SKIN

ORIGINAL ARTICLE

The Effect of Platelet Rich Plasma Plus Microneedling Versus Tranexamic Acid Plus Microneedling in the Biometric Characteristics of Melasma: A Randomized, Controlled, Assessor-Blind Clinical Trial

Masoumeh Roohaninasab, MD[1,2], Mohammad Ali Nilforoushzadeh, MD[2,3], Zahra Ebrahimi, MD[4], Abolfazl Abouei, MD, MPH[5], Elham Ziaeifar, MD[1,2], Sona Zare, PhD[2,5,6,7], Roya Zeinali[1], Maryam Nouri, MD[2,3], Samaneh Mozafarpoor, MD[8], Azadeh Goodarzi, MD[1,2]

[1] Department of Dermatology, Rasool Akram Medical Complex Clinical Research Development Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2] Skin and Stem Cell Research Center, Tehran University of Medical Sciences, Tehran, Iran
[3] Skin Repair Research Center, Jordan Dermatology and Hair Transplantation Center, Tehran, Iran
[4] Department of General Medicine, Iran University of Medical Sciences, Tehran, Iran
[5] Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[6] Stem Cell and Regenerative Medicine Institute, Sharif University of Technology, Tehran, Iran
[7] Department of Mechanical Engineering, Sharif University of Technology, Tehran Iran
[8] Skin Diseases and Leishmaniasis Research Center, Department of Dermatology, Isfahan University of medical Sciences, Isfahan, Iran

ABSTRACT

Background: Melasma is a persistent, acquired pigmentation disorder characterized by symmetrical hyperpigmentation or hypermelanosis in sun-exposed areas of the face. Tranexamic acid (TXA) has emerged as a prominent therapeutic option for melasma. Notably, the regression of melasma following platelet-rich plasma (PRP) treatment represents an intriguing discovery.
Objectives: The primary aim of this study is to assess the efficacy of PRP combined with microneedling compared to tranexamic acid combined with microneedling in improving the severity of melasma.
Methods: This study employed a split-face comparative design involving twenty patients diagnosed with melasma. Subjects underwent four sessions of PRP with microneedling on one side of the face and tranexamic acid (5%) with microneedling on the opposite side. These sessions are conducted at four monthly intervals. The evaluations were conducted before the treatment and one month following the final session.
Results: A total of 20 female melasma patients, with a mean age of 41 years (range: 34-49 years), were enrolled. The median ΔE, reflecting color changes, exhibited a substantial decrease in follow-up (mean difference = 6.66, $P < 0.001$ in TXA + microneedling group; mean difference = 1.90, $P < 0.001$ in PRP + microneedling group). TXA + microneedling resulted in a notable reduction in melanin measured by the Mexameter. Patient satisfaction was consisted with the other research findings. Additionally, minor transient side effects were

observed, and both procedures were well-tolerated by the participants.
Conclusion: This study demonstrates that PRP and tranexamic acid, when combined with microneedling, significantly contribute to melasma improvement, representing effective treatment modalities. While neither method demonstrated superiority, their comparable efficacy, safety, tolerability, and patient satisfaction suggest that they can be employed as a synergistic combination or as viable alternatives for melasma treatment.

INTRODUCTION

Melasma is the leading cause of acquired skin hyperpigmentation, characterized by irregular light to dark brown macules and patches symmetrically distributed in sun-exposed areas of the body, especially the face.[1] This condition is more prevalent in Hispanic and Asian women of childbearing age[2], particularly those with Fitzpatrick phenotypes III and IV.[3] While the precise pathogenesis of melasma remains unclear, strong associations have been established with genetic and environmental factors.[4] Sunlight and ultraviolet exposure, hormonal influences such as those from pregnancy or birth control pills, thyroid disorders, and familial predisposition are among the recognized contributing factors.[5,6,7]

Clinical diagnosis of this condition often reveals three distinct facial patterns: centrofacial, malarial, and mandibular. The centrofacial pattern, encompassing the forehead, cheeks, nose, upper lip, and chin, is detected in 50% to 80% of cases.[6] The malarial pattern is limited to the cheeks and nose, while mandibular melasma manifests along the jawline and chin, Although predominantly (up to 90%) observed in women, melasma also occurs in men, exhibiting similar clinical and histological characteristics.[7,8]

While melasma itself does not significantly affect physical health, its impact on patients is substantial, particularly in terms of psychological, social, and emotional well-being. The condition significantly influences the quality of life, underscoring the importance of effective management and therapeutic interventions for its resolution.[9,10]

Various treatments, including hydroquinone, triple combination cream (hydroquinone, tretinoin, and corticosteroid), azelaic acid, corticosteroids, chemical peels, microdermabrasion, laser therapy, light-based and optical devices have been employed to treat melasma.[11,12] However, a unanimous consensus on a standardized or singular treatment for all patients has not been established.[13] Notably, the management of resistant melasma often involves a combination of these therapeutic modalities.[14]

