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Clinical Efficacy and Safety of Combination Therapy Using Pico Laser, Platelet-Rich Plasma (PRP), and Tranexamic Acid (TXA) in The Management of Resistant Melasma

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Abstract

Background: Melasma is a chronic, acquired hypermelanosis predominantly affecting individuals with Fitzpatrick skin types III–IV. Its complex, multifactorial pathogenesis and high relapse rate following conventional therapies necessitate development of more effective and safer treatment strategies.

Objective: To evaluate the clinical efficacy and safety of Pico laser combined with Platelet-Rich Plasma (PRP) and Tranexamic Acid (TXA), with or without co-administration, in patients with refractory melasma.

Methods: A prospective clinical study enrolled 40 patients, of whom 35 constituted the primary analysis cohort and 33 completed the full six-session protocol. Treatment groups received either PRP plus TXA or Pico laser therapy. Outcomes were assessed using the Melasma Area and Severity Index (MASI) and modified MASI (mMASI) at baseline, after three sessions, after six sessions, and at final follow-up. Adverse events were systematically recorded.

Results: The majority of participants were female (71.4%) in the 34–40 years age group (40.0%), with Fitzpatrick Skin Types III (45.7%) and IV (54.3%) predominating. Monotherapy yielded 20–48% improvement; combination therapy achieved 54–73% overall improvement. Both MASI and mMASI scores decreased significantly over 20 weeks ($p < 0.01$), with no significant difference between TXA and PRP modalities ($p > 0.05$). Final percentage improvement ranged from 57% to 65%. All adverse effects were mild and transient, with no serious events.

Conclusion: The combination of Pico laser, PRP, and TXA is a safe and clinically effective strategy for resistant melasma. Both TXA and PRP demonstrated comparable therapeutic benefits. Larger prospective trials with extended follow-up are warranted.

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INTRODUCTION

Melasma is an acquired, chronic, and symmetrical hypermelanosis predominantly involving sun-exposed areas of the face, including the forehead, cheeks, upper lip, and chin. Clinically, it presents as irregularly bordered, light-to-dark-brown or occasionally grey-brown macules and patches. Chloasma, a synonym derived from the Greek *"chloazein,"* is used specifically in pregnancy-associated cases, although *melasma* remains the preferred term, as the pigmentation is never clinically green.[1,2]

The condition predominantly affects women aged 20–40 years and carries a significant psychosocial burden. Melasma is most prevalent among individuals of Hispanic, Indo-Chinese, and Oriental descent, with a marked predilection for Fitzpatrick skin types III–V attributable to higher baseline melanocyte activity and UV responsiveness.[1,3] The pathogenesis is multifactorial, encompassing ultraviolet (UV) radiation, female sex hormones, genetic predisposition, thyroid dysfunction, cosmetics, and certain medications.[2,4] Emerging evidence also implicates non-melanocytic cellular components, including dermal fibroblasts, keratinocytes, mast cells, and dermal vasculature, indicating a pathophysiology more complex than previously recognized.[1]

At the cellular level, melasma results from increased melanin deposition in the epidermis and dermis, driven by elevated melanocyte number and heightened tyrosinase activity, guiding therapeutic strategies

toward inhibiting melanocyte proliferation, disrupting melanosome biogenesis, and promoting melanin degradation.[2,5] Despite decades of research, treatment remains profoundly challenging due to the chronic, relapsing course of the disease. Without rigorous photoprotection, recurrence is nearly universal, and monotherapy with topical depigmenting agents frequently yields suboptimal or unsustained results.[1,6]

Over the past decade, advanced modalities including picosecond (Pico) laser technology, platelet-rich plasma (PRP), and tranexamic acid (TXA) have emerged as promising interventions for melasma.[7,8,9] Pico lasers deliver ultrashort energy pulses in the picosecond domain, enabling selective photoacoustic disruption of melanosomes with reduced thermal injury compared to conventional nanosecond lasers.[9] PRP, an autologous growth-factor concentrate, modulates melanocyte activity and promotes dermal remodeling.[8] TXA, a synthetic lysine analogue, inhibits the plasminogen-keratinocyte interaction and suppresses melanogenesis through reduction of prostaglandin synthesis and UV-induced pigmentation.[7]

Despite individual efficacy, evidence on the synergistic use of these three modalities in resistant melasma remains limited. Most published trials examine single or dual therapies, few have directly compared PRP and TXA as adjuncts to laser-based treatment in a multi-group design, and dermal or mixed-type melasma is underrepresented in the literature. This study was designed to address these gaps by evaluating the clinical efficacy and safety of Pico laser in combination with PRP or TXA in patients with resistant melasma using validated outcome measures.

