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The effectiveness and safety of 3% tranexamic acid cream vs. 4% hydroquinone cream for mixed-type melasma in skin of color: a double-blind, split-face, randomized controlled trial

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Abstract

Introduction: Melasma, a chronic acquired skin pigmentation disorder, is characterized by the presence of irregular-edged brown to gray-brown patches with a symmetrical distribution, primarily on sun-exposed areas such as the face. Topical hydroquinone (HQ) is the gold standard for melasma treatment but has numerous side effects. This study assesses the effectiveness of topical tranexamic acid (TA) as an alternative for melasma treatment.
Methods: In a double-blind, split-face, randomized controlled trial involving 20 subjects, the effectiveness of 3% TA versus 4% HQ cream was evaluated over 8 weeks. The modified melasma area and severity index (mMASI), melanin index, erythema index, and side effects were assessed. Subjective improvement was measured using the patient global assessment (PtGA).
Results: A significant decline in the mMASI score was observed at weeks 4 and 8 in both groups compared to baseline. There were no statistically significant differences in PtGA scores between the 3% TA group and the 4% HQ group.
Conclusions: Topical 3% TA is as effective and safe as 4% HQ for treating melasma in the Indonesian population, with potential advantages in terms of side-effect profiles.

Keywords: melasma, split-face, tranexamic acid, hydroquinone, clinical trial

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Introduction

Melasma, a chronic acquired skin pigmentation disorder, is characterized by the presence of irregular-edged brown to gray-brown patches with a symmetrical distribution, occurring primarily on sun-exposed areas such as the face (1, 2). This condition is most frequently found in women of reproductive age, typically between 20 and 40 years old, with darker skin types, such as in populations of Hispanic, Asian, Latin American, and African descent (2, 3). Globally, melasma is recognized as one of the most prevalent pigmentary disorders, with an estimated prevalence ranging from 1% to 50%, rising to 40% in Southeast Asia (2). The distribution of lesions categorizes melasma into four types: centrofacial, malar, mandibular, and extrafacial. Moreover, its classification can be based on depth, resulting in three types: epidermal, mixed, and dermal (1, 2). In Asia, especially in Indonesia, the mixed type of melasma predominates. Mixed-type melasma presents challenges in therapy and is prone to relapse (4). Although it is typically asymptomatic, the cosmetic concerns associated with melasma can substantially affect a patient's quality of life and lead to social withdrawal (5).

The evaluation of melasma severity and treatment efficacy relies on both subjective and objective methods (2). The modified melasma area and severity index (mMASI), a commonly employed subjective method, categorizes melasma based on the extent of the area involved and the degree of pigmentation (6). Objective assessments often utilize the Mexameter to evaluate pigmentation and erythema indices. In addition, Wood's lamp and dermoscopy are employed to assess pigmentation depth (7, 8). Currently, melasma treatment encompasses topical, oral, and procedural modalities, with topical therapy being favored for its ease of application, cost-effectiveness, and higher patient compliance (3, 9). Photoprotection and depigmenting agents are considered the gold standard for melasma treatments (10). Hydroquinone (HQ), a traditional depigmenting agent, is employed either as monotherapy or in combination with tretinoin and topical corticosteroids (1, 11). However, it is recognized that prolonged HQ usage might lead to side effects, including paradoxical hyperpigmentation and exogenous ochronosis (12).

Tranexamic acid (TA) is recognized as one of the topical treatment options for melasma and has gained attention for its safety and effectiveness. Also known as trans-4-(aminomethyl) cyclohexane carboxylic acid, TA is a synthetic derivative of the amino acid lysine, primarily employed as a hemostatic agent in the management of fibrinolysis disorders (13). TA operates through several mechanisms in melasma, at both the epidermal and dermal levels, including inhibition of the tyrosinase enzyme, vascular effects, anti-inflammatory effects, and mast cell inhibition (14). This was demonstrated by Maeda et al. (15) when they reported that TA could inhibit the activity of tyrosinase in epidermal melanocytes by inhibiting the plasminogen/plasmin system, leading to a disruption in the interaction between melanocytes and keratinocytes, ultimately inhibiting melanogenesis. Consequently, TA administration could be used for mixed-type melasma.

