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Efficacy of Topical Hydroquinone 4% with or without Intradermal Autologous Platelet-rich Plasma in Lichen Planus Pigmentosus: A Split-face Randomized Controlled Trial

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Abstract

Lichen planus pigmentosus (LPP) is a chronic acquired hyperpigmentation disorder predominantly affecting sun-exposed areas of the face and neck, for which effective treatment remains challenging. Platelet-rich plasma (PRP) contains growth factors and bioactive mediators, including transforming growth factor-β1 (TGF-β1) and macromolecular activators of phagocytosis, which may modulate melanocyte activity, inflammation, and dermal pigment clearance. This study evaluated whether intradermal autologous PRP provides additive benefit when combined with topical 4% hydroquinone (HQ) in patients with LPP.

In this randomized, single-blinded, split-face controlled trial, 15 patients received intradermal PRP injections on one randomly assigned side of the face at baseline, week 2, and week 4, while both sides received nightly topical 4% HQ throughout the 20-week study period. Outcomes included the melanin index measured by Mexameter®, the hemi-modified acquired macular hyperpigmentation and severity index (DPASI), patient satisfaction, and adverse events, assessed through week 20.

Both treatment arms showed significant reductions in melanin index from baseline to week 20. Earlier reductions were observed on the PRP-treated side, particularly among patients with mild disease and those naïve to PRP. These findings are consistent with PRP-mediated modulation of melanocyte activity and inflammatory pathways. However, no statistically significant between-side differences were detected at any time point, and effect sizes were small. DPASI scores improved modestly in both groups without significant intergroup differences, while patient satisfaction favored the PRP-treated side. Adverse effects were mild and transient.

In conclusion, PRP may exert early localized biological effects on pigmentation through growth factor-mediated mechanisms but did not confer a sustained or clinically dominant advantage over HQ monotherapy. PRP appears to be best positioned as a safe adjunctive therapy in selected patients with LPP.

Keywords: *hydroquinone; autologous platelet-rich plasma; lichen planus pigmentosus; split-face*

1. Introduction

Lichen planus pigmentosus (LPP) is an uncommon variant of lichen planus characterized by an insidious onset of dark brown to grayish macules and patches, predominantly affecting sun-exposed areas of the face and upper limbs. Lesions typically begin as small, ill-defined macules that gradually coalesce into larger areas of hyperpigmentation. Unlike classic lichen planus, LPP is usually asymptomatic or only mildly pruritic and does not involve the scalp, nails, or mucous membranes. The clinical course is chronic, progressive, and unpredictable, with lesions often persisting for months to years and exhibiting periods of remission and exacerbation (Bhutani, et al., 2009; Tanantong et al., 2025).

LPP is classified under the spectrum of acquired dermal macular hyperpigmentation (ADMH), which also includes ashy dermatosis (erythema dyschromicum perstans) and Riehl's melanosis. Although these conditions share overlapping clinical and histopathological features, they differ in demographic distribution, lesion morphology, and disease progression. Ashy dermatosis typically presents at a younger age and favors non-sun-exposed sites, whereas Riehl's melanosis predominantly affects middle-aged women and has been associated with exogenous triggers such as cosmetics and friction (Cheng et al., 2018; Choi et al., 2022). Distinguishing LPP from these entities, as well as from melasma, which commonly presents with symmetric facial hyperpigmentation in younger adults, remains clinically challenging (Honigman & Rodrigues, 2023).

There is currently no universally effective treatment for LPP. Therapeutic options aim to reduce pigmentation and inflammation and include topical corticosteroids, calcineurin inhibitors, depigmenting agents, systemic therapies, and laser-based interventions. Hydroquinone, a tyrosinase-mediated melanogenesis inhibitor, is widely used as first-line therapy for hyperpigmentation disorders such as melasma and has shown efficacy in combination regimens for LPP, although evidence supporting its use as monotherapy in LPP remains limited (Haddad et al., 2003; Klaisung et al., 2024; Kumar & Babu, 2014). Other reported treatments, including oral isotretinoin and Q-switched Nd:YAG laser, have yielded inconsistent results and are limited by adverse effects or disease recurrence. (Muthu et al., 2016; Bhari et al., 2020). Overall, treatment responses are often suboptimal, highlighting an unmet need for effective adjunctive therapies.