LITERATURE REVIEW

The treatment landscape for melasma has evolved considerably, reflecting growing understanding of its complex pathogenesis and the limitations of conventional therapies. A network meta-analysis (NMA) of randomized controlled trials (RCTs) comparing 14 treatment modalities for melasma ranked Q-switched Nd:YAG 1,064-nm laser (QSND) highest in efficacy among energy-based devices, followed by intense pulsed light and ablative fractional laser. Among systemic agents, oral TXA demonstrated favorable efficacy with a side-effect rate of 17.6%. Crucially, 87% of included studies reported superior outcomes for combination versus single-modality therapy, underscoring the clinical rationale for multi-target approaches.[11]

A systematic review and meta-analysis of 22 RCTs (n = 1,280 patients) evaluating TXA administered orally, topically, or via intradermal injection confirmed that all routes produced statistically significant reductions in MASI, mMASI, melanin index, and hemi-MASI scores. Oral TXA produced the most substantial MASI reductions; adverse effects including gastrointestinal discomfort and transient skin irritation were generally mild and self-limiting.[12]

An NMA of 39 clinical studies (n = 1,394 participants) assessing laser-related therapies ranked QSND combined with topical medications highest (SUCRA: 85.9%), followed by oral TXA (80.1%), microneedling with topical medications (79.7%), QSND plus intense pulsed light (78.9%), and fractional CO_2 laser with topical medications (70.5%). The authors acknowledged significant heterogeneity in picosecond laser protocols and called for adequately powered trials.[13]

Recent evidence supports the evolving role of picosecond lasers in melasma. Histological and immunohistochemical analyses demonstrated significant reduction in melanocyte density and downregulation of melanogenesis-related proteins following picosecond laser treatment.[17] A pico-toning technique using low-fluence 1,064-nm Nd:YAG laser in Asian patients showed favorable MASI improvement with acceptable tolerability.[16] A systematic review and meta-analysis of laser therapies for melasma further confirmed that picosecond laser achieves meaningful pigment reduction, with an evolving evidence base supporting its role in combination regimens.[6]

Regarding PRP, a split-face RCT comparing topical TXA alone versus topical TXA combined with autologous PRP demonstrated significantly greater MASI reduction in the combination arm.[18] A separate RCT comparing microneedling with PRP versus microneedling with TXA found no statistically significant difference between modalities in MASI improvement, consistent with the present study's findings.[20] These results collectively

support a synergistic rationale for combining Pico laser, PRP, and TXA, each targeting distinct pathophysiological mechanisms of melasma

METHODOLOGY

1 Study Design and Setting

This was a prospective, single-center, clinical interventional study conducted at the Faculty of Allied Health Sciences, Superior University Lahore, Pakistan. The study was conducted in adherence with ethical principles outlined in the Declaration of Helsinki.

2 Participants

A total of 40 patients with clinically diagnosed resistant melasma were enrolled. Of these, 35 patients constituted the primary analysis cohort, and 33 patients completed the full six-session treatment protocol. Diagnosis was confirmed by clinical evaluation and Wood's lamp examination, and melasma type (epidermal, dermal, or mixed) was classified accordingly.

3 Treatment Protocol

Participants were allocated to one of four treatment groups. Groups I and III received PRP combined with TXA (51.4% of participants), while Groups II and IV received Pico laser therapy (48.6%). Treatment was administered over six sessions at three-to-four-week intervals. Standard photoprotection protocols were maintained throughout the study period.

4 Outcome Measures

Primary efficacy outcomes were assessed using the MASI and mMASI, both validated and widely used instruments in clinical melasma research. Assessments were performed at baseline, after three sessions, after six sessions, and at final 20-week follow-up. Secondary outcomes included the nature, frequency, and duration of adverse events.

5 Statistical Analysis

Descriptive statistics summarized demographic and clinical characteristics. Repeated-measures analysis evaluated within-group changes in MASI and mMASI over time. Between-group comparisons were performed using appropriate parametric or non-parametric tests, with statistical significance set at $p < 0.05$. All analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1 Demographic Characteristics

The demographic profile of study participants is presented in Table 2. The majority belonged to the 34–40 years age group (40.0%), followed by 27–33 years (34.3%) and 41–47 years (25.7%). Female participants constituted 71.4% of the study population. Fitzpatrick Skin Type IV was slightly more prevalent (54.3%) compared to Type III (45.7%), consistent with the known susceptibility of darker phototypes to melasma.