Several studies have delved into various methods of TA administration, encompassing oral intake, intradermal injections, and topical applications (13). Oral TA has displayed promise, but it comes with the risk of systemic side effects (16). Intradermal TA injections proved effective but had the potential drawbacks of causing discomfort and hematoma at the injection site (13). Conversely, topical TA, available in multiple forms such as creams, solutions, gels, and serums, underwent testing with various concentrations

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and protocols, yielding variations in results (17, 18). Currently, 3% TA has emerged as a widely available choice in Indonesia. A previous study comparing 3% TA and 4% HQ creams showed that the TA group exhibited greater reductions in the MASI score and the melanin index (MI) at week 8 for epidermal melasma (19). However, it did not provide specific details about the daily application frequency of TA and HQ creams or reported side effects. HQ was deemed more effective when used twice daily, considering that the peak elimination of HQ occurred 12 hours after application (20, 21). Therefore, further investigation is considered necessary to determine whether 3% TA cream outperforms conventional HQ treatment and to assess its effects on mixed-type melasma in Indonesia, which has darker skin types (Fitzpatrick III–V). Clinical trials are essential to assess the efficacy and safety of 3% TA cream compared to 4% HQ cream when used twice daily for mixed-type melasma in this population.

Methods

A double-blind randomized controlled trial was conducted using a split-face method to evaluate the efficacy of 3% TA cream and 4% HQ cream for treating melasma (ClinicalTrial.gov NCT06010810) from July to August 2023 at the Dermatology and Venereology Department of Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Investigational product

The 3% TA cream was formulated and produced by a pharmacy following good manufacturing practices (GMP). The control group treatment, using a cream obtained from a commercial product containing 4% HQ, was repackaged in similar tubes, which were identical in consistency, color, and aroma to the intervention cream, at the same pharmacy.

Patient selection

Sampling was carried out consecutively, with a total of 20 participants included in the study. The study involved female patients 18 to 60 years old that were diagnosed with melasma and had Fitzpatrick skin types III to V. All the participants met the inclusion criteria and provided informed consent. There were no exclusion criteria.

Randomization and treatment allocation

Randomization was performed using block randomization to assign subjects to receive either 3% TA cream on the right or left side of the face and 4% HQ cream on the opposite side. Patients applied both the intervention and control creams twice daily on the respective randomized sides of the face. All the participants received consistent instructions and education regarding cream application and the use of broad-spectrum sunscreen with sun protection factor 50 with a protection grade of UVA +++ (SPF50 PA++++), and they were also provided with a daily cream usage log.

Baseline and evaluation

The assessment of melasma severity involved a combination of subjective evaluation using the mMASI (6) score and objective measurements with a Mexameter MPA 5 (Courage-Khazaka Electronic®, Cologne, Germany) and a Mexameter® MX 18 probe for the MI and erythema index (EI). In addition, a Wood's lamp examination and dermoscopy were conducted to determine the depth of melasma. Evaluations of mMASI, MI, and EI took place at baseline, at week 4, and at week 8. Compliance was monitored with a minimum requirement of 80% cream application, and daily cream usage log entries were reviewed. At week 8, another Wood's lamp examination and dermoscopy were performed, accompanied by a patient global assessment (PtGA) to assess subjective improvement, categorized as follows: < 25% (no/minimal response), 25%–50% (moderate improvement), 50%–75% (good improvement), > 75% (very good improvement).

Statistical analysis

Statistical analysis was conducted using the SPSS software version 21.0. Numerical data are reported as either mean ± standard deviation (*SD*) or median and interquartile range (IQR) as applicable. Categorical data are presented as percentages. Paired *t*-tests and Wilcoxon tests were employed, as appropriate, to analyze matched data in follow-up assessments. Independent *t*-tests and Mann–Whitney tests were used to compare the intervention and control groups. Chi-squared and McNemar tests were utilized for analysis of categorical data.

Ethical clearance

Written informed consent was obtained from all enrolled participants. This study received approval from the Research Ethics Committee of the Faculty of Medicine, University of Indonesia, with the reference number KET-927/UN2.F1/ETIK/PPM.00.02/2023.

