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A comparative evaluation of the efficacy of intralesional tranexamic acid versus platelet rich plasma in the treatment of melasma

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Abstract

Melasma is a benign, acquired disorder of hyperpigmentation commonly affecting the face. Though easily diagnosable, a tangible treatment for melasma still remains elusive. Our aim was to compare the therapeutic efficacy and safety of tranexamic acid (TXA) and platelet rich plasma (PRP) microinjections in treating patients with melasma. In total, 40 patients with melasma (10 males, 30 females; age range: 21–54 years) were enrolled, and randomly assigned to one of the two groups consisting of 20 patients each. Group A (3 males, 17 females) received intradermal microinjections of TXA (4 mg/ml) and group B (5 males, 15 females) received intradermal microinjections of PRP, once every 4 weeks for a total of five treatment sessions. Clinical images were taken at each visit and improvement in melasma was evaluated using both melasma area severity index (MASI) and modified melasma area severity index (mMASI) scoring systems. Percentage reduction of both MASI and mMASI scores were also assessed at each visit, and the grade of melasma improvement was accordingly outlined for each patient. The study was completed by 18 patients in group A (TXA) and 15 patients in group B (PRP). In group A, both MASI and mMASI scores reduced significantly from 16.6 ± 9.227 at baseline to 10.028 ± 8.07 at end point; and 8.885 ± 5.418 at baseline to 4.639 ± 3.863 at end point, respectively (p value <0.01). Similarly in group B significant reduction in both scores were observed at the end of treatment. MASI declined from 20.42 ± 7.979 to 12.253 ± 7.37; and mMASI plummeted to 5.613 ± 3.98 from 10.673 ± 4.642 (p value <0.01). In group A, the difference in mean reduction of MASI and mMASI from baseline to end point was 6.572 ± 4.528 and 4.211 ± 2.647, respectively. In group B, the difference in mean reduction of both scores at the end of treatment reflected values of 8.167 ± 4.975(MASI) and 5.06 ± 2.977 (mMASI). No significant adverse effects were encountered in both treatment arms during the entire duration of study. Both TXA and PRP microinjections were found to be effective and safe therapeutic options for melasma, providing rapid and substantial improvement even when used as standalone therapies. Although PRP mesotherapy was found to be slightly better than intradermal TXA in our study, the results were not significant statistically.

KEYWORDS
automated centrifugation, intradermal microinjections, melasma, platelet rich plasma, tranexamic acid

1 | INTRODUCTION

Melasma is a chronic, multifactorial disorder of hyperpigmentation, presenting with blotchy brown, to brown black macules, over photo-exposed parts of the body, particularly the face, commonly affecting Fitzpatrick skin types III–IV.

Melasma is commonly observed in the 2nd–5th decade and may be associated with a negative impact on patient's quality of life.[1]

This disorder accounts for 0.25%–4% of patients in Southeast Asian dermatology clinics. Apart from genetics, a number of factors play a role in melasma pathogenesis, and include pregnancy, endocrine dysfunction, cosmetic contact sensitivity, UV radiation and drugs (oral contraceptive pills, phototoxic medications, phenytoin, and phenothiazines) to name a few.

Phenotypically, three variants of melasma are observed, namely centrofacial, malar, and mandibular. Using Wood's lamp, melasma can be further categorized histologically as epidermal, dermal and mixed, based on accentuation of pigmentation, to the light emanated from the device.

A number of topical agents (hydroquinone, azelaic acid, kojic acid, retinoic acid, lactic acid, and glycolic acid) constitute the therapeutic armarmentarium for melasma. Along with these, chemical peels and lasers have also been utilized, with varying results. Though easily diagnosable, a concrete therapy characterizing complete resolution of melasma still remains an enigma.

Recently, intradermal injections of platelet rich plasma (PRP) and tranexamic acid (TXA) have been employed in melasma management with some success.

PRP, in melasma exerts its therapeutic effect by releasing a number of bioactive substances contained within the alpha granules of platelets. Of these, transforming growth factor (TGF)-β and epidermal growth factor (EGF), significantly inhibit melanin synthesis via a delayed extracellular signal regulated kinase activation; and inhibition of tyrosinase activity (along with blockade of prostaglandin E2 [PGE2] expression), respectively.[2,3]

The role of TXA in melasma on the other hand, is explained mainly by two mechanisms, which include its antiplasmin effect, and tyrosinase inhibition (owing to structural similarities with tyrosine).[4,5]

TXA has been utilized orally, topically as well as by microinjections in melasma therapy. PRP however, is delivered intradermally alone. This can be done by microneedling or microinjections.

Our study was done to compare the therapeutic efficacy of intradermal microinjections of TXA and PRP as standalone treatments in melasma. As microneedling was not acceptable to many of our study subjects, microinjections were employed for the purpose of intradermal drug delivery.

2 | MATERIALS AND METHODS

This was a prospective, randomized, open label study that was conducted on 40 clinically diagnosed patients with melasma, after obtaining permission from the institutional ethical clearance committee (Registration number: KMC/ IEC/ Dept. Res./015/ 2021-2024 DVL). Our study was in accordance to the principles of the 1975 declaration of Helsinki.

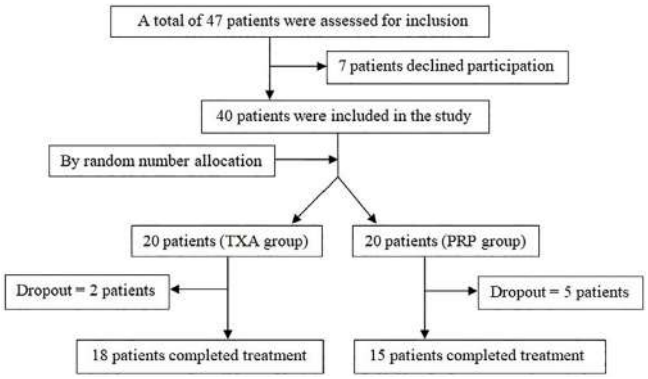

FIGURE 1 A schematic representation of patient inclusion, randomization, dropout and treatment completion in our study.

Based on the study by Mumtaz et al.,[6] to detect a true difference in the mean score of 4 between the two groups, with a standard deviation of 4.5 in both groups, and to achieve a power of 80%, with a two sided level of significance of 5%, a minimum sample size of 20 in each group was estimated. We assessed 47 patients for inclusion. However, 7 of them declined participation in the study.

Patients were randomly selected for PRP and TXA mesotherapy. Randomization was done by random number allocation. A schematic flow diagram depicting patient inclusion, randomization, dropout and treatment completion has been elaborated in Figure 1.