Tranexamic acid (TXA) and platelet-rich plasma (PRP) have emerged as promising approaches in the treatment of melasma.[15,16] TXA, known for its anti-fibrinolytic and plasminogen activities, demonstrates efficacy in various dermatological disorders, including melasma, post-inflammation hyperpigmentation, urticaria, and angioedema.[17] Additionally, PRP, enriched with high concentrations of platelets and growth factors such as chemokines, cytokines, and plasma proteins, serves as another viable method for melasma treatment. PRP promotes the synthesis of hyaluronic acid, enhances skin brightness, and may mitigate pigment formation.[18]

Microneedling represents an additional

method that stimulates collagen and elastin production through the creation of small wounds in the skin.[19] While previous studies have individually explored the effects of TXA and PRP, combined with microneedling on melasma, limited research has directly compared the effectiveness of these methods against each other. Consequently, this study was designed to evaluate and compare the therapeutic impact of PRP + microneedling versus TXA + microneedling, both recognized as promising approaches for the treatment of melasma.

METHODS

This research was conducted as a randomized controlled trial with a single-blind design. Twenty Iranian patients diagnosed with symmetrical melasma were enrolled in this study from the dermatology outpatient clinics, with which the authors are affiliated, between March 2021 and December 2022, using convenience sampling. The ethics committee of Tehran University of Medical Sciences approved this study. Prior to the intervention, the entire procedure and potential side effects were thoroughly explained to the patients. All patients were given informed consent. Demographic data was collected from all of the participants.

Eligibility Criteria

Based on the experimental nature of the study, the primary inclusion criterion was an age of ≥18 years. Additionally, participants were required to be diagnosed with melasma on both sides of their cheeks or other facial areas. Exclusion criteria included individuals with coagulation disorders, a history of cancer, recent fever, chronic medical illness, photosensitivity or hypersensitivity to the treatment components, pregnancy, lactation, or plans for pregnancy in the near future, a history of melasma treatment within the past two months, history of hypertrophic or keloid scars, infections or inflammation in the target area, platelet disorders, thrombocytopenia (platelet count less than 50,000/mcL), and those who lacked informed consent.

Therapeutic Intervention

All patients received tranexamic acid (TXA) on the left side of their faces and platelet-rich plasma (PRP) on the right side during microneedling of the melasma lesions in a single session. Four sessions were planned with 4-week intervals for both methods.

To prepare PRP, a two-stage centrifugation process was employed. Twenty milliliters (mL) of whole blood were drawn from each patient and collected in two sterile tubes, each containing 1.5 cc of ACDA (acid citrate-dextrose anticoagulant). The tubes were gently inverted a few times to mix the anticoagulants with the blood. The first centrifugation (Hettich Universal 320, Germany) was set at 1500 RPM for 10 minutes. In this step red and white blood cells were separated from plasma and platelets at room temperature. For the second centrifugation, all contents of the tubes, except the red blood cells, were transferred to new tubes and centrifuged for 5 minutes at 1200 RPM. Finally, the prepared PRP was comprised of 3-4 times more concentrated platelets than whole blood. Following this, PRP was aspirated from the tubes and transferred into 1-mL insulin syringes. To activate the platelets, 0.1 mL of calcium chloride was added to 0.9 mL of PRP, and five 1-mL insulin syringes of PRP were provided for each participant.

A 500mg/5ml ampule of tranexamic acid, containing 5% of the active ingredient (Caspian Tamin Pharmaceutical Co., Iran), was aspirated into a 5cc syringe.