Results

Sociodemographic and baseline clinical characteristics

Subject characteristics are shown in Table 1. The predominant melasma distribution in the study was centrofacial (65%), followed by malar (35%) and mandibular (5%). All participants in this study presented with mixed-type melasma. No significant differences were found in baseline mMASI, MI, and EI across interventions (Table 2).

Treatment evaluation

In this study, significant reductions in mMASI, MI, and EI values were observed in both the intervention group (3% TA) and the control group (4% HQ) upon reevaluation at weeks 4 and 8 compared to baseline. No statistically significant differences were found between the mMASI and EI values of the two groups. Figure 1 shows the clinical images of participants in the intervention and control groups at the study's initiation and after week 8. A significant decline in the mMASI score was observed at weeks 4 and 8 in both groups compared to baseline. Within the intervention group, mMASI declined on average by 1.14 (29.0%) at week 4 and 2.08 (54.9%) at week 8. Meanwhile, within the control group, it declined by 1.05 (29.2%) at week 4 and 1.92 (53.5%) at week 8, respectively. A significant reduction in MI scores was observed in both the 3% TA and 4% HQ groups after the 4th and 8th weeks. The difference in the reduction of MI scores from baseline to the 8th week between the 3% TA group was found to be statistically significant. However, the control and intervention groups only differed at the

8th week compared to baseline. Concerning the EI, there was a marked reduction of score compared to baseline in both the 3% TA and 4% HQ groups after 4 weeks (17.55 ± 31.01 vs. 16.52 ± 31.96) and 8 weeks (30.90 ± 62.70 vs. 15.37 ± 32.64). Although no statistically significant distinctions were observed in this aspect, it is evident that the reduction in EI scores was more pronounced in the 3% TA group compared to the 4% HQ group. Table 3 shows the detailed difference of mMASI, MI, and EI at weeks 4 and 8 compared to baseline for both groups (for trend visualization, see Fig. 2).

Patient global assessment and side effects

The study results revealed that there were no statistically significant differences in PtGA scores between the 3% TA group and the 4% HQ group. Within the 3% TA group, the majority of patient assessments are noteworthy for being rated as either "good" (50%) or "very good" (40%). All patients exhibited full compliance, using the test and control creams according to the prescribed guidelines. In the evaluation of side effects in this study, the 3% TA group reported no side effects, and the 4% HQ group experienced

Table 1 | **Subjects' sociodemographic and clinical characteristics.**

Variable	Values
Age in years (median, IQR)	46.7 (6.9)
Education (*n*, %)	
Low	0 (0)
Medium	7 (35)
High	13 (65)
Occupation (*n*, %)	
Unemployed	4 (20)
Employed	16 (80)
Melasma distribution (*n*, %)	
Centrofacial	13 (65)
Malar	6 (30)
Mandibular	1 (5)
Melasma types (*n*, %)	
Epidermal	0 (0)
Dermal	0 (0)
Mixed	20 (100)
History of sunscreen usage (*n*, %)	
Yes	10 (50)
No	10 (50)
Triggering factors (*n*, %)	
Sunlight exposure	20 (100)
Hereditary	15 (75)
Pregnancy	2 (10)
Hormonal contraception	2 (10)
Cosmetics	2 (10)

IQR = interquartile range.

Table 2 | **Baseline modified melasma area and severity index, melanin index, and erythema index for both groups.**

Variable	Control (*n* = 20)	Intervention (*n* = 20)	*p*[a]
mMASI (median; IQR)	2.85; 2.60	2.85; 2.83	0.820[a]
MI (mean ± *SD*)	324.16 ± 56.53	323.85 ± 64.23	0.987[b]
EI (mean ± *SD*)	421.25 ± 62.05	419.78 ± 57.04	0.938[b]

mMASI = modified melasma area and severity index, IQR = interquartile range, MI = melanin index, *SD* = standard deviation, EI = erythema index.
[a]Mann–Whitney test, [b]independent t-test.