A written and informed consent was taken from each patient, followed by a relevant history and clinical examination. Lesions were then examined under Wood's lamp and graded categorically. The melasma area severity index (MASI) as well as modified melasma area severity index (mMASI) scoring systems were used to assess the severity of melasma and compare the responses following treatment.

This study included adults with melasma in the age group between 21 and 54 years. Patients who had history of bleeding disorders or of using oral anticoagulants were excluded from the study. Other exclusion criteria were:

- Intake of any photosensitizing drugs
- Known allergy to TXA.
- Diabetic, hypertensive and asthmatic patients.
- Pregnant and lactating women.
- Women on oral contraceptive pills and hormone replacement therapy.
- Patients on any topical therapy for melasma in the past 3 months.
- Patients with known platelet dysfunction syndrome.
- Critical thrombocytopenia less than 50,000/mcl.
- Any history of hemodynamic instability.
- Active herpes simplex at procedure site.

2.1 | Preparation method and injection of TXA

TXA is available as 5 ml vials, containing 500 mg of the drug. Two units of TXA was drawn in a 40 U/ml 30 G insulin syringe and diluted with normal saline upto 1 ml (remaining 38 U out of total 40 U) in order to obtain a concentration of 4 mg/ml of TXA. The face was numbed with ice packs that were kept for a period of 5–10 min, followed by cleansing with alcohol swabs, after which intradermal injections of TXA was administered over the hyperpigmented patches, separating each prick with a 1 cm distance. Based on the area of involvement injections were given, the total dose not exceeding 16 mg of intradermal TXA. Five such sessions were administered at intervals of 4 weeks and advice regarding stringent photoprotection stated. All patients were given the same sunscreen with a sun protection factor of 30, for the entire duration of treatment.

2.2 | Preparation method and injection of PRP

The antecubital fossa of each patient was cleansed with an alcohol swab following which 10 ml of venous blood was withdrawn from that region. The blood was immediately transferred to a PRP tube (Bio-x, Mumbai, India). These PRP tubes are designed in such a way that they contain a separation gel along with sodium citrate (as the anticoagulant).

The collected blood was then sent for centrifugation in the Remi R-8C laboratory centrifuge, at 685*g* for 5 min at room temperature. Following centrifugation, plasma containing platelets occupied a position above the separating gel, with other blood components sedimenting below it. We obtained approximately 1–1.2 ml of PRP from 10 ml of whole blood. This was immediately injected into the melasma areas at 1 cm interval, following numbing and cleansing of the face as described for TXA.

2.3 | Post procedure care

Each patient was instructed to avoid washing the face for 24 h after the procedure and avoidance of direct sun exposure for at least 5 days after that. The patients were also advised regarding regular and timely application of sunscreen. Education regarding some redness, swelling and bruising of transient nature at treatment sites was also iterated. Patients were further instructed against the use of any other treatment for their melasma.

2.4 | Assessment of treatment response

In each group clinical photographs were taken at baseline and at every 4 weeks (0, 4, 8, 12, 16, and 20 weeks) until the end of the study period for evaluation of therapeutic outcome and adverse effects.

Reduction in MASI and mMASI were the primary outcome measures assessed. Pretreatment baseline scoring of MASI and mMASI were serially compared and the percentage reduction analyzed statistically using the independent *t*-test. Serial photography, pre and post treatment was done using Canon (IXUS 285 HS, 20.2 Megapixel), point and shoot Camera with 12× optical zoom for comparative analysis.

2.5 | Statistical analysis

Quantitative data was expressed as mean and standard deviation and categorical data as percentages. Assessment of statistical significance regarding the change in score for each drug at various time points was done using Friedman's test. As there was a baseline difference in scores for participants in both groups the mean reduction of scores from baseline to 20 weeks was compared using the independent *t* test. A *p*-value of <0.05 was considered to be statistically significant. R version 4.0.2 for Windows (Vienna, Austria 2020) was used for statistical analysis. The improvement following treatment (based on MASI and mMASI reduction) in each patient was graded at the end of the study as follows:

- Excellent (>75%–100%): improvement near normal skin.
- Significant (>50%–75%): marked lightning.
- Moderate (>25%–50%): moderate lightning.
- Slight (0%–25%): no change to slight lightning.

3 | RESULTS

Out of 40 patients, 33 successfully completed the treatment. Of them 18 were in the TXA group and 15 in the PRP group. The demographic data and clinical characteristic of our participants have been elucidated in Table 1.

Total MASI and mMASI scores in the TXA group at baseline were 298.8 and 159.3, respectively. At the end of 20 weeks, the total MASI score had reduced to 180.5 and mMASI score had plummeted to 83.5.

In the PRP group, the total MASI score at baseline was 306.3, that had lessened to 183.8 at the end of 20 weeks. Similarly, the total mMASI score depicted a diminution from 159.8 at baseline to 84.2 at the end of 20 weeks.

The mean ± SD of both MASI and mMASI scores, along with the percentage improvement in the two treatment groups comprising all visits has been represented in Tables 2 and 3, respectively.

The *p* values at the end of treatment was found to be statistically significant individually for each group in both scores ($p < 0.01$).

The difference in mean ± SD at end point from baseline for MASI and mMASI in the TXA group was 6.572 ± 4.528 and 4.211 ± 2.647, respectively.

TABLE 1 Demographic data and clinical characteristics of our study subjects

	TXA	PRP	*p* value
Age (years)			0.8
Mean ± SD	33.944 ± 8.335	34.467 ± 5.998	
(Range)	(21–54)	(22–42)	
Sex			0.30
Male	2 (11.11%)	4 (26.67%)	
Female	16 (88.89%)	11 (73.33%)	
Residence			0.43
Rural	6 (33.33%)	3 (20%)	
Semi-rural	12 (66.67%)	12 (80%)	
Occupation			0.90
Working	10 (55.56%)	8 (53.33%)	
Not working	8 (44.44%)	7 (46.67%)	
Family history			0.16
Positive	3 (16.67%)	6 (40%)	
Negative	15 (83.33%)	9 (60%)	
Marital status			0.89
Single	4 (22.22%)	3 (20%)	
Married	14 (77.78%)	12 (80%)	
Skin photo-type			0.44
Type IV	11 (61.11%)	7 (46.67%)	
Type V	7 (38.89%)	8 (53.33%)	
Duration of illness (years)			0.59
1–3 years	9 (50%)	9 (60%)	
>3 years	9 (50%)	6 (40%)	
Distribution of melasma			–
Malar	10 (55.56%)	5 (33.33%)	
Centro-facial	7 (38.89%)	10 (66.67%)	
Mandibular	1 (5.55%)	0	
Triggering factor(s)			0.72
Sun/heat exposure	16 (88.89%)	14 (93.33%)	
Pregnancy	2 (11.11%)	1 (6.67%)	
Type of melasma by Wood's light examination			0.74
Epidermal	7 (38.89%)	5 (33.33%)	
Dermal	11 (61.11%)	10 (66.67%)	

Abbreviations: PRP, platelet rich plasma; SD, standard deviation; TXA, tranexamic acid.