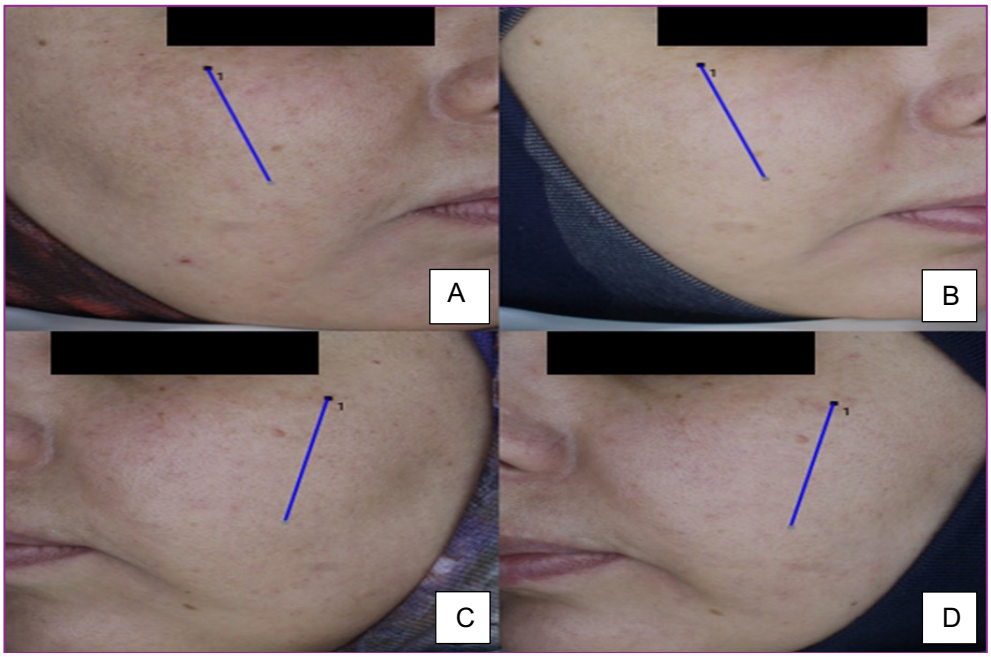

Figure 1. (A) Right side before treatment (B) Right side after treatment (C) left side before treatment (D) Left side after treatment

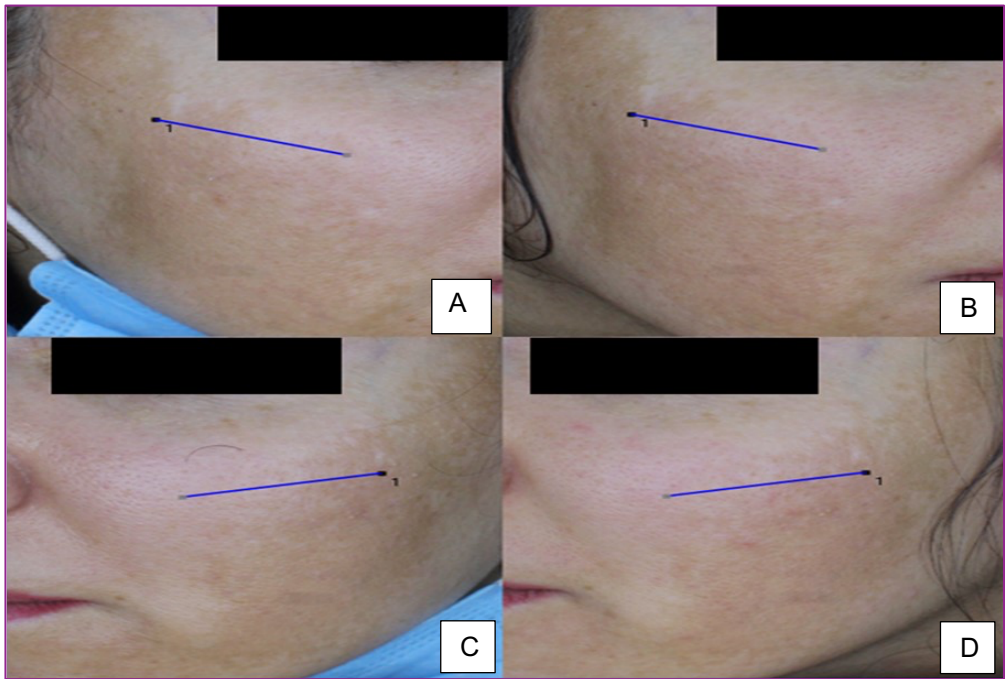

Figure 2. (A) Right side before treatment (B) Right side after treatment (C) left side before treatment (D) Left side after treatment

Microneedling (AMIEA MED microneedling, MT. Derm, Germany) with single-use cartridges, containing 6 sterile needles, was utilized on both sides. Needling was conducted with needle depths ranging from 1 to 1.5 millimeters until pinpoint bleeding was achieved. The procedure involved moving the microneedling cartridge in a circular

Table 1. Colorimeter measurement

Variables		Mean (SD)	Minimum	Maximum	Paired-Samples Test	P-value
Tewameter	Right-before	21.26 (7.11)	10.08	36.01	t=3.457	0.003
	Right-after	17.93 (5.76)	11.05	31.09		
	Left-before	20.36 (5.14)	13.04	30.20	t=1.815	0.003
	Left-after	18.21 (5.46)	8.07	29.07		
Melanin-Mexameter	Right-before	205.48 (28.05)	171.33	262.67	t=0.587	0.565
	Right-after	200.56 (47.34)	101.00	257.67		
	Left-before	205.56 (30.16)	168.00	259.33	t=3.876	0.001
	Left-after	190.02 (30.63)	134.33	229.67		

pattern in a horizontal and vertical vector, with 2-3 passes over the entire face. Simultaneously, both ampoules were dispensed over the melasma using a dropping technique for drug delivery purposes. PRP was applied over the melasma on the right side (PM group), and tranexamic acid was applied on the left side (TM group). The patients were unaware of the side of each procedure. Based on the side of the melasma, 3-5 cc of each drug was used. Any remaining solution was gently massaged over the treated area at the of the procedure.