Platelet-rich plasma (PRP) is an autologous blood-derived product containing a supraphysiologic concentration of platelets and growth factors that promote tissue regeneration and wound healing (Akaranuchat & Kongkunnavat, 2024). Upon activation, PRP releases bioactive molecules, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF), that collectively regulate inflammation, cellular proliferation, and tissue repair (Alsousou et al., 2013). Importantly, TGF-β1 has been shown to inhibit melanogenesis by suppressing tyrosinase activity, suggesting a potential role for PRP in pigmentary disorders (Kim et al., 2004). Additional PRP-derived mediators may enhance macrophage-mediated clearance of dermal melanin, further contributing to pigment reduction (Ogawa et al., 2000; Sakamoto et al., 2011).

Emerging clinical evidence supports the use of PRP in hyperpigmentation. A recent pilot study demonstrated improvement in melanin index and clinical scores following intradermal PRP injections in patients with facial LPP, with minimal adverse effects (Kiatsurayanon et al., 2025). However, controlled comparative studies evaluating PRP as an adjunct to established depigmenting agents are lacking.

Given the chronicity of LPP, its interindividual variability, and the bilateral nature of facial involvement, a split-face randomized design provides an optimal framework for direct comparison of treatment responses while minimizing confounding variables. Therefore, this study aimed to compare the efficacy and safety of topical 4% hydroquinone combined in patients with intradermal autologous PRP versus topical 4% hydroquinone alone in Thai patients with LPP using a split-face randomized controlled trial.

2. Objectives

The primary objective was to compare changes in the mean melanin index, as assessed by Mexameter®, between topical 4% hydroquinone alone and topical 4% hydroquinone combined with intradermal autologous platelet-rich plasma in patients with lichen planus pigmentosus. Secondary objectives included the comparison of clinical severity as assessed by dermatologists, patient satisfaction scores, and treatment-related adverse events.

3. Materials and Methods

3.1 Study Design

This was a single-blind randomized, split-face, controlled study conducted at the Institute of Dermatology, Department of Medical Services, Ministry of Public Health in Bangkok, Thailand from June 2024 to December 2024. All participants provided signed consent after being fully informed about the study procedures, potential outcomes, and possible side effects. This study protocol was approved by the Ethics Committee of the Institute of Dermatology with IRB number 028/2566 and registered in the Thai Clinical Trials Registry (ID: TCTR20240430003).

3.2 Sample Size Calculation

Sample size estimation was calculated based on data from a prior pilot study (Kiatsurayanon et al., 2025), which reported a reduction in the mean melanin index from 448.19 ± 18.76 at baseline to 409.64 ± 19.13 at week 12 following PRP treatment. Using a two-tailed alpha level of 0.05 and a power of 80%, the minimum required sample size to detect a significant difference between paired facial sides was calculated to be 13 participants. To account for potential dropouts, 15 patients were recruited.

3.3 Patient Selection

Fifteen patients aged 18 to 70 years with clinically and histopathologically confirmed symmetrical LPP involving the face or neck for at least six months were enrolled. All participants had negative standard and special series patch tests prior to study initiation.

Exclusion criteria included pregnancy or lactation; use of hormonal contraceptives; a history of hypersensitivity to PRP; use of isotretinoin, dapsone, or hydroxychloroquine within the preceding six months; anticoagulant therapy, chemotherapy, or bleeding disorders; use of topical corticosteroids, calcineurin inhibitors, or depigmenting agents within one month; laser procedures to the face or neck within three months; antioxidant supplementation (including vitamin C) within three months; active severe acne, a keloid tendency, herpes infection, HIV or hepatitis B infection; recent cosmetic procedures (botulinum toxin within six months or fillers within two years); and concurrent facial dermatitis, malignancy, or other inflammatory skin conditions involving the face or neck.