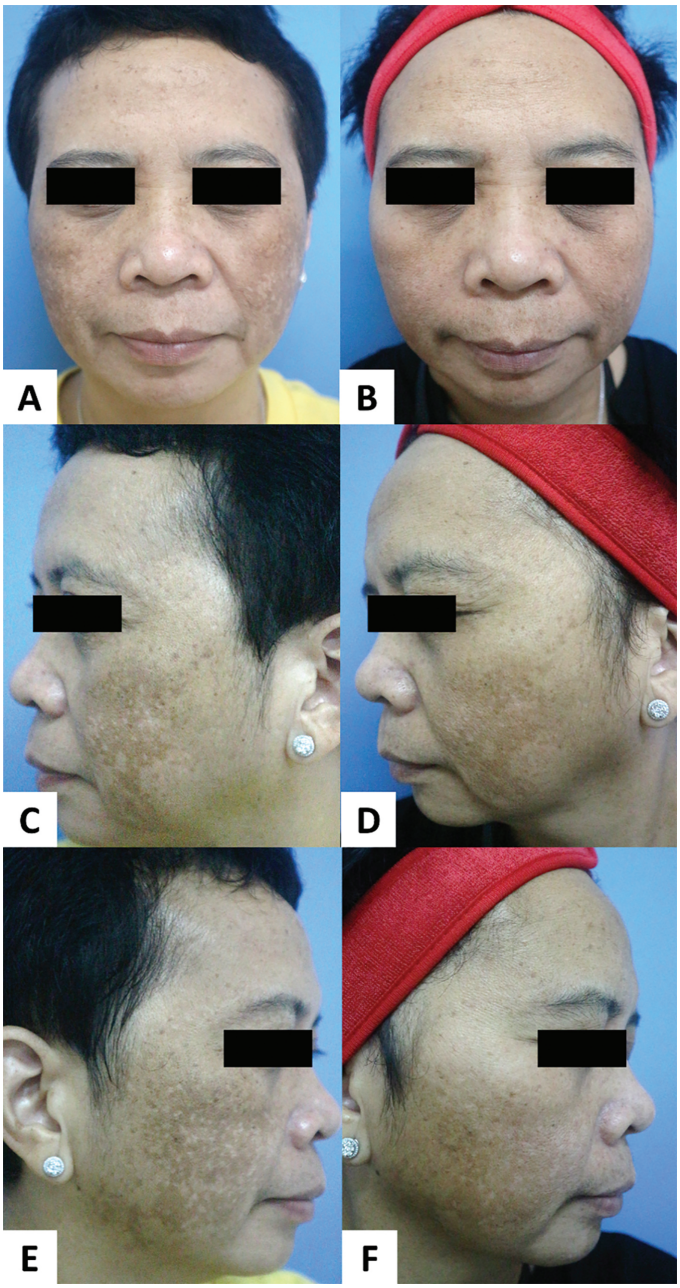

Figure 1 | Clinical improvement of mixed-type melasma lesions after 8 weeks of therapy. No significant difference was observed in the reduction of the modified melasma area and severity index scores between the intervention and control groups. (A) Entire face before therapy, (B) entire face after therapy, (C) left side of face prior to applying 3% tranexamic acid (TA) cream, (D) left side of face following administration of 3% TA cream, (E) right side of face prior to initiation of treatment with 4% hydroquinone (HQ) cream, (F) right side of face after application of 4% HQ cream.

Table 3 | **Differences of modified melasma area and severity index, melanin index, and erythema index between week 4 and week 8 compared to baseline on both groups.**

		Control		Intervention		Control – intervention	
Parameters	**Week**	**Value**	***p*-value**	**Value**	***p*-value**	**Mean ± *SE***	***p*-value**
mMASI;	Δ0–4	1 (0.98)	0.001*[a]	1.25 (1)	0.000*[a]	N/A	0.718[c]
median (IQR)	Δ0–8	1.50 (1.90)	0.000*[a]	1.80 (1.68)	0.000*[a]	N/A	0.495[c]
MI;	Δ0–4	19.90 ± 16.51	0.000*[b]	9.15 ± 18.86	0.043*[b]	10.75 ± 5.61	0.063[d]
mean ± *SD*	Δ0–8	40.58 ± 29.94	0.000*[b]	18.79 ± 25.04	0.003*[b]	21.79 ± 8.73	0.017*[d]
EI;	Δ0–4	16.52 ± 31.96	0.032*[b]	17.55 ± 31.01	0.024*[b]	−1.03 ± 10.11	0.919[d]
mean ± *SD*	Δ0–8	15.37 ± 32.64	0.049*[b]	30.90 ± 62.70	0.040*[b]	−15.53 ± 15.81	0.332[d]

mMASI = modified melasma area and severity index, IQR = interquartile range, MI = melanin index, *SD* = standard deviation, EI = erythema index, *SE* = standard error, N/A = not applicable.
[a]Wilcoxon, [b]paired t-test, [c]Mann–Whitney, [d]independent *t*-test, *$p < 0.05$.

mild side effects, specifically mild erythema (25%). A significant difference in side effect occurrence was evident between the intervention and control groups (Table 4).

