

Therapeutic efficiency and safety assessment of intradermal platelet-rich plasma combined with oral tranexamic acid in patients with facial melasma

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Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2025;34(4):529–537

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Funding sources

This study was funded by Walailak University, Thailand (grant No. WU-66236).

Conflict of interest

None declared

Received on October 2, 2023

Reviewed on November 20, 2023

Accepted on April 23, 2024

Published online on June 27, 2024

Cite as

Tawanwongsri W, Siri-Archawawat D, Sindhusen S, Eden C. Therapeutic efficiency and safety assessment of intradermal platelet-rich plasma combined with oral tranexamic acid in patients with facial melasma. *Adv Clin Exp Med.* 2025;34(4):529–537. doi:10.17219/acem/187874

DOI

10.17219/acem/187874

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Abstract

Background. Melasma is a chronic, acquired hypermelanosis that primarily affects the face. Platelet-rich plasma (PRP) and tranexamic acid (TXA) are promising treatments for melasma. However, only a few randomized clinical trials have examined the efficacy and safety of combining these therapies for melasma.

Objectives. We aimed to compare the efficacy and safety of combining PRP and oral TXA with those of PRP alone in the treatment of facial melasma.

Materials and methods. A randomized controlled trial was conducted at Walailak University Hospital, Nakhon Si Thammarat, Thailand, between March and September 2023. Participants with mixed-type melasma were randomly allocated in a 1:1 ratio to either group A (PRP injection alone without placebo) or group B (PRP injection with oral TXA). Therapeutic efficacy and safety assessments were performed over a 12-week follow-up period.

Results. The study included 26 participants (mean age: 45.9 years, standard deviation ($\pm$ SD): 5.0) who were predominantly female (84.6%). In group A, the modified Melasma Area and Severity Index (mMASI) scores significantly decreased from a median of 4.30 interquartile range (IQR): 4.10 to 3.60 (IQR: 3.10) between week 0 and week 12, respectively. In group B, the median mMASI decreased from 6.40 (IQR: 7.80) to 3.60 (IQR: 3.70) over the same period. The median change in mMASI scores in group B (2.90, IQR: 2.40) was significantly larger than in group A (0.90, IQR: 0.60) ($p < 0.001$, $U = 160.50$). However, there were no significant differences in the physicians' global assessment (PGA), melasma quality of life scale (MelasQoL) or patient satisfaction during follow-up. Four patients (15.4%) experienced transient erythema and swelling. In group B, 1 participant (7.7%) experienced transient mild gastrointestinal discomfort after receiving oral TXA.

Conclusions. The combination of intradermal PRP injection and oral TXA is effective for melasma, even in patients with poor prognostic treatment response factors. No serious adverse reactions were observed in either group.

Key words: efficiency, safety, platelet-rich plasma, tranexamic acid, melasma

Background

Melasma is a chronic, acquired hypermelanosis characterized by asymmetric, irregular, brown, reticulated macules and patches on photoexposed areas of the skin, especially the face. The most commonly affected facial sites are the zygomatic, labial superior and frontal areas,¹ with a prevalence ranging from 9% to 50% (higher in the Asian population).² Risk factors include genetic predisposition, sun exposure, skin tone, hormonal influences, and certain medications (e.g., antiepileptics and phototoxic drugs).^{1,3,4} Based on clinicopathologic findings, melasma is classified into 3 types: epidermal, dermal and mixed.⁵

Although melasma does not result in serious physical morbidities, approx. 80% of patients with melasma report psychiatric comorbidities, such as major depressive disorders, adjustment disorders and higher functional disabilities.⁶ To date, the treatment of melasma is challenging. The general recommendations include the avoidance of triggers, sun protection, avoiding the application of cosmetics containing excessive mercury and lead, sleeping well, and maintaining a good mood.⁷ According to the European Society of Laser Dermatology,⁸ lasers and intense pulsed light sources are recognized as viable treatment modalities for a variety of hyperpigmented lesions. This is primarily because melanosomes, which are the storage sites for melanin, are the principal target in most hyperpigmented disorders. Consequently, the majority of lasers employed for treating hyperpigmented lesions are Q-switched (QS). These lasers facilitate appropriate pulse durations based on the principle of selective photothermolysis.⁹ Notably, in the case of melasma, the combined use of Kligman's trio and a pulsed dye laser has been observed to significantly reduce the severity and recurrence of melasma.⁸ The therapeutic landscape has recently expanded to include an alternative treatment approach, particularly during a hydroquinone holiday. This novel method involves the combination of platelet-rich plasma (PRP) and oral tranexamic acid (TXA), which has been garnering increasing attention as an effective treatment option. Transforming growth factor- β 1 in PRP plays a crucial role in inhibiting melanin synthesis via extracellular signal-regulated kinases.¹⁰ Moreover, platelet-derived growth factor (PDGF) increases the skin volume with pigmentary improvement via the stimulation of blood vessel formation and synthesis of collagen and other components of the extracellular matrix (ECM).¹¹ Meanwhile, the anti-plasmin effect of TXA is regarded as the major hypopigmentary mechanism. Additionally, it competitively inhibits tyrosinase enzyme activity and decreases the intensity of keratinocyte–melanocyte interactions.^{12,13}