3.4 Outcome Measures and Research Instruments

Objective pigmentation was assessed using a narrow-band reflectance spectrophotometer (Mexameter® MX18; Courage+Khazaka electronic GmbH), which quantifies the melanin index. On each facial side, three representative hyperpigmented lesions of maximal intensity were identified and marked with transparent film overlays to ensure consistent measurement across visits.

Clinical severity was assessed using the hemi-modified dermal pigmentation and severity index (DPASI), a validated tool for acquired dermal macular hyperpigmentation (Kumaran et al., 2019; Vinay at al., 2018). Facial regions were divided according to standardized scoring criteria (Table 1, Figure 1). Three independent board-certified dermatologists, blinded to treatment allocation and follow-up sequence, evaluated standardized clinical photographs. Interobserver reliability testing was performed prior to study initiation, yielding an intraclass correlation coefficient greater than 0.8.

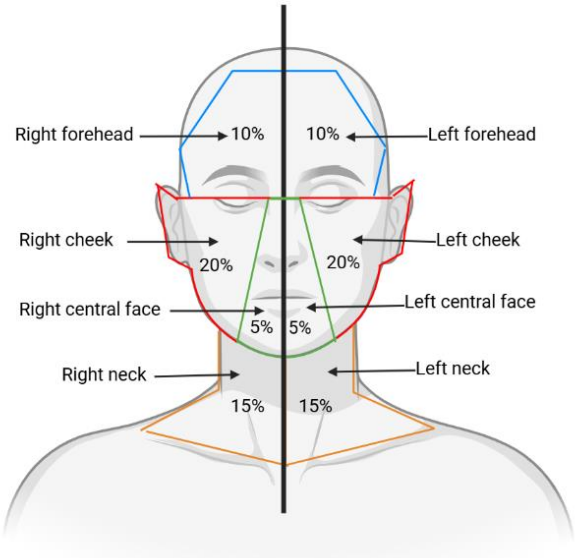

Figure 1 Hemi-modified acquired dermal macular hyperpigmentation and severity index.
Adapted from "A novel scale for measurement of acquired dermal macular hyperpigmentation severity" by K. Vinay, G. Dabas, D. Parsad, and M. S. Kumaran, 2018, *Journal of the European Academy of Dermatology and Venereology*, *32*(6), p. e251-253. Copyright 2017 by the European Academy of Dermatology and Venereology.

Table 1 Determination of the Hemi-modified DPASI[1]

Facial Region	Weighting Factor	Calculation
Forehead	1.0 × (A) × (G)	
Cheek	2.0 × (A) × (G)	Total hemi-modified DPASI score = Forehead DPASI score + Cheek DPASI score + Central face DPASI score + Neck DPASI score
Central face	0.5 × (A) × (G)	
Neck	1.5 × (A) × (G)	

Abbreviations: DPASI, acquired dermal macular hyperpigmentation and severity index

a. Scoring system:
   - A (Percentage area of involvement)
   - G (Grade rated 0 to 4)
     i. 0 = no change in color
     ii. 1 = light brown color
     iii. 2 = bluish/violaceous color
     iv. 3 = slate grey/brown color
     v. 4 = dark brown to black color

b. Total score range:
   - The total hemi-modified DPASI score ranges from 0 to 20 and is calculated by adding scores of the 4 areas of the face and neck.

[1]Adapted from "A novel scale for measurement of acquired dermal macular hyperpigmentation severity" by K. Vinay, G. Dabas, D. Parsad, and M. S. Kumaran, 2018, *Journal of the European Academy of Dermatology and Venereology*, *32*(6), p. e251-253. Copyright 2017 by the European Academy of Dermatology and Venereology.

