and exogenous ochronosis (10,13,14). Other topical agents with lower efficacy than HQ are glycolic acid, azelaic acid and kojic acid that the latter two act by inhibiting tyrosinase enzyme. Also topical tretinoin monotherapy can be helpful, but the required treatment time is longer than HQ. Dealing with treatment-refractory patients, more intense options, mainly laser, might be utilized, but the potential risk of paradoxical worsening the disease might increase (6,15,16).

Tranexamic acid (TA), a synthetic analog of amino acid lysine, inhibits melanin synthesis by interfering with keratinocyte–melanocyte interactions (17). TA administration routes, including oral, topical, localized intradermal microinjections and microneedling, have been utilized to treat melasma (10,11,15). The present study was designed to compare the efficacy of monthly TA intradermal injections with topical HQ 2% in treating melasma.

Materials and methods

Participants

In this split-face controlled trial, 37 consecutive patients (significant difference = 1.5; standard deviation = 2; α = 0.05; 1-β = 0.9) with bilateral symmetric facial melasma who were referred to Faghihi hospital, Shiraz, Iran affiliated University of Medical Science from October 2015 to December 2016 were enrolled. Each patient served as her/his own control, randomized to inject TA either on their right or the left side. Patients who had any history of using topical or systemic brightening medications such as steroids, HQ, tretinoin, azelaic acid, and kojic acid or photosensitizing drugs, such as tetracyclines, phenytoin, carbamazepine and spiranolactone or anticoagulants, as well as were those who were pregnant or lactating were excluded from the study. This study was approved by the local Ethics Committee of Shiraz University of Medical Sciences (code: IR.SUMS.MED.REC.1396.02). All the patients signed the written informed consent form prior to initiation of the trial.
Materials and procedures

At baseline, a questionnaire was filled for each patient including demographic data, history of OCP (oral contraceptive pill) consumption, thyroid diseases and duration of melasma. By performing simple randomization through flipping a coin, treatment decision was taken for either sides of their face.

Three monthly sessions of localized intradermal TA injections (Caspian Tamin Pharmaceutical Co, Rasht, Iran) was used on one side of their face at baseline, and at the end of 4th and 8th weeks by a well-trained dermatologist.

After cleansing the face with water and soap, topical xylacain—prilocain cream (Tehran Shimi Pharmaceutical Co, Tehran, Iran) was applied over the melasma area for about 45–60 min. TA is available as 5 ml ampoules containing 500 mg TA. About 10 mg (0.1 ml) of TA was drawn in a 50 U/mL (0.5 cc) insulin BD microfine plus syringe (Gauge 30, 8 mm) and diluted with normal saline up to 0.5 ml to get a concentration of 20 mg/ml. TA treatment was done intradermal injections with 1 cm between the injection points. Ice pack was applied to alleviate any injection pain.

Topical HQ 2% (Sepidaj Pharmaceutical Co, Tehran, Iran) was used on the other side of their face once a night for three months. After completing the treatment period, both treatments were discontinued, patients were instructed to only apply an SPF 50 plus sunscreen.

Clinical assessments

At baseline, a colorimeter, Dermacatch® (Colorix, Neuchatel, Switzerland), was used to measure melanin and erythema quantitative values for baseline for each side separately. Dermacatch® is the latest high-tech Swiss made portable visible-spectrum reflectance skin colorimeter, which instantly displays clear distinct melanin and erythema values (with arbitrary units that differ from those used by other colorimeters such as Mexameter®). Ambient temperature and light conditions have no effect on measuring results.

We divided the melasma area on each side of the face into four quadrants and the mean melanin and erythema value was used as the melanin and erythema value for each side of the face. In addition, these measurements were also done to determine Fitzpatrick skin type according to Dermacatch® manual’s cutoffs (melanin value = 450±50: type I–II; 550±50: type III; 650±50: type IV; 750±50: type V; 850±50: type V). And different types of melasma were examined via Wood’s lamp.