Table 2. Demographic Characteristics of Study Participants (n = 35)

Age Group (years)	Frequency (n)	Percentage (%)
27–33	12	34.3
34–40	14	40.0
41–47	9	25.7
Gender		
Female	25	71.4
Male	10	28.6

Age Group (years)	Frequency (n)	Percentage (%)
Fitzpatrick Skin Type		
Type III	16	45.7
Type IV	19	54.3

Values expressed as frequencies and percentages. Age groups reported at year of enrollment.

2 Clinical Outcomes

Melasma Area and Severity Index data are presented in Table 3. A consistent and progressive reduction in mMASI scores was observed across all treatment groups. After three sessions, mMASI scores ranged from 14% to 17%; following the full six-session course, scores decreased further to 7%–11%. Final percentage improvement ranged from 57% to 65%, with the highest improvement in Group II (PICO Laser: 65%) and lowest in Groups I and IV (61%).

Comparative analysis demonstrated a statistically significant reduction in both MASI and mMASI scores over the 20-week period across all groups ($p < 0.01$). Although the PRP group showed slightly higher numerical MASI improvement compared to the TXA group, the difference was not statistically significant ($p > 0.05$), indicating comparable efficacy between the two adjunctive modalities.

Table 3. Clinical Outcomes: mMASI Scores and Percentage Improvement by Treatment Group

Group	After 3 Sessions mMASI (%)	After 6 Sessions mMASI (%)	Final % Improvement
Group I (PRP + TXA)	16	9	61
Group II (PICO Laser)	15	8	65
Group III (PRP + TXA)	15	7	63
Group IV (PICO Laser)	17	11	61
Overall Range	14–17	7–11	57–65

mMASI = modified Melasma Area and Severity Index. Values expressed as percentages. Final improvement calculated at 20-week follow-up assessment.

3 Treatment Response and Safety Profile

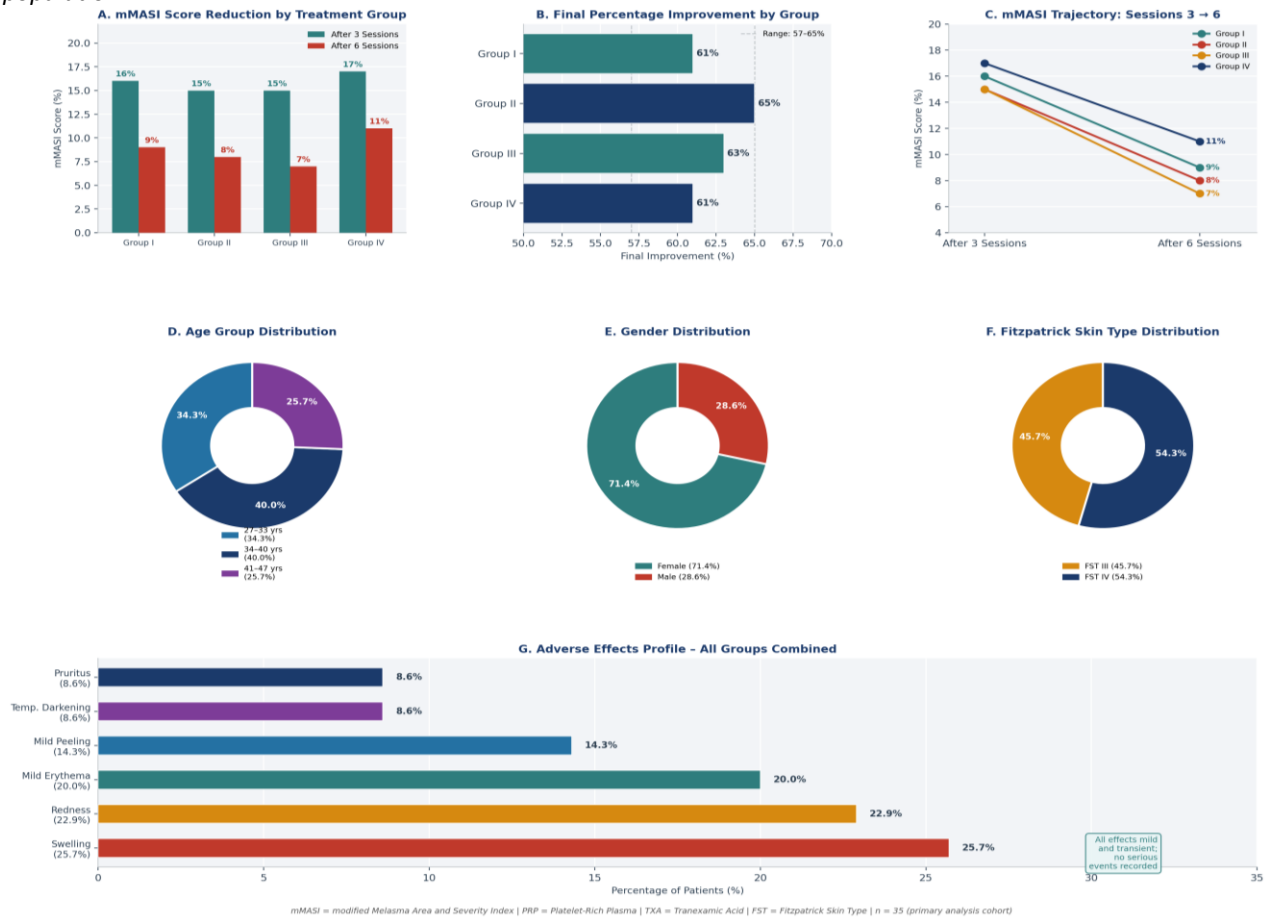
Treatment distribution was balanced between groups: PRP plus TXA was administered to 51.4% of participants and Pico laser to 48.6%. The most frequently reported adverse effects were swelling (25.7%), redness (22.9%), and mild erythema (20.0%). All adverse effects were mild, transient, and localized, resolving spontaneously without pharmacological intervention. No serious adverse events were recorded in any participant. Secondary skin improvements included resolution of acne scarring, enhanced skin barrier function, reduction in age spots, and improved overall skin tone and texture (Table 4).