TABLE 2 Mean MASI scores and percentage improvement of both groups at each visit

	Baseline	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks
Tranexamic acid group						
MASI (mean ± SD)	16.6 ± 9.227	14.972 ± 876	13.2 ± 8.583	11.572 ± 8.614	10.772 ± 8.869	10.028 ± 8.07
Percentage improvement		9.80%	20.48%	30.29%	35.11%	39.59%
Platelet rich plasma group						
MASI (mean ± SD)	20.42 ± 7.979	19.1 ± 7.891	16.293 ± 7.025	14.047 ± 7.568	12.66 ± 7.522	12.253 ± 7.374
Percentage improvement		6.46%	20.21%	31.21%	38%	39.99%

Abbreviations: MASI, melasma area severity index; SD, standard deviation.

TABLE 3 Mean mMASI scores and percentage improvement of both groups at each visit

	Baseline	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks
Tranexamic acid group						
mMASI (mean ± SD)	8.85 ± 5.418	7.489 ± 4.926	6.456 ± 4.837	5.711 ± 4.883	5.211 ± 4.892	4.639 ± 3.863
Percentage improvement		15.37%	27.05%	35.47%	41.11%	47.58%
Platelet rich plasma group						
mMASI (mean ± SD)	10.673 ± 4.642	9.567 ± 4.548	7.327 ± 3.677	6.413 ± 3.979	5.78 ± 4.014	5.613 ± 3.989
Percentage improvement		10.36%	31.35%	39.91%	45.84%	47.41%

Abbreviations: mMASI, modified melasma area severity index; SD, standard deviation.

TABLE 4 Percentage improvement of MASI and mMASI scores in both groups

Percentage improvement in the MASI score (%)	Tranexamic acid (no. of patients)	Platelet rich plasma (no. of patients)
<25	7 (38.89%)	3 (20%)
25–50	5 (27.78%)	8 (53.34%)
51–75	2 (11.11%)	3 (20%)
76–100	4 (22.22%)	1 (6.66%)
Percentage improvement in the mMASI score (%)	**Tranexamic acid (no. of patients)**	**Platelet rich plasma (no. of patients)**
<25	2 (11.11%)	3 (20%)
25–50	9 (50%)	5 (33.34%)
51–75	3 (16.66%)	6 (40%)
76–100	4 (22.23%)	1 (6.66%)

Abbreviations: MASI, melasma area severity index; mMASI, modified melasma area severity index.

In the PRP group, the difference in mean ± SD for MASI and mMASI at end point from baseline was 8.167 ± 4.975 and 5.06 ± 2.977, respectively.

On comparing the mean reduction for each therapy in both scoring systems, it was observed to be slightly greater for the PRP treatment arm. However, p values were not statistically significant (mean MASI: $p = 0.3$, mean mMASI: $p = 0.4$).

Four (22.22%) patients in the TXA group showed excellent improvement whereas only one (6.66%) patient from the PRP group demonstrated an improvement >75%, as per the MASI scoring. More details regarding the same has been expounded in Table 4.

On analyzing the extent of improvement using the mMASI scoring system, we obtained differing results when compared to MASI. This has also been exemplified in Table 4.

No serious adverse effects were encountered in any of our patients. Mild pruritus and erythema, of transient nature, lasting for around 1–2 days were the only complaints documented.

Clinical improvement following both treatments can be gauged by baseline and end point photographs (Figures 2 and 3).

Graphical representation of mean reduction for both scores in each group has been described in Figure 4.

4 | DISCUSSION

Localized microinjections of highly diluted drug mixtures, or single drugs into the corium or subcutaneous tissue was pioneered in France by Pistor, and described as mesotherapy; a technique widely employed in medicine. Mesotherapy utilizes all intravenous injectable compounds, except for oily and alcoholic solvents.

The discovery of oral TXA as a successful therapeutic option for melasma eventually paved way for its topical and mesotheraputic utility.

Localized administration of TXA further avoids adverse effects that could possibly occur with long term treatment schedules associated with oral intake of the drug.

TXA has been administered by microneedling and intradermal injections with both techniques elaborating therapeutic improvement for melasma. As our study employed intradermal injections of TXA, we consider it peremptory to compare our findings with studies of a similar modus operandi.

The profitability of localized microinjections of TXA for melasma was first reported in 2006 by Lee et al.,[7] in their series of 85 patients. TXA (4 mg/ml) was injected intradermally using 30 G, 0.5 ml insulin syringes, every week for 12 consecutive weeks. A statistically significant reduction in the mean MASI score was documented from baseline (13.22 ± 3.02) to 12 weeks (7.57 ± 2.54). Out of their 85 patients, 9.4% demonstrated significant improvement, 76.5% portrayed moderate improvement and the remaining 14.1% had only slight improvement.

Favorable outcomes with intradermal microinjections of TXA were further reprised in three similar studies from India and one study from Pakistan; salient features of which in comparison to our findings have been depicted in Table 5.

The smaller sample size, absence of the mixed variant of melasma amongst our cohorts and introduction of five sessions of intradermal injections of TXA were the three contrasting features observed, while juxtaposing our findings with the above reports. In addition, we utilized both MASI and mMASI scoring systems to evaluate the treatment response in our study subjects, unlike the previous studies, wherein only one score was availed.[6,8–10] The percentage improvement at end point in our study depicted considerable similarity with the finding of Khurana et al.,[10] but showed disparate results with the other three studies described above.[6,8,9] In addition, the degree of