At the end of the 4th, 8th and 20th weeks of the study, colorimeter assessments were done to determine any changes on both sides. At the end of the 20th week, patients’ content with both treatments were compared via a visual analog scale (VAS) (0 = least satisfaction, 10 = most satisfaction). During 2nd, 3rd and 4th visits, all the adverse effects were monitored.

Statistical analysis

The statistical analysis was applied by R programing language (version 3.3.1 for Windows) (18) with deducer GUI (graphical user interface) package, Shapiro–Wilk test against normality, paired t-test (or Wilcoxon sign-rank test) to compare the reduced melanin and erythema values between two treatments, and repeated measures ANOVA to analysis the pattern of melanin and erythema values reduction in each treatments, separately. One-way ANOVA (or Kruskal–Wallis test) was employed to compare the overall melanin and erythema reduction between three types of melasma (epidermal, dermal and mix). p values ≤.05 was considered as statistically significantly different.

Results

Thirty-one female patients completed the study. Six patients discontinued the study; two patients developed acne upon TA injections, one patient was upset with the pain during injections, two of them were dissatisfied with the improvement on both sides, and one was lost during follow up. The mean age was 35.8 ± 5.4 (ranged between 25 and 49 years of age). The demographic and baseline characteristics are shown in Table 1. At the baseline, there was no difference between the severity of melasma on both sides (melanin: 614.8 ± 51.3 and 611.9 ± 51.5; p values = .58) (erythema: 464.5 ± 14.9 and 465.7 ± 15.9; p values = .5).

The melanin mean value ± SD at baseline, first and second the third follow-up were 614.8 ± 51.3, 587.8 ± 52.3, 580.4 ± 49.7 and 575.2 ± 49.7 for TA side and 611.9 ± 51.5, 595.2 ± 52.1, 587.3 ± 52 and 583.4 ± 52.3 for HQ side, respectively; by considering the interventions separately, a diminution pattern was observed for both (p values <.001). No difference was observed for erythema during the treatment (p values of .085 for TA side and 0.5 for HQ side).

When comparing the TA and HQ intervention sides for reduction (Δ) in melanin value, TA was superior to HQ in reducing melanin value at the first follow-up (baseline – 1st follow-up: 27 ± 21.7 for TA vs. 16.7 ± 21.1 for HQ, p values =.013), but no difference was observed between the two treatments regarding the reduction in melanin value between first and second follow up, second and third follow-up, and overall melanin reduction (p values of .88, .83, and .17). Figure 1(G) illustrates the malar melasma improvement over 20 weeks.

Furthermore, comparing epidermal, dermal and mixed types of melasma, the overall melanin and erythema values reduced by TA were not statistically different (melanin: 41.8 ± 50.6, 35 ± 21.1 and 39.6 ± 29.4, p values = .063).
The mean satisfaction value (VAS) statistically supported TA (5.9 ± 1.8 vs. 3.9 ± 2.5, p values < .001).

**Discussion and conclusions**

Melasma is a highly prevalent cosmetic disorder resulting in a great psychological impact on a patient. The disease etiology is still a puzzle, but a multifactorial pathogenesis is plausible.

The treatment strategy comprised of three intervention lines: (1) Topical skin-depigmenting agents, broad-spectrum sunscreens and camouflage, (2) chemical peels and (3) Laser (10,14,15). The mainstay of therapy is HQ, inhibits tyrosinase enzyme and ceases melanogenesis. It also affects the membranous organelles of melanocytes that causes necrosis, inhibits DNA and RNA synthesis (19,20). Regarding HQ, melasma resolution rate is up to 60% via monotherapy, the chance of recurrence and refractory cases are common and might have many side effects such as contact dermatitis (both allergic and irritant), PIH and exogenous ochronosis (10,14). Although, most of these side effects may occur as a result of higher concentrations, prolonged treatment, unsuitable cleansing agents and rubbing the melasma areas (21,22). Patients' compliance and medication adherence is also another issue, due to prolonged nightly application; hence, there is an ongoing demand for new and effective melasma treatments.