Both PRP and TXA have proven to be promising treatment options for melasma treatment.^{14,15} In Thailand, randomized clinical trials are limited in assessing the efficacy and safety of intradermal PRP combined with oral TXA for facial melasma. Sirithanabadeekul et al. conducted

a split-face, single-blinded trial comparing PRP to normal saline in treating this condition.¹⁶ The study noted a significant improvement in the PRP group with a mean modified Melasma Area and Severity Index (mMASI) score increase of 1.03 ± 0.44 from baseline to week 10. However, further research is needed to confirm the efficacy of this combination treatment of intradermal PRP combined with oral TXA for facial melasma.

Objectives

Our primary objective was to compare the effectiveness of combining PRP and oral TXA with PRP alone for treating facial melasma. The secondary objective was to assess the safety of these interventions.

Materials and methods

Participants

This prospective investigator-blinded randomized trial was conducted between March and September 2023 at the Walailak University Hospital, Nakhon Si Thammarat, Thailand. The inclusion criteria were as follows: 1) age between 18 and 55 years and 2) a clinical diagnosis of bilateral mixed-type melasma by a board-certified dermatologist. In patients with mixed-type melasma, assessments were conducted using a Wood's light. This type of melasma was identified by the simultaneous presence of both epidermal and dermal patterns. When examined under Wood's light, the epidermal type of melasma showed intensified pigmentation, characterized by uniform enhancement and a well-defined border. In contrast, the dermal type did not exhibit intensified pigmentation under Wood's light and was marked by an ill-defined border.^{17,18} The exclusion criteria included: 1) participants who refused to participate in the study; 2) having an allergic history to lidocaine, prilocaine, TXA, sodium citrate, chlorhexidine, or isopropyl alcohol; 3) any concurrent melasma treatments within 6 months; 4) pregnancy or lactation; 5) hematologic, neurologic or oncological diseases; 6) smoking or alcohol abuse; 7) taking hormonal therapy, retinoids, or antiarrhythmic medications, including amiodarone, bretylium, sotalol, dofetilide; and 8) severe hepatic or renal impairment. The participants were randomly allocated in a 1:1 ratio to either group A (PRP injection alone without placebo) or group B (PRP injection with oral TXA).

This clinical trial was registered with the Thai Clinical Trials Registry (No. TCTR20230317003). The ethics committee took into account and complied with Thailand's laws, including the Personal Data Protection Act. To ensure confidentiality, all data files and sensitive personal information were encrypted, password-protected, and saved on a secure computer that was accessible only by study coordinators.

The participants accessed their own data by directly contacting the study coordinators. No information linking individuals to the data was revealed. Twelve months after the completion of the study, all data were deleted.

This prospective study was approved by the Walailak Ethics Committee (approval No. WUEC-23-069-01). Written informed consent was obtained from all participants after a full explanation of the study. This study complied with the principles of the Declaration of Helsinki and the International Conference on the Harmonization of Good Clinical Practice.

Preparation of platelet-rich plasma

At each treatment session, whole blood (16 mL) was obtained by venipuncture and divided into 2 10-mL tubes containing acid citrate dextrose and gel (8 mL each; Bio-Medica, Gyeonggi-do, South Korea). A single centrifugation technique was used as the preparation method.¹⁹ Blood plasma was obtained by centrifugation of the whole blood at 3,200 rpm for 10 min, followed by collection of the final sample (0.8 mL) from the lower $\frac{1}{3}$ of the plasma. In accordance with the classification system for platelet concentrates established by Dohan Ehrenfest et al.,²⁰ which is based on 2 key parameters: the presence or absence of cellular content (such as leukocytes) and the characteristics of the fibrin architecture, we collected the blood component situated in the lower $\frac{1}{3}$ of the portion above the separation gel following centrifugation.¹⁹ This process resulted in our PRP being categorized as pure PRP (P-PRP). During the 1st treatment, additional blood (8 mL) was collected for PRP preparation and sent for platelet counting.