Discussion

Patients' sociodemographic and clinical profiles

Marpaung et al. (19) found similar results for melasma distribution, with the centrofacial type (76.7%) being the most prevalent, followed by malar (16.7%) and mandibular (6.7%). These findings align with global research, in which centrofacial melasma is the most common type (65%), followed by malar (20%), and mandibular (15%) (1, 2). The centrofacial and malar types are frequently reported in various countries, likely due to the increased sun exposure received by the forehead, nose, upper ears, upper lip, infraorbital and supraorbital rims, zygomatic area, and neck, which are front-facing areas (22). The prevalence of mixed-type melasma as the most common type corresponds with similar research conducted in India and Brazil, where mixed-type melasma is also reported as the most common (65%). Mixed-type melasma is characterized by features of both epidermal and dermal types, demonstrating elevated melanin levels in both the epidermal and dermal layers. Furthermore, our results are consistent with the observation that individuals of Asian descent are more likely to experience mixed-type melasma (23).

Mixed-type melasma tends to exhibit higher resistance to therapy and may have a propensity for recurrence (4). This could be attributed to the histopathological complexity commonly found in this type. In the epidermal layer, melanin content sees an escalation throughout various epidermal layers, especially in the the basal and suprabasal layers, forming pigmentary caps. Notably, there are melanocytes protruding into the dermis (pendulous melanocytes) along with melanocyte hyperactivity (24). Within the dermal layer, several features are detected, including mononuclear infiltrates, dermal melanophages, pigment incontinence, solar elastosis, mast cells, stem cell factor, c-stem cell factor receptor tyrosine kinase (c-KIT), increased vascularity with vascular endothelial growth factor (VEGF) expression, disruption of the basement membrane, thinning of the lamina densa, and loss of anchoring fibrils from the lamina lucida (12, 24).

TA has the potential to improve melasma by targeting both the epidermal and dermal layers. A study demonstrating the efficacy of topical TA in melasma, conducted by Kim et al. (17), using 2% TA emulsion cream twice daily and a face mask containing 2% TA three times per week, showed histopathological improvement in melasma lesions. Fontana–Masson staining revealed a significant reduction in melanin content in the epidermis. The number of CD31-positive vessels and the expression of VEGF both tended to decrease. As a result, topical TA is expected to be beneficial in managing mixed-type melasma.