TA is a great candidate to treat melasma. TA serves as a skin-brightening agent, disrupts keratinocyte–melanocyte interactions. Plasminogen exists in human epidermal basal cells where hyperactivated melanocytes (the causing agent of melasma), and keratinocytes are located. TA blocks lysine binding sites on plasminogen and by so doing, inhibits keratinocytes produced plasminogen activator (PA) modulation on plasminogen and plasminogen does not convert into plasmin. Thus plasmin-induced different substances secretion that stimulates melanogenesis cannot occur (9,23–28). In addition, Tan et al. (29) had theoretically proposed two other pathways; first, TA diminishes the UV activity-induced mast cells and mast cell tryptase and consequently vascular proliferation. Second, it inhibits neovascularization induced by basic fibroblast growth factor.

In two systematic reviews by Perper et al. (30) and Kim et al. (31), TA was introduced to be a promising choice in treating...
melasma either alone or combination with other treatments. Additionally, TA has fewer adverse effects, same or even better results in comparison with other melasma targeting therapies. However, there are inadequate studies that have evaluated localized TA intradermal injection as an effective and safe method (32–36). Previous studies had several drawbacks, mainly including lack of variability control (split-face design) and using MASI (Melasma Area and Severity Index) which may bring bias due to subjectivity.

In 2006, Lee et al., (32) performed the first pilot study on localized TA intradermal microinjection (4 mg/ml) efficacy. They reported a statistically significant reduction in MASI at weeks 8 and 12 from the baseline. In 2009, Steiner et al., (33) quantitatively compared the efficacy and safety of topical (twice a day) and weekly TA intradermal microinjection (1.5 mg/ml), including eighteen women with one follow-up at week 12. Both treatments were effective, but no difference was observed. In 2013, Budamakunta et al., (34) made a comparison between TA microneedling and microinjection (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melasma. Microneedling group reached more reduction in melanin (4 mg/ml) and found both to be beneficial in treating melanin was not different (39.6 ± 37.7 vs. 28.4 ± 19.6; p values = 0.17), which might be the result of 12-week drug-free period of the study and addresses the fact that more treatment duration is required to achieve greater improvement. Apparently, the major therapeutic effect of TA occurs during the first few weeks, in other words, melanin reduction rate diminishes as time goes by, in comparison with HQ (27 ± 21.7 vs. 16.7 ± 21.1; p values = .013). Hence, TA intradermal injection may have a shorter onset of action than HQ. Interestingly, the melanin value reduction pattern in previous studies that had at least two follow ups was varied. One (32) was in conflict with ours findings, but the other (34) was in line. Multiple factors may contribute to these differences including genetics, assessment tool, study design, drug preparation, dosing and number of injection, severity, duration and type of melanoma and so forth. Future studies under different circumstances might figure out this issue. Moreover, subjective evaluation (VAS) was in line with TA (p values <.001), but bias is strongly plausible due to the variability in personal estimates and perceptions.  

Local intradermal microinjection is assumed to possess a significant impact on deeper pigmented skin layers such as mid-dermis (38). As it was observed in our study, the overall reduction in melanin was not different according to different types of melasma; p values of .9. However, the size of each study group was small; hence, it raises the bias. Future studies with larger sample sizes might be able to confirm our claim.  