Patients were instructed to apply 2.5% lidocaine/prilocaine cream (Xyla-P, Tehran Chemie Pharmaceuticals, Iran) for local analgesia 30 minutes before the intervention session. Sterile gauze was used to remove the cream, and the face was disinfected and cleaned with 70% alcohol swabs.

Following each session, zinc oxide ointment, topical antibiotics, and Acyclovir 400 mg tablets were prescribed for all patients. Patients were advised to avoid sun exposure for the first four days and to apply a sunscreen with at least SPF 50 throughout the entire treatment course.

Outcome Assessments

The outcomes were assessed one month following the final treatment session by the same attending physician. To the best of our knowledge, this study represents the first investigation utilizing biometric characteristics for the assessment of melasma improvement.

For biometric evaluation, a Colorimeter was employed to measure skin lightness, the Tewameter served as the measure of transepidermal water loss, the Corneometer was utilized to evaluate skin hydration, and the Visioface 1000 D, a method for full-face photographic analysis for facial skin was used (all purchased from Courage + Khazaka Electronics, Germany).20 The Mexameter MX 18 probe (Units: arbitrary Mexameter units [0–999]; Measurement uncertainty: ±5%; Device: Multi Probe Adapter MPA 10 [Courage + Khazaka electronic GmbH, Germany]) was utilized to quantify melanin content and skin erythema intensity. Furthermore, the ΔE using Visioface

Table 2. Colorimeter measurement

Variables		Median (IQR)	Minimum	Maximum	Wilcoxon Test	P-value
Erythema-Mexameter	Right-before	354.33 (57.34)	301.67	431.00	Z=-1.766	0.077
	Right-after	342.67 (58.66)	178.67	407.67		
	Left-before	342.00 (49.42)	13.42	463.33	Z=-0.414	0.679
	Left-after	347.33 (21.42)	316.00	427.00		
Corneometer	Right-before	48.77 (7.27)	38.23	75.03	Z=-0.719	0.472
	Right-after	50.67 (10.16)	38.37	58.93		
	Left-before	49.93 (7.58)	27.87	71.07	Z=-0.894	0.371
	Left-after	48.57(10.89)	39.43	66.05		
Colorimeter	Right-before	26.66 (17.25)	9.00	33.33	Z=-1.898	0.058
	Right-after	27.00 (12.06)	14.60	39.66		
	Left-before	23.00 (8.09)	10.33	32.66	Z=-3.728	<0.001
	Left-after	29.66 (5.59)	21.47	35.32		
Delta E	Right-before	6.95 (3.20)	3.51	11.38	Z=-3.728	<0.001
	Right-after	5.05 (2.54)	2.21	9.30		
	Left-before	9.06 (2.24)	6.89	21.44	Z=-3.728	<0.001
	Left-after	4.06 (4.05)	2.17	18.74		

measured the color difference between the darkest and brightest points of the target area.

Participants' satisfaction with the treatment and tolerance levels were evaluated one month post the final treatment session using a visual analogue scale (VAS). Patient satisfaction scores were categorized into four groups: 0 (unsatisfied; 0%), 1 (slightly satisfied; <25%), 2 (satisfied; 25 - 60%), and 3 (very satisfied; >60%).

The outcomes were examined one month after the last treatment session by the same physician.

Statistical Analysis

The mean and standard deviation were employed for reporting quantitative variables with a normal distribution. For quantitative variables lacking a normal distribution, the median, mode, and interquartile range (IQR) were utilized. Descriptive statistics such as frequency and percentage were employed to characterize qualitative variables. A paired T-test was conducted to compare quantitative outcomes between pre- and post-intervention stages, while a T-test was employed for comparing quantitative outcomes between the two interventions. A Chi-square test was utilized to assess differences in satisfaction with the intervention based on its type. All

analyses were two-tailed, and P-values equal to or less than 0.050 were deemed statistically significant. IBM SPSS version 25 was used for data analysis.

RESULTS

This study enrolled twenty participants with symmetric melasma. Of these, 90% (n=18) successfully completed the intervention sessions, while the remaining 10% (n=2) were lost to follow-up. The participants were all female with a mean age of 41 years, ranging from 34 to 49 years old.

Regarding Fitzpatrick skin phototypes, five (25%) participants were classified as type II, eleven (55%) as type III, and four (20%) as type IV. Despite having no melasma treatment in the two months before enrollment, all (100%) participants had a history of unsuccessful topical treatment, and six (30%) had previously undergone unsuccessful laser therapy.