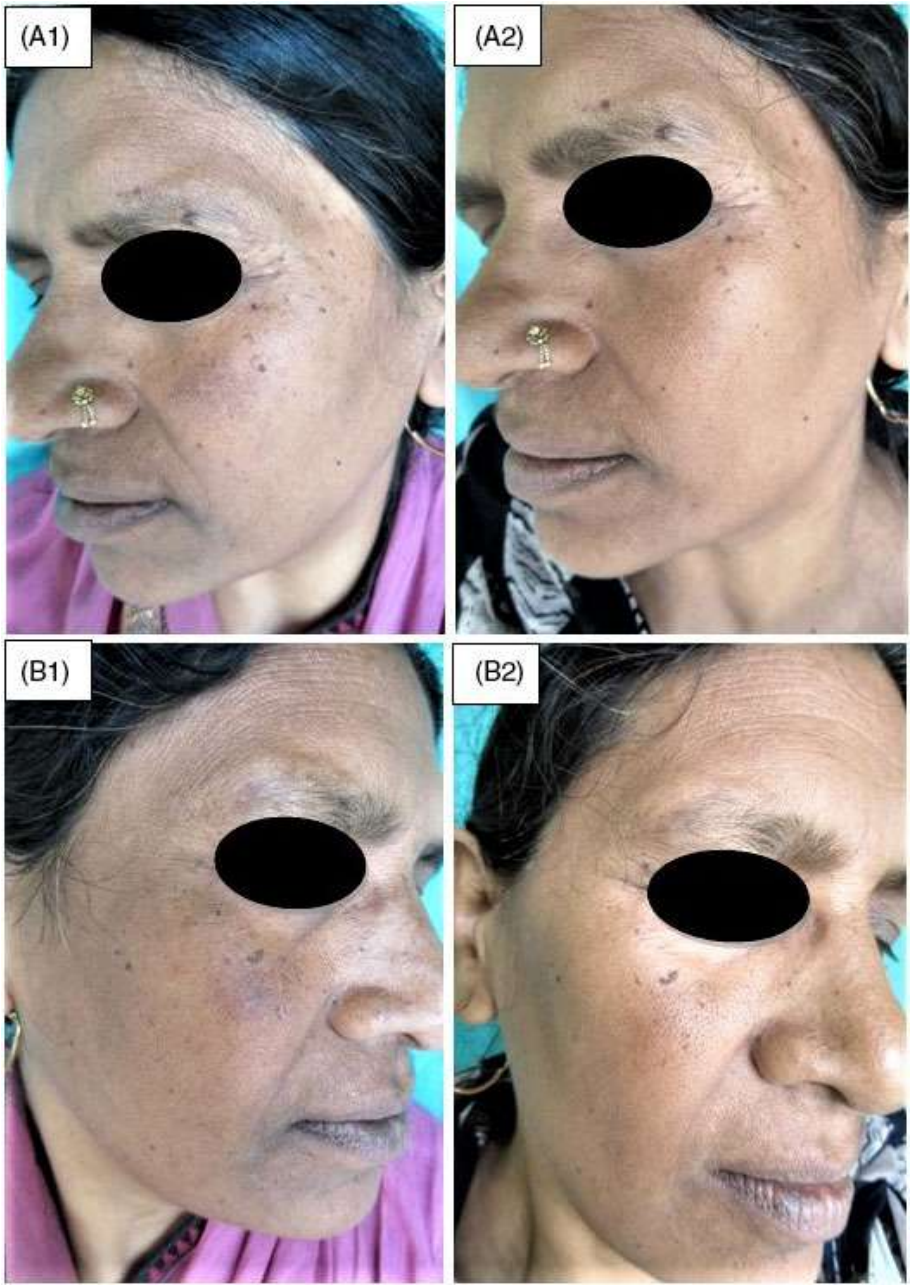

FIGURE 2 (A1) Left cheek at initiation of treatment (intralesional tranexamic acid [4 mg/ml]) (patient 1). (A2) Left cheek after 20 weeks of treatment (intralesional tranexamic acid [4 mg/ml]) (patient 1). (B1) Right cheek at initiation of treatment (intralesional tranexamic acid [4 mg/ml]) (patient 1). (B2) Right cheek after 20 weeks of treatment (intralesional tranexamic acid [4 mg/ml]) (patient 1)

improvement, witnessed amongst our participants, when collated with previous studies, displayed contrasting results.

A possible explanation regarding this variation could be linked to the heterogeneous patho-mechanisms involved in melasma. Broadly, six principle mechanisms have been proposed; and include inappropriate melanocyte activation, increased mast cell count, solar elastosis, increased dermal vascularization (secondary to increased vascular endothelial growth factor/endothelin 1 expression), epidermal/dermal aggregation of melanosomes/melanin and disruption of skin basement membrane.[11–16] Further, the representation of each of the above mechanisms tends to vary from one individual to another.

TXA, primarily channelizes its effects against the first four stated pathomechanisms.[16] Therefore, in those patients where basement membrane disruption and melanosome/melanin aggregation predominate, it is but likely to observe a lower efficacy of TXA when compared to those patients in whom other factors are majorly expressed.

Besides, there may also be a genetic component involved in relation to this expression.

These changes however, can only be determined by histology and/or dermoscopy (to some extent). In this way, the clinician would be able to get a clue regarding the reason for varying levels of responses seen following administration of TXA in different patients.

Moreover, we spotted nonconformity in the values for the degree of improvement with both MASI and mMASI scoring, thereby indicating that each score differs in its expression while evaluating the therapeutic response to drugs in patients with melasma. Apart from this, no other difference was specifically observed. We therefore feel that