Procedure and evaluation

We adhered to the protocols recommended in previous studies.^{16,21} A local anesthetic cream containing 2.5% lidocaine and 2.5% prilocaine (EMLA; Recipharm Karlskoga AB, Karlskoga, Sweden) was applied to lesions and occluded with a film for 40 min before wiping, leaving the skin dry. After disinfecting the skin with 2% chlorhexidine in 70% isopropyl alcohol, PRP (0.1 mL/cm²) was injected intradermally into the bilateral affected areas. This procedure entailed multiple injections with a 30G needle into the dermis, spacing each injection about 1 cm apart. This treatment was administered 3 times at 4-week intervals. All participants were instructed to apply broad-spectrum sunscreen, avoid sun exposure, and not use any topical skin-whitening treatments on the lesions during the study. In group B, participants were given oral TXA at a dosage of 500 mg/day for 12 weeks, in addition to receiving PRP treatment. Assessments were conducted at baseline and 4, 8 and 12 weeks. The mMASI²² and Physician's Global Assessment (PGA)¹⁸ were evaluated by a blinded investigator (D.S.). The mMASI score ranged from 0 to 24, and the PGA scores ranged from 0 to 6. A score of 0 indicated

clear skin, except for possible residual discoloration, while a score of 6 indicated a worsening condition compared to week 0. Patient satisfaction and the Melasma Quality of Life Scale (MelasQoL) were collected for further analysis.²³ The instrument was constructed to evaluate the social life, recreation, leisure, and emotional wellbeing of patients. The MelasQoL score ranges from 7 to 70, with a higher score indicating worse melasma-related health-related quality of life (HRQoL). Their satisfaction levels were categorized as follows: very satisfied (>75% improvement), satisfied (51–75% improvement), average (25–50% improvement), or dissatisfied (<25% improvement).⁷

Statistical analyses

Our sample size calculation, determined by a preceding study,²⁴ was based on an alpha level of 0.01, a power of 90% and an effect size (Cohen's *d*) of 1.86. The total sample size initially included 22 adult participants. However, to accommodate a potential follow-up loss of 20%, we determined that approx. 26 participants would need to be recruited for the study, thereby ensuring the robustness of our findings.

Continuous data were reported as means and standard deviations ($\pm$ SDs) or medians and interquartile ranges (IQRs). Categorical data were presented as frequencies and percentages. A paired *t*-test or Mann–Whitney–Wilcoxon test was used to compare variables, such as age, Fitzpatrick skin type, onset of melasma, mMASI, PGA, MelasQoL, and satisfaction scores. Spearman's rho was used to assess the correlation between ordinal or non-normally distributed variables. Due to the small sample size, Fisher's exact test was employed for analyzing associations among categorical data. The independent *t*-test was applied to compare means between 2 independent groups under the assumption of normal distribution. The Mann–Whitney *U* test, a non-parametric alternative, was used for comparing 2 independent groups when data did not follow a normal distribution. The statistical significance was determined using 2-tailed tests with a *p*-value of less than 0.05. Statistical analyses were performed using SPSS v. 18 software (SPSS Inc., Chicago, USA).

In addition, we employed a robust heteroscedastic repeated measures analysis of variance (ANOVA), complemented by post hoc tests, to evaluate within-group differences across repeated measurements and to conduct between-group comparisons of the mMASI and MelasQoL scores between groups A and B. This robust ANOVA approach allowed for the integration of both types of comparisons into a single model, thereby enhancing the coherence and statistical power of our analysis. The analyses were conducted using the WRS2 package in the R program (R Foundation for Statistical Computing, Vienna, Austria).²⁵ Supplementary Tables 3–8 display the detailed, robust ANOVA for mMASI, including main effects for the group and time, the interaction between group and time, and effect sizes for between-group and within-group comparisons at different

times. Supplementary Methods 1–4 detail the analysis methods and include the corresponding R scripts, ensuring the reproducibility of the statistical analyses.

Results

A total of 26 participants were enrolled in the study, and no patients were lost to follow-up. The participants had a mean age of 45.9 years with a SD of ± 5.0 , with the majority of participants being female (84.6% of the group). The majority ($n = 17$, 65.4%) of participants had no comorbidities. However, some participants had comorbidities, including dyslipidemia ($n = 7$, 26.9%), allergic rhinitis ($n = 3$, 11.5%), type 2 diabetes mellitus ($n = 1$, 3.8%), and essential hypertension ($n = 1$, 3.8%). Table 1 presents the characteristics of participants in both groups.

In group A, the median baseline mMASI score was 4.30 with an IQR of 4.10, while in group B, it was 6.40 with an IQR of 7.80. In group A, the mMASI scores demonstrated a notable decline from baseline. The scores were 3.70 (IQR: 3.80), 3.70 (IQR: 2.30) and 3.60 (IQR: 3.10) at weeks 4, 8 and 12, respectively. The mMASI scores showed a significant decrease from baseline at week 0 to week 12 ($p < 0.001$; test statistic = 0.922, 95% confidence interval (95% CI): 0.407–1.438), with a median change of 0.90 and an IQR of 0.60. In group B, the mMASI scores also demonstrated a notable decline from the baseline. The scores were 4.50 (IQR: 6.50), 4.00 (IQR: 4.60) and 3.60 (IQR: 3.70) at weeks 4, 8 and 12, respectively. From baseline to week 12, the mMASI scores showed a significant decrease ($p = 0.002$, test statistic = 3.344, 95% CI: 0.752–5.937), with a median change of 2.90 and an IQR of 2.40. The median change in mMASI from week 0 to week 12