Furthermore, 30% of the patients (n=6) exhibited melasma on their entire face, 15% (n=3) had melasma on the cheeks and chin, and 55% (n=11) had melasma specifically on the cheeks.

Biometric characteristic results

In all patients, the biometric assessment of the right and left sides of the face affected by melasma was conducted before and one month after the last session of intervals. Visioface results revealed a significant decrease in the median ΔE for both TM and PM groups (mean difference = 6.66, P<0.001 and mean difference = 1.90, P<0.001, respectively) (**Figures 1 and 2**).

The median colorimeter measurement exhibited a significant increase after treatment in the TM group (mean difference = 6.66, P<0.001) but did not show significant changes in the PM group (mean difference = 0.34, P=0.058) (**Table 1 and 2**). Mexameter results indicated a significant reduction in melanin content on the left side (mean difference = 15.54, P=0.001) compared to the right side (mean difference = -4.92, P=0.565).

Tewameter measurements demonstrated a notable change in both groups, with patients receiving PRP + microneedling (mean difference = -3.33, P=0.003) and TXA + microneedling (mean difference = -2.15, P=0.003) experiencing a significant shift after the intervention.

Patients' satisfaction results

In the context of this study, it was observed that 66.6% (n=12) and 61.1% (n=11) of patients expressed a high level of satisfaction with PRP and TXA, respectively. Additionally, 33.3% (n=6) and 38.8% (n=7) of patients were satisfied with PRP and TXA respectively. It is noteworthy that the level of satisfaction within each treatment side did not yield statistically significant differences (P-value=0.999) (**Table 3**). Importantly, none of the patients within either group reported experiencing slight satisfaction or dissatisfaction.

Side effects

The incidence of side effects associated with the microneedling treatment, conducted with local analgesia, was low. The procedure was generally well-tolerated, and patients reported a painless experience. Any instances of burning and erythema attributed to the microneedling procedure were transient, resolving within a day of each treatment session. Notably, no significant adverse effects were documented, and

Table 3. Patients' satisfaction

	Group 1 (PRP + microneedling) n=18	Group 2 (TXA + microneedling) N=18	X^2	P-value
Very satisfied	12(66.6%)	11(61.1%)	0.129	0.999
Satisfied	6(33.3%)	7(38.8%)		
Slightly satisfied	0(0%)	0(0%)		
Unsatisfied	0(0%)	0(0%)		

overall, the treatment was well-tolerated by all patients involved in the study.

DISCUSSION

Melasma, the most prevalent cause of skin hyperpigmentation, is a common concerning problem among women of childbearing age. This condition arises from various etiologies for which there is no singular preferred treatment. This split-face clinical trial aimed to assess the efficacy of micro-needling in conjunction with autologous PRP or Tranexamic acid. Our results indicated that both TXA and PRP yielded satisfactory and effective outcomes for melasma improvement.

According to our current study, TXA improves melasma by reducing melanin and transepidermal water loss. Our findings align with previous studies demonstrating the positive impact of TXA on melasma.[15,21] Ebrahim et al. highlighted that the percentage of change in modified Melasma Area Severity Index (mMASI) score with intradermal injection of tranexamic acid and tranexamic acid with microneedling over 6 sessions at 2-week intervals was 74.8% and 73.6%, respectively. Both methods significantly improved melasma, with no meaningful difference between the two modalities, although microneedling side effects were associated with greater patient satisfaction ($p < 0.001$).[22]

In a similar split-face clinical trial, Kaur et al. concluded that four sessions with 2-week intervals, topical application of a 10% tranexamic acid solution significantly improved the mean mMASI score (65.92%) compared to distilled water on the control side (20.75%).[23] Another study found that microneedling with tranexamic acid led to a statistically significant higher reduction in melasma severity score compared to microneedling alone (62.1 versus 22.5%).[24]

The mechanism of TXA activity remains unclear, but experiments suggest that it can reduce melanin in the epidermis, decrease dermal vascularity, and reduce the number of mast cells. TXA may also prevent the hormonal activation of UV-induced, keratinocyte-derived melanocytes; showing promising results for melasma and pigmentation due to ultraviolet radiation, when compared to other treatments.[25,26] Similarly, Mexameter measurements in this study revealed a significant reduction in melanin content of melasma after tranexamic acid delivery with microneedling.