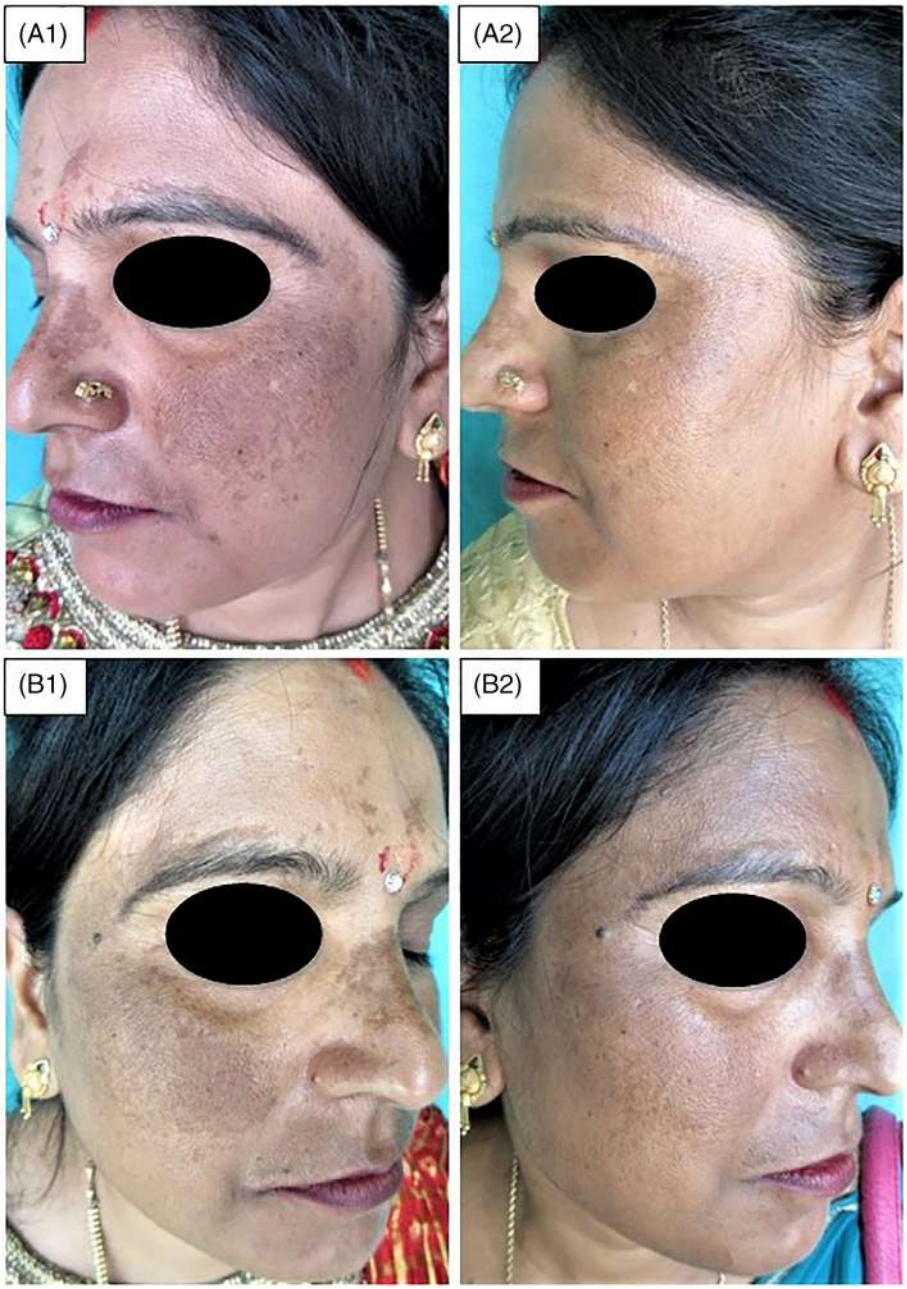

FIGURE 3 (A1) Left cheek at initiation of treatment (platelet rich plasma) (patient 2). (A2) Left cheek after 20 weeks of treatment (platelet rich plasma) (patient 2). (B1) Right cheek at initiation of treatment (platelet rich plasma) (patient 2). (B2) Right cheek after 20 weeks of treatment (platelet rich plasma) (patient 2)

while evaluating melasma patients, it would be sufficient to use either one of the two scoring systems. The only component that mMASI does not include is homogeneity; which in no way alters reliability of the score.[17] However, while conducting large scale studies, utilizing both these scores could help in comparative analysis, owing to the fact that currently not all studies have adhered to just one scoring system.

Further, we also realized that despite the use of one/two additional session(s) of TXA in our participants, it did not necessarily give us better results when compared with previous studies where only three/four sessions of intradermal TXA had been administered.

Therefore, the appropriate interval of intradermal TXA administration, as well as the number of drug delivery schedules, remain important aspects for consideration. Comparative studies, evaluating the same, would certainly contribute in delineating a standard therapeutic protocol for dispensing intradermal TXA while managing patients with melasma.

A notable finding witnessed by us was a zero value of MASI/mMASI at end point in one of our patients who was receiving TXA. This observation however, was not duplicated in any of our PRP recipients.

Besides, excellent improvement of melasma was witnessed in 22.22% of the TXA cohorts, in contrast to 6.66% of the PRP subjects. This observation could be possibly attributed to the clinical pattern of melasma. Majority of patients in the TXA group demonstrated malar melasma, in contrast to centrofacial melasma which was the predominant morphology in the PRP group. As malar melasma is more localized unlike the widely distributed centrofacial pattern (often difficult

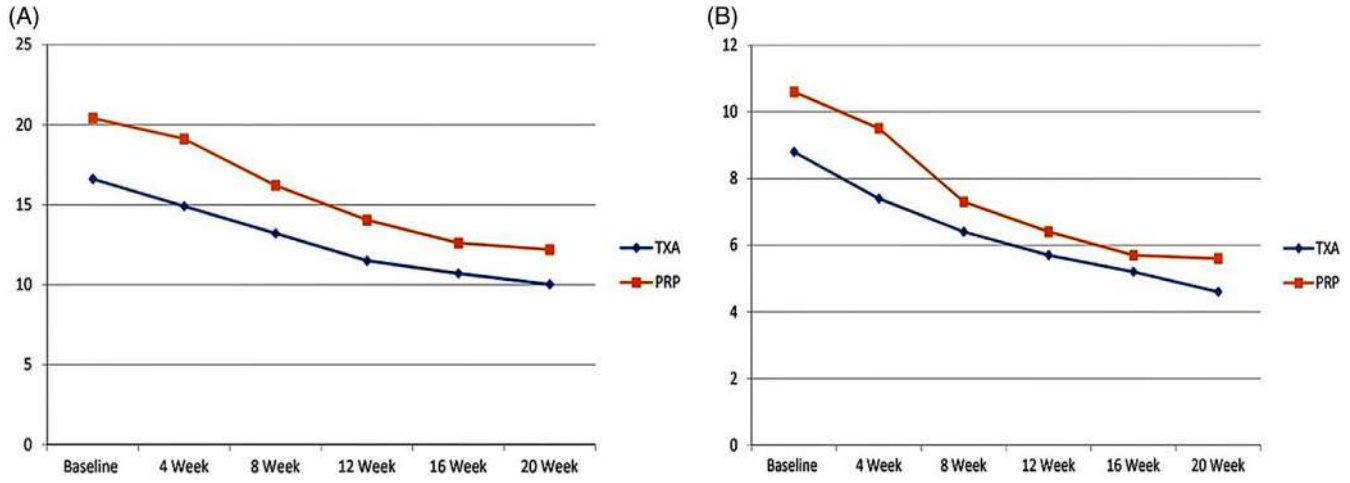

FIGURE 4 (A) Graphical representation depicting reduction of mean MASI from baseline to end point of treatment for both groups. (B) Graphical representation depicting reduction of mean mMASI from baseline to end point of treatment for both groups. MASI, melasma area severity index; mMASI, modified melasma area severity index

to treat); this could potentially explain why more TXA patients had excellent improvement.

The propitious effects of PRP as a standalone therapy in melasma was first described in 2014 by Cayrili and colleagues[18] in a 27 year old women with centrofacial melasma. After three fortnightly sessions of intradermal microinjections of PRP, >80% reduction in hyperpigmentation was noted, without any recurrence even after 6 months.