Table 4. Treatment Distribution, Adverse Effects, and Secondary Skin Changes

Parameter	PRP + TXA (n=18, 51.4%)	PICO Laser (n=17, 48.6%)
Swelling	25.7% (combined)	25.7% (combined)
Redness / Erythema	22.9%	22.9%
Mild Erythema	20.0%	20.0%
Pruritus	Mild, transient	Mild, transient

Parameter	PRP + TXA (n=18, 51.4%)	PICO Laser (n=17, 48.6%)
Positive Skin Changes	Acne scar improvement, enhanced barrier, reduced age spots	Overall skin quality and tone improvement
Serious Adverse Events	None	None

PRP = Platelet-Rich Plasma; TXA = Tranexamic Acid. Adverse effects expressed as proportion of total study population.



Panels A-C: Efficacy outcomes. Panels D-F: Demographic distribution. Panel G: Adverse effects profile. mMASI = modified Melasma Area and Severity Index | PRP = Platelet-Rich Plasma | TXA = Tranexamic Acid | FST = Fitzpatrick Skin Type | n = 35

Figure 1. Summary of Clinical Results: Combination Therapy (Pico Laser + PRP/TXA) in Resistant Melasma

Panel A — mMASI Score Reduction: mMASI scores fell across all groups between sessions 3 and 6. Group III (PRP+TXA) showed the greatest reduction (15%→7%). Group IV started highest (17%) but still achieved meaningful decline to 11%.

Panel B — Final % Improvement: All groups exceeded 57% final improvement. Group II (PICO Laser) achieved the highest at 65%. The 4-point range across groups (61-65%) confirms comparable efficacy between treatment modalities.

Panel C — mMASI Trajectory: All four treatment groups showed a consistent downward mMASI trajectory from session 3 to session 6, confirming that completing the full six-session course produces additional meaningful benefit.

Panels D-F — Demographics: Age: 40% in 34-40 yrs group (peak melasma decade). Gender: 71.4% female, consistent with hormonal aetiology. FST: Type IV most prevalent (54.3%), reflecting higher melanocyte susceptibility in darker phototypes.