Over recent years, there has been an increase in application of autologous Platelet-Rich Plasma (PRP) in various medical fields, particularly in dermatology. Platelet-Rich

Plasma (PRP) is characterized by a higher platelet concentration obtained from whole blood, along with a broad range of growth factors (GF), chemokines, cytokines, and other plasma proteins.[27] Melanin synthesis inhibition, achieved through the reduction of transforming growth factor β1 (TGF-β1) and decreased tyrosinase activity, is one of PRP's mechanisms.[28] The presence of Epidermal Growth Factor (EGF) in PRP, known to enhance anti-melanogenic effect, supports its efficacy in melasma therapy.[29] Studies, such as the one by Tukyanat et al., recognize PRP as a promising treatment for melasma by decreasing tyrosinase and tyrosinase-related proteins via TGF-β action.[30] Based on our study findings, PRP effectively reduced biometric parameters including ΔE and transepidermal water loss. While this trial demonstrated meaningful patient satisfaction with the PM side, it is noteworthy that neither the colorimeter nor the Mexameter revealed a significant improvement in this area. The improvement in pigmentation observed in PRP treatment can be attributed to the increased synthesis of hyaluronic acid facilitated by platelet-derived growth factors. This process contributes to an overall enhancement in skin firmness, volume, and radiance.[5]

Melasma improvement can be obtained by PRP based on several studies.[31] In a previous investigation, melasma improvement exceeding 80% was reported at the end of the third PRP session.[32] Additionally, Mutlu Cayırlı et al.'s study demonstrated significant melasma improvement with no recurrence during a six-month follow-up, consistent with our findings.[33] Combining PRP with oral tranexamic acid treatment resulted in enhanced treatment outcomes and reduced recurrence within six months post-treatment ($p<0.05$).[34] Eman et al.'s study did not identify a significant difference between intradermal microinjection of PRP and PRP delivery by microneedling; both methods were notably effective in improving melasma ($p < 0.05$).[35]

Adel et al. concluded that PRP is equally effective on its own as it is in combination with Intense Pulsed Light (IPL) for melasma treatment (p-value > 0.05).[36] To the best of our knowledge, no study has contradicted our findings.

Throughout recent years, transdermal drug delivery has evolved into an effective method for different conditions such as the treatment of melasma.[37,38,39] Microneedling technology can enhance drug penetration through the creation of micropores in the stratum corneum.

In our study, the side effects of both procedures were minor, and both methods were considered tolerable with topical anesthesia. Previous studies have similarly reported manageable pain during Tranexamic Acid (TXA) treatment.[40] Also, post-PRP swelling resolved over 2-3 days, consistent with our findings.[16]

It is noteworthy that all aforementioned studies used the mMASI (modified Melasma Area and Severity Index) and MASI (Melasma Area Severity Index), clinical objective scales for assessing melasma severity. Our study employed more precise objective measurements, assessing biometric indexes before and after intervention, and evaluated color difference, melanin content, and transepidermal water loss. These biometric alterations inevitably influenced the development of MASI scores.

Finally, we have not discovered a study comparing the combination of tranexamic acid plus microneedling versus PRP plus microneedling. Tranexamic acid injection is widely recognized for its effectiveness in

melasma treatment, and PRP presents itself as an effective alternative therapy for this condition.

The limitations of this study include a small sample size and a short follow-up period, which may result in insignificant differences between the two groups.

CONCLUSION

This study demonstrates that the combination of both PRP and tranexamic acid with microneedling significantly improves melasma. While no superiority was observed between these two approaches, they prove to be a promising combination or alternative for melasma treatment due to their high efficacy, safety, tolerability, and patient satisfaction levels.

In patients treated with tranexamic acid and microneedling, a significant decrease in melanin, as measured by the Mexameter, was noted.

The effectiveness of both methods is evident, suggesting their practical utility in treating patients with resistant melasma under appropriate conditions. However, we suggest that further studies be conducted with larger sample sizes and extended follow-up periods.

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:
Elham Ziaeifar, MD
Iran University of Medical Sciences
Tehran, Iran
Email: sciencetfm@gmail.com

References:

1. Sheth VM, Pandya AG. Melasma: a comprehensive update: part II. *J Am Acad Dermatol*. 2011;65(4):699-714. doi:10.1016/j.jaad.2011.06.001
2. Mosher D, Fitzpartick T, Ortonne J. Hypomelanoses and hypermelanoses. In: *Dermatology in General Medicine*. 5th ed. New York: McGraw-Hill; 1999:945-1016.
3. Achar A, Rathi SK. Melasma: a clinico-epidemiological study of 312 cases. *Indian J Dermatol*. 2011;56(4):380-382. doi:10.4103/0019-5154.84722
4. Espósito ACC, Cassiano DP, da Silva CN, et al. Update on Melasma—Part I: Pathogenesis. *Dermatol Ther (Heidelb)*. 2022;12(9):1967-1988. doi:10.1007/s13555-022-00779-x
5. Guinot C, Cheffai S, Latreille J, et al. Aggravating factors for melasma: a prospective study in 197 Tunisian patients. *J Eur Acad Dermatol Venereol*. 2010;24(9):1060-1069. doi:10.1111/j.1468-3083.2010.03592.x
6. Ponzio HA, Favaretto AL, Rivitti EA. Proposal of a Quantitative Method to Describe Melasma Distribution in Women.
7. Jadotte YT, Schwartz RA. Melasma: insights and perspectives. *Acta Dermatovenerol Croat*. 2010;18(2):124-129.
8. Sarkar R, Puri P, Jain RK, Singh A, Desai A. Melasma in men: a clinical, aetiological and histological study. *J Eur Acad Dermatol Venereol*. 2010;24(7):768-772. doi:10.1111/j.1468-3083.2009.03524.x
9. Dominguez AR, Balkrishnan R, Ellzey AR, Pandya AG. Melasma in Latina patients: cross-cultural adaptation and validation of a quality-of-life questionnaire in Spanish language. *J Am Acad Dermatol*. 2006;55(1):59-66. doi:10.1016/j.jaad.2006.01.049
10. Handel AC, Miot LDB, Miot HA. Melasma: a clinical and epidemiological review. *An Bras Dermatol*. 2014;89(5):771-782. doi:10.1590/abd1806-4841.20143063
11. Roohaninasab M, Sadeghzadeh-Bazargan A, Goodarzi A. Effects of laser therapy on periorbital hyperpigmentation: a systematic review on current studies. *Lasers Med Sci*. 2021;36(9):1781-1789. doi:10.1007/s10103-020-03241-6
12. Gupta AK, Gover MD, Nouri K, Taylor S. The treatment of melasma: a review of clinical trials. *J Am Acad Dermatol*. 2006;55(6):1048-1065. doi:10.1016/j.jaad.2006.02.009
13. McKesey J, Tovar-Garza A, Pandya AG. Melasma Treatment: An Evidence-Based

Review. *Am J Clin Dermatol*. 2020;21(2):173-225. doi:10.1007/s40257-019-00488-w
14. Rigopoulos D, Gregoriou S, Katsambas A. Hyperpigmentation and melasma. *J Cosmet Dermatol*. 2007;6(3):195-202. doi:10.1111/j.1473-2165.2007.00321.x
15. Behrangi E, Shemshadi M, Ghassemi M, Goodarzi A, Dilmaghani S. Comparison of efficacy and safety of tranexamic acid mesotherapy versus oral tranexamic acid in patients with melasma undergoing Q-switched fractional 1064-nm Nd:YAG laser: A blinded RCT and follow-up. *J Cosmet Dermatol*. 2022;21(1):279-289. doi:10.1111/jocd.14496
16. Sarkar R, Gupta M. Platelet-Rich Plasma in Melasma-A Systematic Review. *Dermatol Surg*. 2022;48(1):131-134. doi:10.1097/DSS.0000000000003266
17. Hiramoto K, Yamate Y, Sugiyama D, Takahashi Y, Mafune E. The gender differences in the inhibitory action of UVB-induced melanocyte activation by the administration of tranexamic acid. *Photodermatol Photoimmunol Photomed*. 2016;32(3):136-145. doi:10.1111/phpp.12231
18. Chatterjee M, Vasudevan B. Recent advances in melasma. *Pigment International*. 2014;1:70. doi:10.4103/2349-5847.147044
19. Pavlovic V, Ciric M, Jovanovic V, Stojanovic P. Platelet Rich Plasma: a short overview of certain bioactive components. *Open Med (Wars)*. 2016;11(1):242-247. doi:10.1515/med-2016-0048
20. Meng X, Xu CC. Progress and prospect of non-invasive detection techniques in the therapeutic evaluation of melasma. *Chin Med J (Engl)*. 2020;133(17):2104-2106. doi:10.1097/CM9.0000000000000984
21. Patil NK, Bubna AK. A comparative evaluation of the efficacy of intralesional tranexamic acid versus platelet rich plasma in the treatment of melasma. *Dermatol Ther*. 2022;35(7):e15534. doi:10.1111/dth.15534
22. Ebrahim HM, Said Abdelshafy A, Khattab F, Gharib K. Tranexamic Acid for Melasma Treatment: A Split-Face Study. *Dermatol Surg*. 2020;46(11):e102-e107. doi:10.1097/DSS.0000000000002449
23. Kaur A, Bhalla M, Pal Thami G, Sandhu J. Clinical Efficacy of Topical Tranexamic Acid With Microneedling in Melasma. *Dermatol Surg*. 2020;46(11):e96-e101. doi:10.1097/DSS.0000000000002520
24. Saleh FY, Abdel-Azim ES, Ragaie MH, Guendy MG. Topical tranexamic acid with microneedling versus microneedling alone in treatment of melasma: clinical, histopathologic, and immunohistochemical study. *Journal of the Egyptian Women's Dermatologic Society*. 2019;16(2):89. doi:10.4103/JEWD.JEWD_25_19
25. Tehranchinia Z, Saghi B, Rahimi H. Evaluation of Therapeutic Efficacy and Safety of Tranexamic Acid Local Infiltration in Combination with Topical 4% Hydroquinone Cream Compared to Topical 4% Hydroquinone Cream Alone in Patients with Melasma: A Split-Face Study. *Dermatol Res Pract*. 2018;2018:8350317. doi:10.1155/2018/8350317
26. Combination of skin micro-needling and topical application of tranexamic acid and vitamin C: New clinical application: A pilot study for treatment of persistent post acne erythema. *Journal of the American Academy of Dermatology*. 2016;74(5):AB4. doi:10.1016/j.jaad.2016.02.014
27. Alves R, Grimalt R. A Review of Platelet-Rich Plasma: History, Biology, Mechanism of Action, and Classification. *Skin Appendage Disorders*. 2017;4(1):18-24. doi:10.1159/000477353
28. Kim DS, Park SH, Park KC. Transforming growth factor-beta1 decreases melanin synthesis via delayed extracellular signal-regulated kinase activation. *Int J Biochem Cell Biol*. 2004;36(8):1482-1491. doi:10.1016/j.biocel.2003.10.023
29. Yun WJ, Bang SH, Min KH, Kim SW, Lee MW, Chang SE. Epidermal growth factor and epidermal growth factor signaling attenuate laser-induced melanogenesis. *Dermatol Surg*. 2013;39(12):1903-1911. doi:10.1111/dsu.12348
30. Tuknayat A, Bhalla M, Thami GP. Platelet-rich plasma is a promising therapy for melasma. *J Cosmet Dermatol*. 2021;20(8):2431-2436. doi:10.1111/jocd.14229
31. Tuknayat A, Thami GP, Bhalla M, Sandhu JK. Autologous intralesional platelet rich plasma improves melasma. *Dermatol Ther*. 2021;34(2):e14881. doi:10.1111/dth.14881
32. Sirithanabadeekul P, Dannarongchai A, Suwanchinda A. Platelet-rich plasma treatment for melasma: A pilot study. *J Cosmet Dermatol*. 2020;19(6):1321-1327. doi:10.1111/jocd.13157
33. Çayırlı M, Çalışkan E, Açıkgöz G, Erbil AH, Ertürk G. Regression of Melasma with Platelet-Rich Plasma Treatment. *Ann*