Apart from various growth factors released by platelets, it has been speculated that the curative properties of PRP in melasma may also be related to its reparative functions, antibacterial effects and its ability to bring about vascular remodeling, derangement of which have been found to be contributory in the pathogenesis of melasma.[19]

Salient features of other reports employing PRP as monotherapy for melasma, including ours have been outlined lucidly in Table 6.

In all the above studies a statistically significant improvement of melasma was observed at end point. Further, an excellent to significant improvement in the degree of melasma utilizing the mMASI scoring system was noticed in >45% of our patients, which was in consonance with the findings of Hofney et al.,[22] and Tuknayat et al.[23]

The percentage reduction of MASI from baseline to end point was significantly higher in both studies from Pakistan, when compared to our findings.[6,20] In the study by Tuknayat et al.,[23] the mMASI decline was moderately higher, when equated with our observation. On the other hand, the alleviation of both mMASI and MASI scores from the Egyptian study (though only slightly higher) was almost comparable with our values.[22]

One major difference in our study with the above mentioned reports was the use of a commercial (gel separation technique) kit for PRP preparation. Although these kits are easy to use, and prepare almost a pure PRP ideal for the face; there exists an altercation regarding platelet counts obtained by many of these kits.

In reports by Mazzucco et al.,[24] and Franka Klatte-Shulz et al.,[25] lower platelet concentrations as well as lower growth factor concentrations were found in gel separation kits when compared with the double spin method.

Kushida and colleagues[26] on the other hand, demonstrated similar concentrations of platelets and important growth factors in one of the gel separating systems which they analyzed while comparing it with the double spin method of PRP procurement.

These findings thereby demonstrate the existence of great variability in commercial PRP separation systems.

To compound things further, currently there exists no standardized protocol with regard to preparation, composition, administration or regulation of PRP for any dermatologic indication.[27]

Besides, in our study, we did not determine various parameters like the platelet dose, leukocyte concentration, erythrocyte concentration and levels of various growth factors in the resultant PRP.

Interestingly, this information was neither available in any of the other studies described above. Lack of this information could possibly be ascribed to the absence of an optimal protocol regarding PRP administration in melasma.

So, without clearly outlining PRP metrics; it becomes extremely difficult to compare studies or even recreate protocols.

Ensuring a standardized technical consistency and specificity for PRP in various cutaneous indications therefore becomes a major necessity, requiring scrupulous exploration.

Faiz et al.,[20] employed a biweekly administration schedule of PRP that was dispensed for a total of five sessions. Their reduction of MASI was significant. However, in another study by Mumtaz et al.,[6] where monthly injections of PRP was given, the reduction of MASI was even better (though only slightly) than the values obtained by Faiz et al.[20] However, in all other studies where monthly injections of PRP were used, the decline in MASI/mMASI was definitely lower when compared to the study that utilized shorter intervals of PRP administration.

An important point to ponder here is what exactly could be the dosing schedule of PRP and the number of sessions needed for best

TABLE 5 Comparative analysis of previous studies utilizing intradermal microinjections of tranexamic acid for melasma along with our study

Author(s)/year	Total number of patients who received tranexamic acid microinjections	Age range (years)	Fitzpatrick skin type	Clinical type of melasma	Pattern of melasma on Wood's lamp	Procedure highlights	Scoring system used	Percentage improvement of score from baseline to end point	Degree of improvement witnessed amongst patients
Budamakuntla et al.,[8] (2013)	30 (females 28, males 2)	18–60	IV-19 V-11	Centrofacial-15 Malar-15	Epidermal-3 Dermal-4 Mixed-23	Intradermal injections of TXA (4 mg/ml) at monthly intervals (0, 4, and 8 weeks) Total number of sessions: 3	mMASI	35.72%	Excellent: 0% Significant: 26.09% Moderate: 47.82% Slight: 26.09%
Sharma et al.,[9] (2017)	50 (females 45, males 5) (Out of which 41 patients completed the study, whose details have not been clearly elaborated)	18–55	Not available	Centrofacial-31 Malar-19	Epidermal-32 Dermal-11 Mixed-7	Intradermal injections of TXA (4 mg/ml) at monthly intervals (0, 4, and 8 weeks) Total number of sessions: 3	MASI	79%	Excellent: 78% Significant: 22%
Khurana et al.,[10] (2019)	32 (females 28, males 4)	20–50	IV-15 V-17	Centrofacial-8 Malar-24	Epidermal-11 Mixed-21	Intradermal injections of TXA (4 mg/ml) at monthly intervals (0, 4, and 8 weeks) Total number of sessions: 3	mMASI	43.55%	Excellent: 9% Significant: 43.75% Moderate: 34.38% Slight: 12.5%
Mumtaz et al.,[6] (2021)	32 (females 16, males 16)	20–40	Not available	Not available	Not available	Intradermal injections of TXA (4 mg/ml) at monthly intervals (0, 4, 8, and 12 weeks) Total number of sessions: 4	MASI	49.35%	Not available
Current study	18 (females 16, males 2)	21–54	IV-11 V-7	Centrofacial-7 Malar-10 Mandibular-1	Epidermal-7 Dermal-11	Intradermal injections of TXA (4 mg/ml) at monthly intervals (0, 4, 8, 12, and 16 weeks) Total number of sessions: 5	Both MASI and mMASI	39.59% (MASI) 47.58% (mMASI)	According to MASI score Excellent: 22.22% Significant: 11.11% Moderate: 27.77% Slight: 38.88% According to mMASI Excellent: 22.22% Significant: 16.66% Moderate: 50% Slight: 11.11%

Abbreviations: MASI, melasma area severity index; mMASI, modified melasma area severity index; TXA, tranexamic acid.