Table 1. Participants' characteristics

Measured parameters		Group A (n = 13)	Group B (n = 13)	p-value
Gender, n (%)	female	10 (76.9)	12 (92.3)	0.593
	male	3 (23.1)	1 (7.7)	
Age [years], mean ($\pm$ SD)		44.5 (± 3.5)	47.2 (± 6.0)	0.174
Fitzpatrick skin type, n (%)	type III	3 (23.1)	4 (30.8)	1.000
	type IV	10 (76.9)	9 (69.2)	
Onset [years], median (IQR)		5.0 (3.0)	5.0 (6.0)	0.545
mMASI, median (IQR)	week 0	4.30 (4.10)	6.40 (7.80)	0.208
	week 4	3.70 (3.80)	4.50 (6.50)	0.397
	week 8	3.70 (2.30)	4.00 (4.60)	0.523
	week 12	3.60 (3.10)	3.60 (3.70)	0.892
Changes of mMASI scores, median (IQR) (from week 0 to week 12)		0.90 (0.60)	2.90 (2.40)	0.006
MelasQoL, median (IQR)	week 0	26.00 (34.00)	45.00 (18.00)	0.810
	week 4	23.00 (16.00)	40.00 (24.00)	0.606
	week 8	20.00 (11.00)	40.00 (17.00)	0.223
	week 12	18.00 (12.00)	36.00 (27.00)	0.186
Changes of MelasQoL scores, mean ($\pm$ SD) (from week 0 to week 12)		7.92 (± 12.33)	5.85 (± 11.55)	0.834
PGA week 12, n (%)	score 0	0 (0)	0 (0)	1.000
	score 1	0 (0)	0 (0)	
	score 2	3 (23.1)	4 (30.8)	
	score 3	7 (53.8)	7 (53.8)	
	score 4	3 (23.1)	2 (15.4)	
	score 5	0 (0)	0 (0)	
Patient satisfaction week 12, n (%)	score 6	0 (0)	0 (0)	0.215
	score 1	0 (0)	0 (0)	
	score 2	2 (15.4)	0 (0)	
	score 3	6 (46.2)	4 (30.8)	
	score 4	5 (38.5)	9 (69.2)	

Group A – PRP injection alone without placebo; Group B – PRP injection with oral tranexamic acid; IQR – interquartile range; MelasQoL – Melasma Quality of Life scale; mMASI – modified Melasma Area Severity Index; PGA – Physician's Global Assessment; PRP – platelet-rich plasma; SD – standard deviation. The names and values of the tests are presented in Supplementary File 1.

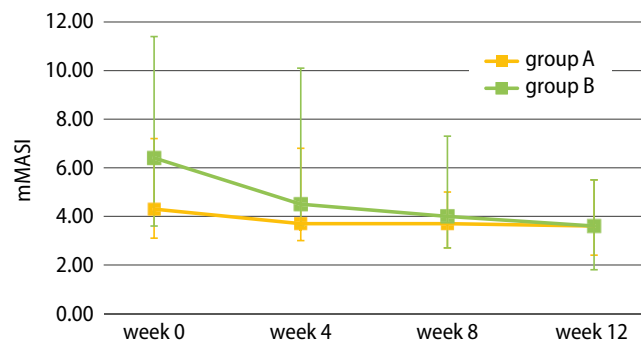


Fig. 1. The modified Melasma Area Severity Index (mMASI) scores recorded during follow-up visits

This line graph illustrates the mMASI. Group A, shown with a yellow line, consisted of participants who received platelet-rich plasma (PRP) injections without a placebo. Group B, indicated by a green line, included participants treated with PRP injections in conjunction with oral tranexamic acid. Squares represent the median mMASI scores for each group over a span of 12 weeks and error bars display the interquartile range (IQR).

was significantly greater in group B compared to group A ($p = 0.006$, test statistic = 3.610, 95% CI: -3.950 — 0.895 , $df = 9$). The comparative analysis between the 2 groups and the comparison of repeated data in groups A and B are provided in Supplementary File 1. The presentation of mMASI scores during the follow-up visit is depicted in Fig. 1. Photographs taken before (at week 0) and after (at week 12) the intervention, showcasing the comparison between groups A and B, are presented in Fig. 2,3. At week 12, melasma severity in group A was assessed using PGA scores, with 3 participants (23.1%) scoring 2, 7 participants (53.8%) scoring 3 and 3 participants (23.1%) scoring 4. In contrast, in group B, the melasma severity was rated by 4 participants (30.8%) with a score of 2, 7 participants (53.8%) with a score of 3 and 2 participants (15.4%) with a score of 4.