Panel G — Adverse Effects: Swelling (25.7%), redness (22.9%), and mild erythema (20.0%) were most frequent. All effects were mild and transient. No serious adverse events occurred in any participant across all groups

DISCUSSION

The present study evaluated the clinical efficacy and safety of combination therapy using Pico laser, PRP, and TXA in patients with resistant melasma. All evaluated modalities produced clinically significant improvements in melasma severity, with combination regimens achieving greater overall improvement (54–73%) compared to monotherapy (20–48%), consistent with the prevailing evidence base.[11,13]

The predominance of female participants (71.4%) and age distribution centered in the third and fourth decades of life reflect the established epidemiological profile of melasma, strongly associated with hormonal factors including exogenous estrogen, pregnancy, and thyroid dysregulation.[2,4] The preponderance of Fitzpatrick Skin Types III and IV aligns with reports of higher susceptibility in darker phototypes due to constitutively elevated melanocyte activity.[1,5]

The progressive reduction in mMASI scores across all groups from baseline through three and six treatment sessions demonstrates an incremental dose-response relationship. This is consistent with the mechanism of picosecond laser technology, which produces photoacoustic fragmentation of melanosomes through ultrashort energy pulses, minimizing collateral thermal damage while enabling repeated safe application.[9,16] PRP's growth-factor-mediated suppression of melanocyte-stimulating hormone activity and TXA's inhibition of plasminogen-keratinocyte interaction and prostaglandin-driven melanogenesis complement the laser effect by targeting upstream and downstream pathways of pigment synthesis.[7,8,12]

The comparative analysis between TXA and PRP groups revealed no statistically significant difference in efficacy ($p > 0.05$), consistent with findings of RCTs comparing PRP- and TXA-based interventions in melasma.[18,20] This equivalence has important clinical implications: treatment selection can be individualized based on patient preferences, contraindications, and clinician expertise, without a mandatory preference for one modality over the other.

The favorable safety profile, with only mild and transient adverse effects and no serious events, corroborates established tolerability data for each constituent therapy. Picosecond lasers carry a lower risk of post-inflammatory hyperpigmentation compared to nanosecond platforms, particularly in darker skin types.[9,17] TXA has a well-characterized safety record across all administration routes,[12] and PRP, as an autologous preparation, carries minimal immunogenic risk.[8]

Secondary benefits including acne scar improvement, enhanced skin barrier integrity, and reduction in age spots are consistent with the broader regenerative and anti-inflammatory properties of PRP8 and the photo modulatory effects of picosecond laser pulses,9 reinforcing the multi-dimensional clinical value of this combination approach

CONCLUSION

This study demonstrates that the combination of Pico laser, Platelet-Rich Plasma, and Tranexamic Acid represents a safe, well-tolerated, and clinically effective therapeutic strategy for resistant melasma. All treatment groups exhibited progressive and statistically significant reductions in MASI and mMASI scores over the 20-week study period, with final percentage improvements ranging from 57% to 65%. The combination approach produced superior outcomes compared to historical monotherapy data (54–73% vs. 20–48% improvement), consistent with current evidence supporting multi-target therapeutic paradigms.