TABLE 6 Notable findings of previous studies utilizing platelet rich plasma as monotherapy in melasma in comparison with our findings

Author(s)/ year	Total number of patients who received platelet rich plasma microinjections	Age range	Fitzpatrick skin type	Clinical type of melasma	Pattern of melasma on Wood's lamp	Procedure highlights	Scoring system used	Mean percent reduction of score at end point	Degree of improvement amongst patients (%)
Faiz et al.,[20] (2017)	15 (females 12, males 3)	21–42 years	III-4 IV-11	Not available	Not available	• Double centrifugation method employed • Fortnightly intradermal injections of PRP given • Total 5 sessions	MASI	68.30%	• Excellent: 0% • Significant: 13.3% • Moderate: 60% • Poor: 26.7%
Sirithanabadeekul et al.,[21] (2019)	10 females	18–65 years	III-2 IV-8	Mixed-10	Not available	• Single centrifugation method employed • Fortnightly intradermal injection of PRP given • Total 4 sessions • Split face study, with PRP on one side and normal saline on the other	mMASI	28.9% reduction of mMASI on the PRP side, and 9% reduction on the placebo site	Not available
Hofney et al.,[22] (2019)	23 (females 19, males 4)	21–50 years	III-7 IV-16	Centrofacial-22 Malar-1	Epidermal-18 Mixed-5	• Double centrifugation method employed • 4 sessions of intradermal injection of PRP given at 4 weekly intervals to the left side of face • On the right side of the face PRP was administered with microneedling • This was a split face study	Both MASI and mMASI	49.21% reduction in mMASI, and 41.31% reduction in MASI	MASI • Excellent: 13.1% • Significant: 21.7% • Moderate: 43.5% • Slight: 21.7% mMASI • Excellent: 13% • Significant: 34.8% • Moderate: 39.2% • Slight: 13.0%
Tuknayat et al.,[23] (2021)	40 (females 36, males 4)	Not available	IV and V (exact numbers not specified)	Centrifacial-31 Malar-8 Mandibular-1	Epidermal-29 Mixed-11	• Double centrifugation method employed • 3 sessions of intradermal injections of PRP given at monthly intervals	mMASI	54.5%	• Excellent: 10% • Significant: 47.5% • Moderate: 40% • Slight: 2.5%

TABLE 6 (Continued)

Author(s)/ year	Total number of patients who received platelet rich plasma microinjections	Age range	Fitzpatrick skin type	Clinical type of melasma	Pattern of melasma on Wood's lamp	Procedure highlights	Scoring system used	Mean percent reduction of score at end point	Degree of improvement amongst patients (%)
Mumtaz et al.,[6] (2021)	32 (females 13, males 19)	20–40 years	Not available	Not available	Not available	• double centrifugation method employed • 4 sessions of intradermal injections of PRP given at monthly intervals	MASI	70.77%	Not available
Current study	15 (females 11, males 4)	22–42 years	IV-7 V-8	Centrifacial-10 Malar-5	Epidermal-5 Dermal-10	• Single centrifugation method employed using a gel separation kit • 5 sessions of intradermal PRP given at monthly intervals	Both MASI and mMASI	41.41% reduction in mMASI, and 39.99% reduction in MASI	According to MASI • Excellent: 6.66% • Significant: 20% • Moderate: 53.34% • Slight: 20% According to mMASI • Excellent: 6.66% • Significant: 40% • Moderate: 33.34% • Slight: 20%

Abbreviations: MASI, melasma area severity index; mMASI, modified melasma area severity index; PRP, platelet rich plasma.

results. PRP, unlike TXA is not a drug and possesses considerable differing properties, particularly its sustained cutaneous rejuvenative effects, that are responsible for its promising role in a number of dermatological conditions, including melasma. Further, withdrawing blood too often may not be very acceptable to many patients. All these aspects therefore, require meticulous introspection before finally suggesting the optimal treatment schedule with intradermal PRP in melasma.

Besides, we detected that PRP is effective in all skin types with no preference for lighter skin shades in the management of melasma.

Head on studies comparing intradermal TXA with PRP in melasma are very few. Literature search revealed two studies that evaluated the efficacy of each option for melasma. One study was from Pakistan, where intradermal injections of TXA and PRP were compared, and the other study was conducted in Egypt where TXA and PRP were administered utilizing microneedling.

The study from Pakistan revealed statistically significant improvement of melasma in both individual treatment groups. On comparing the MASI score reduction between the two groups, the percentage reduction in MASI at end point for PRP and TXA was 70.77% and 49.35%, respectively. The difference in the score was also statistically significant, thereby making the authors of this study conclude regarding the superiority of PRP over TXA in treating melasma.[6]

Gharib et al.,[28] from Egypt also revealed statistically significant improvement of melasma in both individual treatment groups. The percentage reduction in MASI at end point for PRP and TXA was 54.97% and 34.98%, respectively, in their study. Their finding also revealed that improvement in the PRP group was much better than the TXA group, which again was statistically significant.

Our study on the other hand, did reiterate the statistically significant reduction of both mean MASI and mMASI scores for each of the two treatment modalities individually. However, although the overall effect of PRP was better than TXA, the values were not significant statistically.

5 | LIMITATIONS OF OUR STUDY

Our study was limited by the small sample size, short duration of follow up (1 month) and possible observer bias as it was an unblinded study. In addition, the high dropout rate in the PRP group was not foreseen or expected prior to the study. A clear cut explanation regarding this dropout was not obtainable. Reasons speculated included long distance travel, unrealistic expectations and monthly withdrawal of 10 ml of whole blood (which may not have been acceptable to some of the patients after initiation of therapy). Besides, we observed that the five patients (PRP group) who left treatment did so after the first session of PRP administration. As the clinical outcome of these participants was not available, hence "intention to treat protocol" was not performed. Moreover, as the outcome measurement was quantitative in nature, it further posed challenges for intention to treat analysis.

6 | CONCLUSION

We therefore feel that PRP could be a viable alternative in treating patients with melasma who have no contraindication for its administration. Owing to its autologous nature, it offers a higher safety profile. In addition, the presence of abundant growth factors within its mileu, serve in orchestrating a series of mechanisms that bring about facial rejuvenation, which is an added advantage.

Intradermal TXA also, is an effective and safe therapeutic option in melasma. As melasma is a localized disorder of hyperpigmentation, we feel intradermal TXA injections should be preferred over the oral route. The only disadvantage encountered is multiple pricks following drug injections, which can be minimized by adequately numbing the skin.

Our study demonstrated a very narrow difference in improvement between both treatment groups. Although the improvement witnessed was slightly higher in the PRP group, based on our findings we cannot vehemently state that it is a far more superior form of treatment when compared to intralesional TXA.

In order to expound things better more studies with a larger sample size would be of substantial help.

Lastly, combining TXA/PRP mesotherapy with safer topical alternatives like vitamin C, tretinoin, glycolic acid, niacinamide and plant extracts having hypopigmentary as well as anti-aging properties would be of immense value.

In semi rural India, where the authors practice, despite adequately counseling patients, topical steroid/hydroquinone abuse is extremely common. This makes safety a major concern while managing melasma.

Moreover, as melasma therapy is a prolonged one, it would be prudent to advocate treatments that are safe, yet effective at the same time. For this, apart from an adequate knowledge regarding melasma therapeutics, it becomes imperative for the clinician to familiarize himself with the local customs as well as the level of patient understanding (regarding the disease) prior to initiation of any form of therapy. Further, the decision to select a particular treatment for different patients again becomes crucial in our setting, owing to numerous accounts of adverse effects encountered following unsupervised application of certain topical preparations for prolonged periods. Therefore, a holistic approach would certainly be of great help while treating melasma, especially in settings like ours.