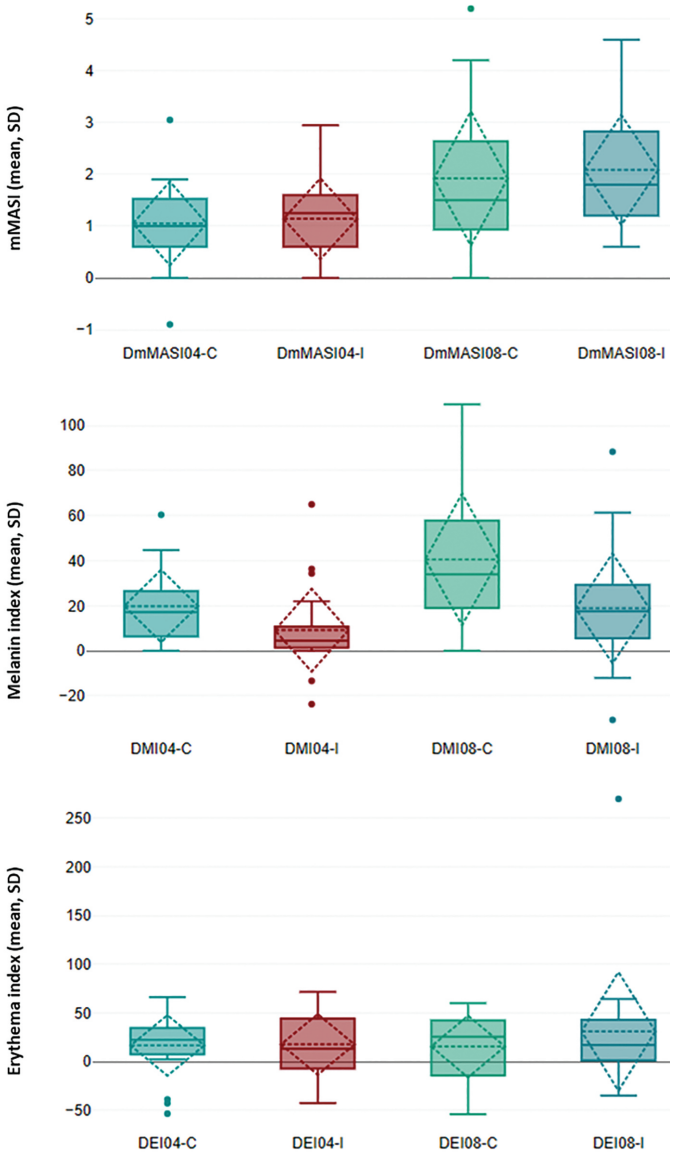

Figure 2 | Changes in modified melasma area and severity index, melanin index, and erythema index from baseline to week 4 (04) and to week 8 (08) in both groups.
mMASI = modified melasma area and severity index, *SE* = standard deviation, MI = melanin index, EI = erythema index C = control, I = intervention.

Treatment evaluation

A noteworthy reduction in mMASI scores was evident in both the intervention group and the control group upon reevaluation at the 4th week (29.0% vs. 29.2%) and the 8th week (54.8% vs. 53.48%) compared to baseline in this study. Importantly, no statistically significant differences were observed in the change of

Table 4 | Patient global assessment and side effects at week 8 in both groups.

Measure	Control (*n* = 20)	Intervention (*n* = 20)	p-value
PtGA (*n*, % within group)			
Minimal	0 (0)	1 (5)	0.378[a]
Moderate	4 (20)	1 (5)	
Good	10 (50)	10 (50)	
Very good	6 (30)	8 (40)	
Side effects (n, % within group)			
None	15 (75)	20 (100)	0.047[b]
Mild	5 (25)	0 (0)	

PtGA = patient global assessment.
[a]chi-squared, [b]Fisher's exact test.

mMASI scores between the intervention and control groups at either the 4th or 8th week. In a study conducted by Kim et al. (17) that investigated the effectiveness of 2% topical TA in melasma patients in Korea, a significant reduction in mMASI scores was observed, decreasing from the baseline value of 33.6% after 12 weeks of administering 2% topical TA. Similarly, in a study by Janney et al. (23) involving 100 participants, which included 84 women and 16 men with mixed melasma (63%), epidermal (22%), and dermal (15%) types, there was no significant difference in the reduction of MASI scores between the TA group and the HQ group after 12 weeks. In research conducted in Indonesia, Marpaung et al. (19) undertook a comparative analysis of the effectiveness of 3% TA cream versus 4% HQ over an 8-week timeframe, focusing on epidermal-type melasma. Their findings revealed a notably greater reduction in mMASI scores by week 8 in the TA group compared to the HQ group.

TA operates through various mechanisms to address melasma. At the epidermal level, it inhibits the interaction between melanocytes and keratinocytes, thereby thwarting UV-induced pigmentation. This inhibition occurs by impeding the action of plasminogen activators through reversible binding to lysine binding sites and inhibiting the conversion of plasminogen to plasmin. Consequently, the interaction between melanocytes and keratinocytes is disrupted. The suppression of the plasminogen/plasmin system leads to decreased production of arachidonic acid and prostaglandins, which serve as inflammatory mediators and melanocyte stimulators, ultimately diminishing tyrosinase activity in melanocytes (15). Histologically, TA administration results in reduced epidermal melanin, mast cell count, and dermal vascularization. Thus, this study further underscores the notion that topical TA exhibits efficacy comparable to topical HQ in ameliorating melasma, particularly the mixed type, among individuals in Indonesia.