According to the MelasQoL scores, the median baseline scores were 26.00 (IQR: 34.00) in group A and 45.00 (IQR: 18.00) in group B. In group A, the score declined to 23.00 (IQR: 16.00), 20.00 (IQR: 11.00), and 18.00 (IQR: 12.00) at weeks 4, 8 and 12, respectively. From baseline to week 12, the MelasQoL scores exhibited a statistically

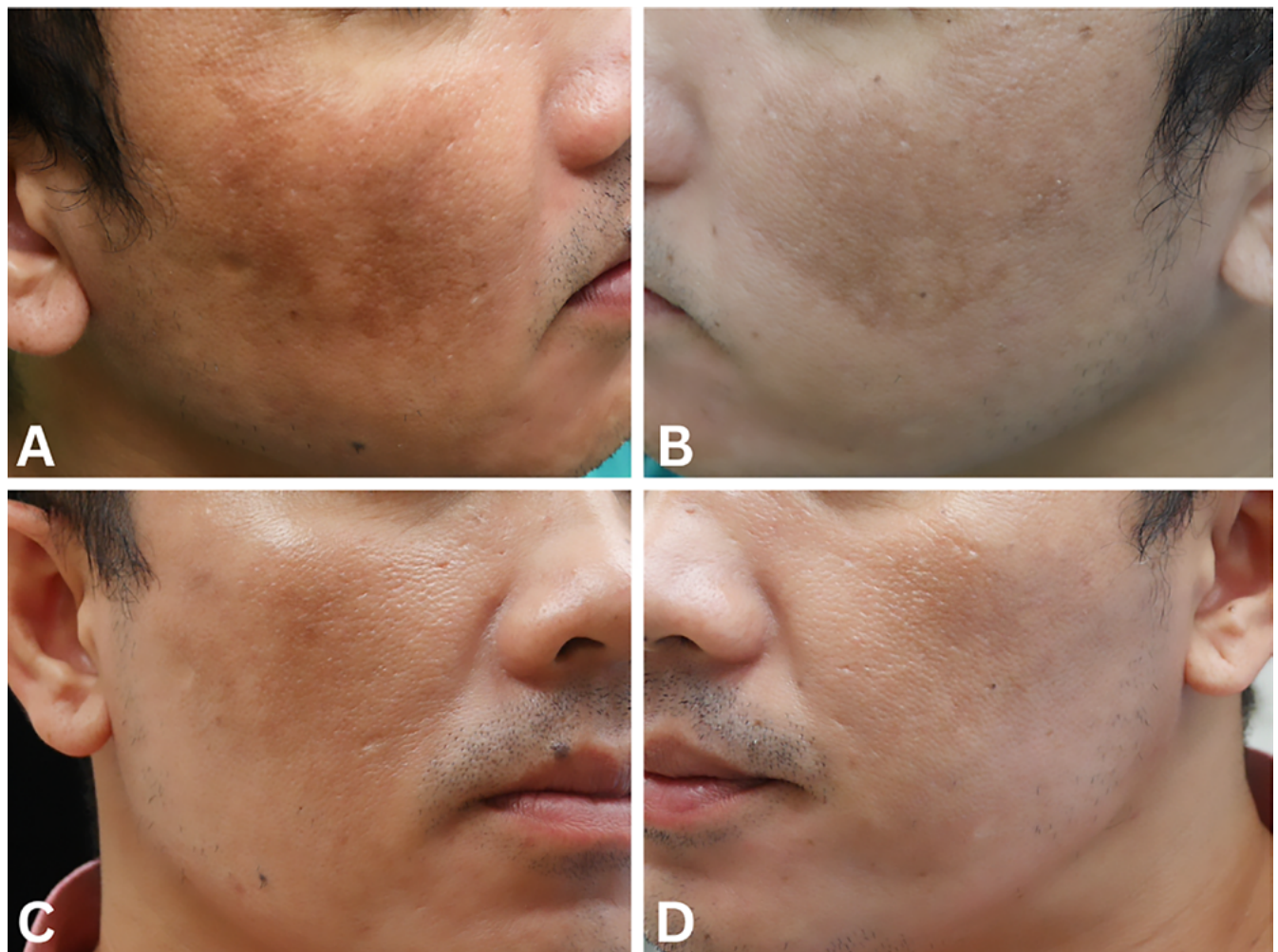


Fig. 2. Comparative photographs of group A, taken before the intervention (week 0) and after the intervention (week 12), illustrating the observed changes. The right side of the face (A) and the left side of the face (B) are shown at week 0, and the right side of the face (C) and the left side of the face (D) are shown at week 12