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CONFLICTS OF INTEREST

The authors declare no potential conflict of interest.

DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given consent for their

images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

DATA AVAILABILITY STATEMENT

Our data was based on the patients attending the out patient department in the speciality of dermatology. This data is only available in the medical records department of our institute.

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REFERENCES

1. Suthanther CB, Bubna AK, Sankarasubramanium A, Veeraraghavan M, Rangarajan S, Muralidharan K. A clinical study of melasma and assessment of dermatology life quality index at a tertiary health care center in South India. *Pigment Int*. 2016;3:377-382.
2. Kim DS, Park SH, Park KC. Transforming growth factor-beta 1 decreases melanin synthesis via delayed extracellular signal regulated kinase activation. *Int J Biol*. 2004;3618:1482-1491.
3. 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;39:1903-1911.
4. Ando H, Matsui MS, Ichihashi M. Quasi-drugs developed in Japan for the prevention or treatment of hyperpigmentary disorders. *Int J Mol Sci*. 2010;11(6):2566-2575.
5. Li D, Shi Y, Mi L, Liu J, Feng X. Tranexamic acid can treat ultraviolet radiation-induced pigmentation in guinea pigs. *Eur J Dermatol*. 2010; 20(3):289-292.
6. Mumtaz M, Chandio TH, Shahzad MK, Hanif N, Anwar S, Rafique S. Comparing the efficacy of platelet rich plasma (PRP) versus tranexamic acid (4 mg/ml) as intradermal treatments of melasma. *J Coll Physicians Surg Pak*. 2021;31:502-505.
7. Lee JH, Park JG, Lim SH, et al. Localized intradermal microinjection of tranexamic acid for treatment of melasma in Asian patients: a preliminary clinical trial. *Dermatol Surg*. 2006;32:626-631.
8. Budamakuntla L, Loganathan E, Suresh DH, et al. A randomized, open-label, comparative study of tranexamic acid microinjections and tranexamic acid with microneedling in patients with melasma. *J Cutan Aesthet Surg*. 2013;13:1012-1014.
9. Sharma R, Mahajan VK, Mehata KS, Chauhan PS, Rawat R, Shiny TN. Therapeutic efficacy and safety of oral tranexamic acid and that of tranexamic acid local infiltration with microinjections in patients with melasma: a comparative study. *Clin Exp Dermatol*. 2017;42:728-734.
10. Khurana VK, Misri RR, Agarwal S, Thole AV, Kumar S, Anand T. A randomized, open-label, comparative study of oral tranexamic acid and tranexamic acid microinjections in patients with melasma. *Indian J Dermatol Venereol Leprol*. 2019;85:39-43.
11. Kang HY, Ortonne JP. What should be considered in treatment of melasma. *Ann Dermatol*. 2010;22:373-378.
12. Hernandez-Barrera R, Torres-Alvarez B, Castanedo-Cazares JP, Oros-Ovalle C, Moncada B. Solar elastosis and presence of mast cells as key features in the pathogenesis of melasma. *Clin Exp Dermatol*. 2008;33:305-308.
13. Regazzetti C, De Donatis GM, Ghorbel HH, et al. Endothelial cells promote pigmentation through endothelin receptor B activation. *J Invest Dermatol*. 2015;135:3096-3104.
14. Kang WH, Yoon KH, Lee ES, et al. Melasma: histopathological characteristics in 56 Korean patients. *Br J Dermatol*. 2002;146:228-237.
15. Torres-Alvarez B, Mesa-Garza IG, Castanedo-Cazares JP, et al. Histochemical and immunohistochemical study in melasma: evidence of damage in the basal membrane. *Am J Dermatopathol*. 2011;33: 291-295.
16. Artzi O, Horovitz T, Bar-Ilan E, et al. The pathogenesis of melasma and implications for treatment. *J Cosmet Dermatol*. 2021;00:1-14.
17. Pandya AG, Hynan LS, Bhore R, et al. Reliabilty assessment and validation of the melasma area and severity index (MASI) and a new modified MASI scoring method. *J Am Acad Dermatol*. 2011;64:78-83.e2.
18. Cayrili M, Caliskan E, Acikgoz G, Erbil AH, Erturk G. Regression of melasma with platelet rich plasma treatment. *Ann Dermatol*. 2014;26: 401-402.
19. Rodriguez-Arambula A, Torres-Alvarez B, Cortes-Garcia D, Fuentes-Ahumada C, Castanedo-Cazares JP. CD4, IL-17, and COX-2 are associated with subclinical inflammation in malar melasma. *Am J Dermatopathol*. 2015;37:761-766.
20. Faiz F, Shehzad A, Farooq R, Mufti S, Nasir A, Ahmad TJ. Efficacy of platelet rich plasma in the treatment of melasma: a pilot study. *J Pak Assoc Dermatol*. 2017;28:348-353.
21. Sirithanabadeekul P, Dannarongchai A, Suwanchinda A. Platelet rich plasma treatment for melasma: a pilot study. *J Cosmet Dermatol*. 2019;00:1-7.
22. 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;30:396-401.
23. Tuknayat A, Thami GP, Bhalla M, Sandhu JK. Autologous platelet rich plasma improves melasma. *Dermatol Ther*. 2021;34:e14881.
24. Mazzucco L, Balbo V, Cattana E, Guaschino R, Borzini P. Not every PRP gel is born equal. evaluation of growth factor availability for tissues through for PRP gel preparations: Fibrinet, Regen PRP-kit, Plateltex and one manual procedure. *Vox Sang*. 2009;97:110-118.
25. Klatte-Schulz F, Schmidt T, Uckert M, et al. Comparative analysis of different platelet lysates and platelet rich preparations to stimulate tendon cell biology: an in vitro study. *Int J Mol Sci*. 2018;19:212.
26. Kushida S, Kakudo N, Morimoto N, et al. Platelet and growth factor concentrations in activated platelet rich plasma: a comparison of seven commercial separation systems. *J Artif Organs*. 2014;17: 186-192.
27. Hausauer AK, Humphrey S. The physician's guide to platelet rich plasma in dermatologic surgery part I: definitions, mechanisms of action and technical specifications. *Dermatol Surg*. 2020;46:348-357.
28. Gharib K, Mostafa FF, Ghonemy S. Therapeutic effect of microneedling with platelet rich plasma versus microneedling with tranexamic acid for melasma. *J Clin Aesthet Dermatol*. 2021;14:44-48.

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