The MI serves as a crucial parameter in various studies evaluating therapy efficacy in melasma. For instance, a study conducted by Ayuthaya et al. (25) in Thailand demonstrated a significant decrease in MI scores following the administration of topical 5% TA over a 12-week period. Notably, the study employed a higher concentration of topical TA, which was hypothesized to enhance therapy effectiveness. However, no comparative studies have been conducted to ascertain the superiority of topical TA at varying concentration levels. Nonetheless, this study corroborates the efficacy of topical TA in reducing skin pigmentation levels among melasma patients, comparable to HQ, as evidenced by the notable reduction in MI scores.

On the other hand, differences emerge in contrast to previous research conducted in Palembang by Marpaung et al. (19), who reported that the decrease in MI scores after week 8 in epidermal type melasma, when treated with the 3% TA group, exceeded that in the 4% HQ group, although the difference did not reach statistical significance. In Egypt, El-Husseiny et al. (26) also found that the TA 5% group reduced the average level of melanin more than the HQ 4% group in cases of epidermal type melasma. However, our study focused on mixed-type melasma. This discrepancy is believed to be attributed to differences in the study subjects: 78% of the patients in the study of mixed-type melasma had previously been recognized as having the most common type in Asia, especially in Indonesia, and it exhibited greater resistance to therapy (23, 27).

A study by Shihab et al. (28) reported that changes in MI were less pronounced compared to the alterations observed in mMASI scores. This distinction arises from the fact that MI focuses solely on pigmentation and measures it at a single point within the melasma-affected facial region, whereas mMASI comprehensively evaluates the entire area. Pandya et al. (6) pointed out that the MASI score demonstrated superior reliability and validity when compared to the melasma severity scale (MSS), the Mexameter, and other computer-based measurements. In addition, variations in skin color could influence the MI values measured by the Mexameter.

This observation concurs with several studies conducted in Japan and New Zealand, which noted that MI measurements with the Mexameter tended to be higher in patients with darker skin tones. Likewise, in our study, we also noticed that patients with darker skin tones exhibited higher MI values. Furthermore, other factors that might have influenced the MI scores in this study included challenges in limiting UV exposure. It is established that melanogenesis processes reach their peak, resulting in increased skin pigmentation, after 3 to 7 days of UV exposure (29). Despite our efforts to educate and provide sunscreen to all study participants, Indonesia's tropical location near the equator subjects it to stronger sun exposure. This environmental aspect could have impacted the MI scores in the study subjects (30).

Patient global assessment and side effects

This study determined that there are no statistically significant differences in PtGA scores between the 3% TA group and the 4% HQ group. In a separate study conducted by Janney et al. (23), which compared the effectiveness of 5% TA with 3% HQ on melasma patients, it was revealed that the satisfaction score in the 5% TA group significantly outperformed the 3% HQ group. Furthermore, all participants in our study exhibited full compliance (100%). These findings underscore the favorable response of melasma patients to the use of 3% TA cream, suggesting it as a viable therapeutic alternative to HQ cream. Similarly, Janney et al. (23) reported a notably higher incidence of side effects in patients treated with HQ compared to those treated with TA. The side effects due to TA were limited to irritation (6%), and none of the patients experienced erythema.

Systemic side effects from the use of topical TA have not been reported. This lack of systemic effects is attributed to the minimal absorption of topical TA into the bloodstream, and, up to this point, no studies have explored the pharmacokinetics of topical TA (15). Furthermore, our research reveals that the administration of 3% TA cream results in fewer side effects compared to the use of 4% HQ cream. Consequently, it can be concluded that 3% TA cream is a safe and well-accepted treatment option for melasma patients, especially for those that cannot use or tolerate HQ cream.

Limitations of this study include its relatively short duration, which precludes the assessment of the long-term effectiveness and safety of topical TA.

Conclusions

The topical application of 3% TA cream notably reduces both mMASI and MI scores compared to baseline. However, there is no significant disparity in the reduction of mMASI scores between the 3% TA group and the 4% HQ group. These findings suggest that topical 3% TA cream holds promise as an effective therapeutic option for mixed-type melasma. In addition, it is well-tolerated and accepted by melasma patients, exhibiting significant differ-

ences in side effects compared to topical HQ.

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