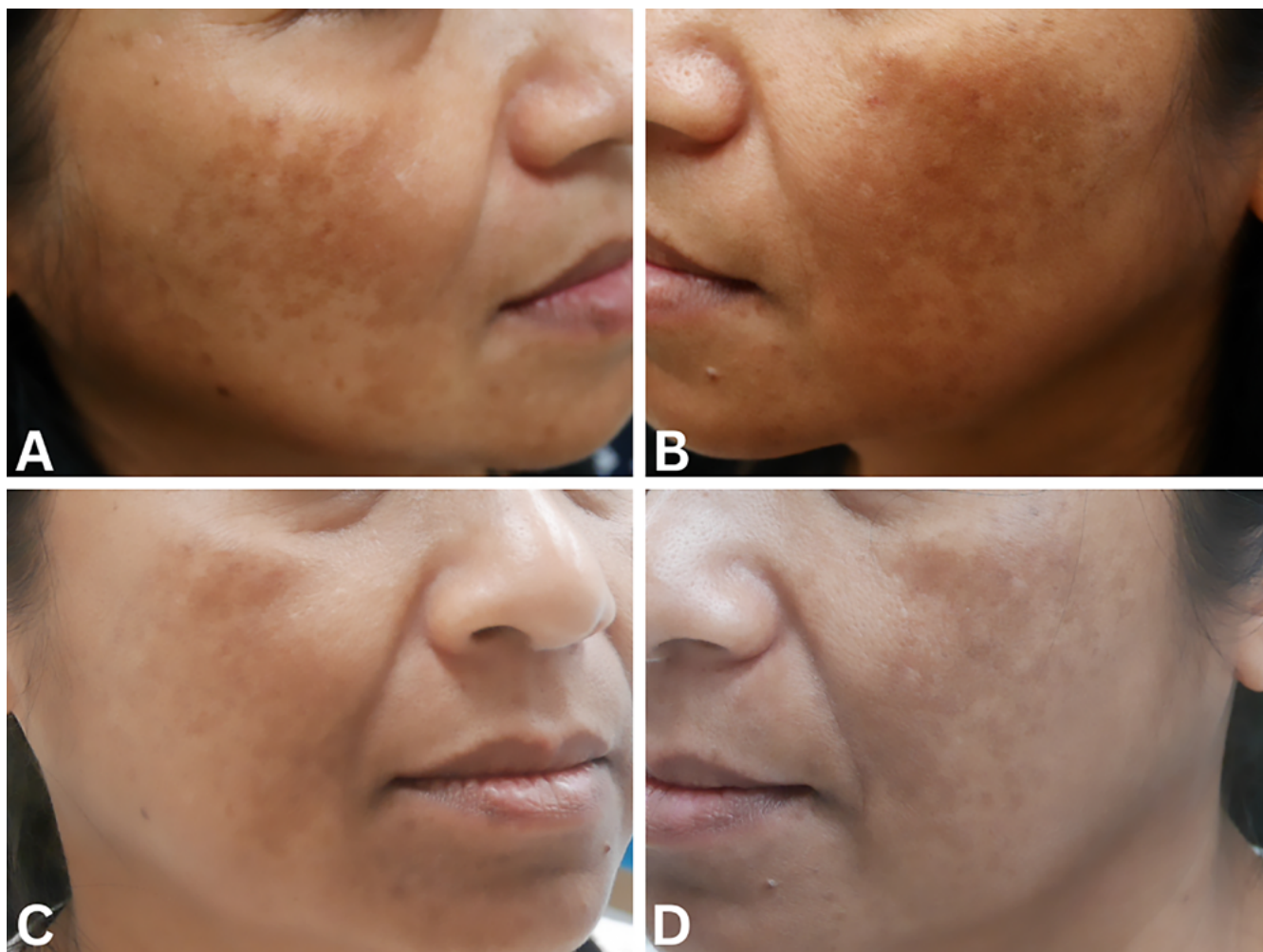


Fig. 3. Comparative photographs of group B taken before the intervention (week 0) and after the intervention (week 12), illustrating the observed changes. The right side of the face (A) and the left side of the face (B) are shown at week 0, and the right side of the face (C) and the left side of the face (D) are shown at week 12

significant decrease ($p = 0.047$, test statistic = 4.889, 95% CI: $-2.376-12.154$), with a mean change of 7.92 and an SD of 12.33. In group B, the score also declined to 40.00 (IQR: 24.00), 40.00 (IQR: 17.00) and 36.00 (IQR: 27.00) at weeks 4, 8 and 12, respectively. Between baseline and week 12, there was a nonsignificant reduction in MelasQoL scores ($p = 0.050$, test statistic = 9.444, 95% CI: $-4.841-23.730$), characterized by an average change of 5.85 with a SD of ± 11.55 . The mean change in MelasQoL from week 0 to week 12 did not differ significantly between both groups ($p = 0.834$, test statistic = 0.214, 95% CI: $-8.051-9.829$, $df = 13$). At week 12, in group A, patient satisfaction with treatment was rated as a score of 2 by 2 participants (15.4%), a score of 3 by 6 participants (46.2%) and a score of 4 by 5 participants (38.5%). In group B, 4 participants (30.8%) rated it with a score of 3, while 9 participants (69.2%) rated it with a score of 4. We utilized Spearman's correlations to analyze this ordinal or non-normally distributed data. There was no significant correlation between the mMASI and MelasQoL scores either at week 0 ($r = 0.34$, $p = 0.090$) or at week 12 ($r = 0.20$, $p = 0.321$). Additionally,

no correlation was observed between PGA and satisfaction levels at week 12 ($r = 0.15$, $p = 0.478$). However, a significant correlation was found between the improvement in mMASI scores and satisfaction levels at the conclusion of the study ($r = 0.52$, $p = 0.007$).