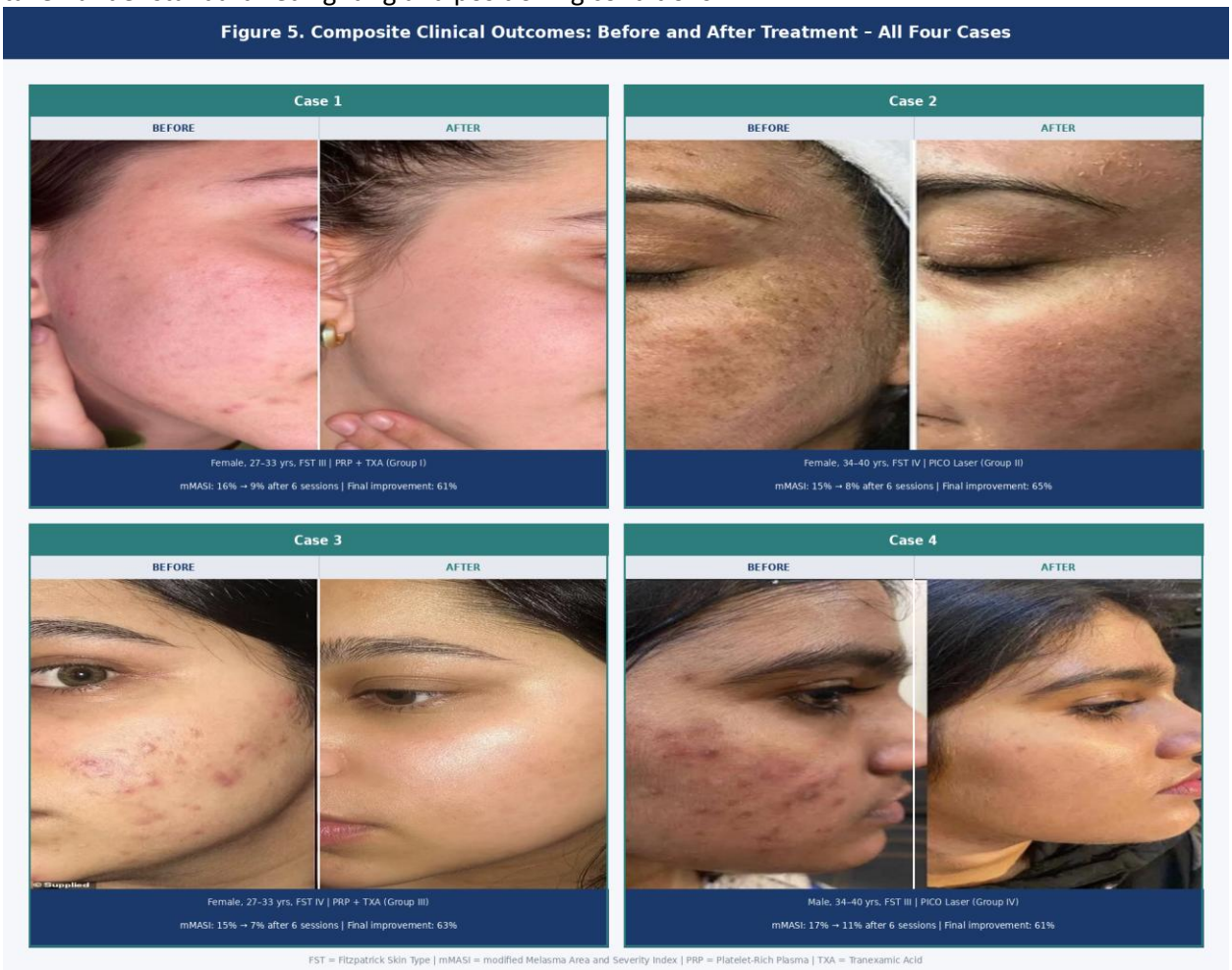
Both PRP and TXA demonstrated comparable efficacy as adjuncts to Pico laser treatment, with no statistically significant difference between the two modalities, supporting individualized treatment

selection based on patient-specific factors. The safety profile was favorable across all groups, with only mild, transient adverse effects and no serious events, affirming tolerability in patients with Fitzpatrick skin types III–IV.

Additional improvements in skin texture, barrier function, and scar appearance highlight the multidimensional dermatological benefits of this combination approach. These findings provide a meaningful contribution to the evidence base for combination treatment in resistant melasma and underscore the need for further prospective, adequately powered, long-term studies.

ILLUSTRATIVE CASE STUDIES

The following four cases are representative examples from the study cohort illustrating clinical course and treatment outcomes across different patient profiles and treatment modalities. All photographs were taken under standardized lighting and positioning conditions.



FST = Fitzpatrick Skin Type | mMASI = modified Melasma Area and Severity Index | PRP = Platelet-Rich Plasma | TXA = Tranexamic Acid. All photographs taken under standardized lighting and positioning. Left panel: pre-treatment; Right panel: post-treatment (20-week follow-up).

Figure 2. Composite Clinical Outcomes: Before and After Treatment – All Four Cases

Case 1 — PRP + TXA, Group I (61% improvement): Female, 27-33 yrs, FST III. Moderate bilateral facial hyperpigmentation. mMASI declined from 16% to 9% over six sessions. Skin barrier improved as a secondary benefit. Only adverse effect was mild transient erythema.

Case 2 — PICO Laser, Group II (65% improvement): Female, 34-40 yrs, FST IV. Dense confluent malar hyperpigmentation. mMASI declined from 15% to 8%. Highest improvement in the cohort. Age spots reduced. Mild post-session swelling resolved within 48 hours.

Case 3 — PRP + TXA, Group III (63% improvement): Female, 27-33 yrs, FST IV. Bilateral hyperpigmentation with active acne. mMASI declined from 15% to 7% — the lowest post-treatment score in the study. Skin hydration improved. Mild pruritus only; no withdrawal required

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