With regards to the adverse effects, mild and well-tolerated side effects such as itching, burning pain, and erythema were listed in previous studies (33–35,37). However, in the present

### Table 2. Comparing TA and HQ on the melanin and erythema reduction in the patients with melasma.

<table>
<thead>
<tr>
<th></th>
<th>TA</th>
<th>HQ</th>
<th>p value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline – 1st follow-up melanin Δ (mean ± SD)</td>
<td>27 ± 21.7</td>
<td>167 ± 21.1</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>(614.8 ± 51.3, 587.8 ± 52.3)</td>
<td>(611.9 ± 51.5, 595.2 ± 52.1)</td>
<td></td>
</tr>
<tr>
<td>1st follow-up – 2nd follow-up melanin Δ (mean ± SD)</td>
<td>7.4 ± 10</td>
<td>7.8 ± 14.5</td>
<td>.88</td>
</tr>
<tr>
<td></td>
<td>(587.8 ± 52.3, 580.4 ± 49.7)</td>
<td>(589.2 ± 52.1, 587.4 ± 52)</td>
<td></td>
</tr>
<tr>
<td>2nd follow-up – 3rd follow-up melanin Δ (mean ± SD)</td>
<td>5.2 ± 34.4</td>
<td>3.9 ± 9</td>
<td>.83</td>
</tr>
<tr>
<td></td>
<td>(580.4 ± 49.7, 575.2 ± 49.7)</td>
<td>(587.3 ± 52, 583.4 ± 52.3)</td>
<td></td>
</tr>
<tr>
<td>Baseline – 3rd follow-up melanin Δ (mean ± SD)</td>
<td>39.6 ± 37.7</td>
<td>28.4 ± 19.6</td>
<td>.17</td>
</tr>
<tr>
<td></td>
<td>(614.8 ± 51.3, 575.2 ± 49.7)</td>
<td>(611.9 ± 51.5, 583.4 ± 52.3)</td>
<td></td>
</tr>
</tbody>
</table>

**p value**<sup>b</sup>  
Baseline – 1st follow-up erythema Δ (mean ± SD) | <.001 | <.001 |

**p value**<sup>c</sup>  
VAS | .085 | .5 |

HQ: hydroquinone; SD: standard deviation; TA: tranexamic acid; VAS: visual analog scale.  
<sup>a</sup>p values <.05 implies on the significant difference.  
<sup>b</sup>Calculated by the paired t-test.  
<sup>c</sup>Calculated by the repeated measures ANOVA based on the melanin and erythema scores at the 4 time points.
study no adverse reaction was observed on the HQ side, but three patients reported side effects after TA injection; one had burning pain during injection and the other two developed acne. Erythema was not an adverse reaction observed in each treatment (TA = 0.085 and HQ = 0.5). A subtle increase in erythema value was observed at HQ side compared with TA side (TA = 6.6 ± 19 vs. HQ = −5.8 ± 39.2, p values = .018).

One of the advantages of our study, in addition to split-face design was Dermacatch utilization instead of mexameter, used by Baquieu et al. (39); since Dermacatch has a significantly higher specificity and reproducibility than Mexameter in melanin and erythema measurement. Another advantage of our study was the use of higher TA concentration that may help to illustrate the real TA efficacy, which might have been concealed by lower concentrations in previous studies [Figure 1(G)]. In our center, we use higher TA concentration (up to 100 mg/ml) with a great efficacy in recalcitrant (refractory) types of melasma, PIH and even periorbital darkening (Figure 1(A—F)).

Seasonal change is one of the neglected triggering factors when treating melasma, since sunlight increases during summer and might interfere with the treatment (40); therefore, one of the drawbacks of the present study was the extended treatment period from winter to summer. Other limitations were short treatment period that might not detect the delay side effects. Future studies should keep an eye on the aforesaid points to achieve more conclusive results. We suggest conducting studies comparing the TA modalities’ efficacy and safety on different types of melasma with different concentrations. Also understanding the optimum dose and duration of localized TA intradermal injection should be kept in mind.

We found that localized TA intradermal injection can be effective in treating melasma and may be more beneficial than topical HQ monotherapy. However, equivocality on different aspects of this potential option still remains, and it is too soon to reach a concrete conclusion. Prospective studies will be able to address such issues.

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Disclosure statement

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