Four participants (15.4%) in our study experienced transient erythema and swelling, which mostly resolved within 4 h (IQR: 3.5). They also reported mild pain during the injection, with a mean of 3.4 (SD: ± 1.7). In group B, 1 participant (7.7%) experienced transient mild gastrointestinal discomfort within the 1st week of oral TXA administration, with no subsequent symptoms reported. The medication was not discontinued and was well tolerated for the entirety of the study period.

Discussion

Both PRP and TXA have proven to be efficacious treatments for melasma. However, there are still a limited number of controlled clinical trials to confirm the efficacy

of this combination.¹⁷ Our findings revealed a significantly larger decrease in melasma severity, as measured using mMASI, among participants treated with PRP injection combined with oral TXA compared to those treated with PRP injection alone. Additionally, no serious adverse reactions were noted in participants treated with oral TXA, except for mildly tolerable gastrointestinal symptoms.

Platelet-rich plasma consists of a mixture of growth factors and cytokines, which includes transforming growth factor beta 1 (TGF- β 1), PDGF and epidermal growth factor (EGF).²⁶ Transforming growth factor beta 1 inhibits melanogenesis by suppressing the signal transduction of microphthalmia-associated transcription factor, resulting in a decrease in tyrosinase and tyrosinase-related proteins.^{21,27} Furthermore, it promotes the expression of laminin, type IV collagen and tenascin, facilitating basement membrane repair and preventing the infiltration of melanocytes and melanin into the dermis.²⁸ Platelet-derived growth factor plays a pivotal role in angiogenesis and contributes to the synthesis of collagen and various components of the ECM, including hyaluronic acid, ultimately enhancing skin homogeneity and volume.²⁹ Epidermal growth factor curtails melanogenesis by suppressing prostaglandin E2 and tyrosinase activity.³⁰ The effectiveness of PRP in treating melasma resulted in a decrease in the mMASI score of 1.18 (95% CI: 0.89–1.47; $p = 0.02$).¹⁴

The main mechanism of action of TXA in the treatment of melasma is its anti-plasmin activity. Plasmin is involved in converting pro-opiomelanocortin (POMC) into melanocyte-stimulating hormone (MSH) and releasing basic fibroblast growth factor (bFGF), which promotes melanocyte proliferation.³¹ Tranexamic acid, due to its structural similarity to tyrosine, can competitively inhibit the tyrosinase enzyme's activity.¹³ Additionally, TXA decreases the quantity of blood vessels in the dermal layer and prevents neovascularization triggered by bFGF.³² The oral administration of TXA leads to a reduction in melasma severity, as measured using the MASI score, compared to its topical (–1.85, 95% CI: –2.56––1.14) and intradermal forms (–1.67, 95% CI: –1.99––1.36), with a greater reduction of –1.87 (95% CI: –2.46––1.28). Moreover, a meta-analysis revealed that oral TXA treatment exhibited less heterogeneity compared to that of topical TXA.³³

Gamea et al. demonstrated that individuals with melasma who received a combination of PRP and topical TXA experienced a significant improvement in the mMASI score compared with those treated solely with topical TXA. In the combination therapy group, the mMASI score decreased from 12.1 ± 2.9 to 3.6 ± 1.9 ($p < 0.001$).¹⁵ Our findings revealed that the improvement in the mMASI score within the combination therapy group was 2.90, with an IQR of 2.40. This change was more significant than that of PRP-alone or oral TXA-alone groups in previous studies.^{14,33} However, when compared to the findings of Gamea et al., the observed change appeared to be lower. The plausible explanation for this could be that

the participants in this study had poorer prognostic factors for melasma treatment, including a longer duration of disease (≥ 2 years) and mixed-type melasma.³⁴ Furthermore, the severity of melasma in our study was categorized as mild-to-moderate.³⁵ Therefore, it might not have been possible to observe a significant improvement.