Dermatol. 2014;26(3):401-402. doi:10.5021/ad.2014.26.3.401
34. Zhang C, Wu T, Shen N. Effect of platelet-rich plasma combined with tranexamic acid in the treatment of melasma and its effect on the serum levels of vascular endothelial growth factor, endothelin-1 and melatonin. *Pak J Med Sci*. 2022;38(8):2163-2168. doi:10.12669/pjms.38.8.6786
35. Hofny ERM, Abdel-Motaleb AA, Ghazally A, Ahmed AM, Hussein MRA. Platelet-rich plasma is a useful therapeutic option in melasma. *J Dermatolog Treat*. 2019;30(4):396-401. doi:10.1080/09546634.2018.1524821
36. Adel S, Serri A, Abd El-Raheem T. Study of autologous platelet-rich-plasma versus its combination with intense pulsed light in treatment of melasma. *Dermatol Ther*. 2021;34(4):e15008. doi:10.1111/dth.15008
37. Sadeghzadeh-Bazargan A, Behrangi E, Najar Nobari N, Ghassemi M, Roohaninasab M, Goodarzi A. Systematic review of clinical studies assessing the needling for treatment of melasma: Focusing on efficacy, safety, and recurrence rate. *J Cosmet Dermatol*. 2022;21(5):1857-1873. doi:10.1111/jocd.14836
38. Jung JH, Jin SG. Microneedle for transdermal drug delivery: current trends and fabrication. *J Pharm Investig*. 2021;51(5):503-517. doi:10.1007/s40005-021-00512-4
39. Ziaeifar E, Ziaeifar F, Mozafarpoor S, Goodarzi A. Applications of microneedling for various dermatologic indications with a special focus on pigmentary disorders: A comprehensive review study. *Dermatol Ther*. 2021;34(6):e15159. doi:10.1111/dth.15159
40. Ghassemi M, Roohaninasab M, Kamani SA, Sadeghzadeh-Bazargan A, Goodarzi A. Comparison of the efficacy and safety of intralesional injection of tranexamic acid and the topical application of Kligman combination drug in the treatment of macular amyloidosis. *Dermatol Ther*. 2022;35(1):e15213. doi:10.1111/dth.15213