In our study, we evaluated the efficacy of melasma treatments using 3 measures: The mMASI, PGA and patient satisfaction levels.⁷ The mMASI score has been established as a reliable, valid and responsive method for evaluating the severity of melasma.^{22,36,37} Additionally, PGA assessments have demonstrated moderate intra- and inter-rater agreement.³⁸ However, there is a notable gap in research regarding the correlation between these different evaluation methods. In a study by Tekam and Belgaumkar,³⁹ the efficacy of combining autologous platelet-rich plasma (PRP) with hydroquinone 4% was compared to that of hydroquinone alone. Their findings indicated that the combination therapy led to statistically significant improvements in mMASI, patient satisfaction and PGA scores. Conversely, Beyzaee et al.⁴⁰ discovered that a combination treatment involving Q-Switched Nd:YAG laser and topical methimazole 5% was significantly more effective in improving PGA scores than using methimazole 5% alone. Interestingly, there was no significant difference in mMASI scores between the 2 groups. Similarly, our results indicated significant changes in melasma severity when using mMASI scores but not when employing PGA assessments. We propose that although the PGA is a straightforward and easy-to-use scoring system, it may not capture detailed aspects such as the exact area affected and the depth of color. Therefore, the mMASI could be more sensitive in detecting minor improvements. Furthermore, considering that patient satisfaction levels were assessed by several evaluators, it is crucial to validate these assessments before the study and to re-evaluate the inter-rater reliability coefficient. Studies focusing on this correlation should be conducted to enhance our understanding of these measures in clinical settings. Moreover, a recent meta-analysis revealed that among 5 studies, a statistically significant correlation was observed between MASI and MELASQoL scores. However, 7 other studies reported no such statistical association.⁴¹ We concur that additional research, involving more substantial sample sizes, is necessary to validate the link between melasma and quality of life.

Following PRP injections, the common side effects included mild erythema, bruising, depigmentation, and hyperpigmentation.¹⁴ Similarly, only 4 participants in our study developed transient erythema and swelling, which mostly resolved within 4 h. They also reported mild pain during the injection. When considering the safety of TXA treatment, most studies reported no serious adverse drug reactions.³² They mainly noted mild gastrointestinal symptoms (2.5–5.4%), central nervous system effects (2.5%) and menstrual irregularities (0.7–8.1%). Only

1 study reported a single case of deep vein thrombosis that led to the discontinuation of TXA administration.¹² Similarly, in our study, 1 participant (7.7%) experienced transient, mild gastrointestinal discomfort within the 1st week of oral TXA administration. However, no symptoms were reported thereafter, despite continued use of the medication.

Limitations

Our study had several limitations. First, the study was conducted at a single center. Second, various techniques were used for PRP preparation in the studies, and specific bioactive concentrations were not evaluated.⁴² Therefore, this makes it challenging to directly compare the treatment outcomes between studies. Multicenter randomized controlled studies employing uniform PRP preparation methods and long-term follow-up are necessary to establish the efficacy and safety of these interventions. Third, no clinical data were collected or compared regarding sun exposure during the study period. Nevertheless, comprehensive guidance regarding sun protection and avoidance was provided to all the participants. Fourth, the majority of the participants in our study had mild-to-moderate melasma. To determine the efficacy in individuals with severe melasma, particularly those with poor prognostic treatment response factors, further studies should compare participants across a wider range of severity. Fifth, the use of anesthetics in PRP injections may reduce the effectiveness of PRP.⁴³ However, it is important to note that these in vitro studies mainly focused on tenocytes and did not include other cells or elements related to melasma. Therefore, this underscores the necessity for further verification through both in vitro and in vivo studies.

Conclusions

The combination of intradermal PRP and oral TXA is an effective treatment for melasma, even in patients with poor prognostic treatment response factors. The change in mMASI was significantly different in the combination group compared to the participants treated with intradermal PRP alone. No serious adverse reactions were observed in any group. Only mild, tolerable gastrointestinal symptoms have been reported in patients treated with oral TXA.

Supplementary data

The Supplementary materials are available at <https://doi.org/10.5281/zenodo.11297407>. The package includes the following files:

Supplementary Table 1. Normality assessment and two-group comparative analysis (n = 26).

Supplementary Table 2. Comparison of repeated data in groups A and B (n = 26).

Supplementary Table 3. Robust analysis of variance of mMASI scores by group and time using bootstrapped trimmed means.

Supplementary Table 4. The main effect for group on mMASI scores.

Supplementary Table 5. Main effect for time on mMASI scores.

Supplementary Table 6. Interaction Effect for Group $\times$ Time on mMASI scores.

Supplementary Table 7. Effect sizes from Yuen's test for trimmed means in between-group comparisons over time.

Supplementary Table 8. Effect sizes for within-group comparisons over time using Cliff's delta.

Supplementary Fig. 1. Correlation between the mMASI and MelasQoL scores at week 0 (n = 26).

Supplementary Fig. 2. Correlation between the mMASI and MelasQoL scores at week 12 (n = 26).

Supplementary Fig. 3. Correlation between PGA and satisfaction level at week 12 (n = 26).

Supplementary Fig. 4. Correlation between the improvement in mMASI scores from week 0 to week 12 and the satisfaction level at week 12 (n = 26).

Supplementary Method 1. Implementation of robust tests for two independent groups and analysis of median differences using the WRS2 package in R.

Supplementary Method 2. Implementation of robust ANOVA for repeated measures using the WRS2 package in R.

Supplementary Method 3. Computing a between-within subjects ANOVA on the trimmed means.

Supplementary Method 4. Computing effect sizes.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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