Patient satisfaction was assessed in weeks 2, 4, 8, 12, 16, and 20 using a quartile grading scale (0–25%, 25–50%, 50–75%, and 75–100% improvement), based on patients' comparative assessment of both facial sides. Treatment-related adverse effects were evaluated one, three, and seven days after each PRP session and at all follow-up visits.

3.5 PRP Preparation and Intervention Protocol

Eighteen milliliters of autologous venous blood were drawn using an 18-gauge needle into a syringe pre-loaded with 1.5 mL of acid citrate dextrose anticoagulant. The sample was transferred to a standardized PRP separation tube, MINOS® PRP Kit (Neogenesis, Seoul, South Korea) and centrifuged at 3,500 rpm for five minutes using a Ugaiya® L500 tabletop centrifuge. The platelet-rich plasma layer was separated from platelet-poor plasma and red blood cell sediment.

PRP was injected intradermally into one randomly assigned facial side using a 1-mL syringe with a 30-gauge needle. Injections were spaced approximately 1 cm apart, producing papules measuring 0.5–1 cm in diameter. Injection volume was standardized according to lesion extent to ensure uniform coverage. Post-injection compression with saline soaked gauze was applied for 15 seconds.

3.6 Data Collection and Follow-up

Participants attended seven visits: three PRP treatment sessions at baseline, week 2, and week 4, followed by follow-up visits at weeks 8, 12, 16, and 20. Standardized facial photographs were obtained using the Canfield Visia-CR System®, and neck photographs were captured using a Nikon® D6 digital camera under consistent lighting and positioning (right and left oblique views at 37 degrees).

All participants applied topical 4% hydroquinone nightly to both sides of the face throughout the study period. Sunscreen and moisturizer were provided, and patients were instructed to avoid sun exposure and refrain from using any other topical or systemic treatments.

3.7 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0. Descriptive statistics were used to summarize demographic and clinical characteristics. Given the small sample size, Friedman's test was used to assess within-subject changes in melanin index and DPASI scores across time points. Subgroup analyses of melanin index were conducted based on disease severity (mild, moderate, severe) and prior PRP exposure (PRP-naïve vs. PRP-experienced). Patient satisfaction and adverse events were reported descriptively as percentages.

4. Results

4.1 Patient Characteristics

Fifteen patients were enrolled, including thirteen females (86.7%) and two males (13.3%). The

mean age was 48.7 ± 9.1 years, with a mean disease duration of 2.3 ± 1.5 years. Fitzpatrick skin phototypes ranged from II to V, with type IV being the most common (66.7%). All participants had symmetrical LPP confirmed clinically and histopathologically. The forehead, cheeks, central face, and neck were involved in more than 80% of cases. Baseline demographic and clinical characteristics are summarized in Table 2.

Table 2 Demographic data

	Number	**Percent (%)**	**Mean ± SD (years)**
Gender			
Female	13	86.7	
Male	2	13.3	
Age			48.7 ± 9.1
Duration			2.3 ± 1.5
Onset			3.3 ± 2.4
Fitzpatrick skin type			
II	1	7	
III	3	20	
IV	10	67	
V	1	7	
Lesion type			
LPP	15	100	
Severity			
Mild	6	40	
Moderate	4	27	
Severe	5	33	

4.2 Melanin Index

At baseline, the mean melanin index values were comparable between the PRP + HQ side (455.51 ± 104.92) and the HQ-only side (450.67 ± 105.01; p = 0.90). Both treatment sides demonstrated significant reductions in melanin index over time. In the PRP + HQ group, significant reductions were observed at weeks 16 and 20, whereas in the HQ-only group, significant reductions occurred earlier, beginning at week 12 and continuing through week 20. However, no statistically significant between-group differences in melanin index were observed at any time point. The mean relative change from baseline is illustrated in Figure 2.

Although numerically greater improvement was observed on the HQ-only side, the between-side difference in the mean melanin index change at week 20 was not statistically significant (mean difference: −13.4; 95% CI: −38.9 to 12.1; $p > 0.05$). The corresponding between-side effect size was small (paired Cohen's d = 0.22), indicating minimal additional benefit of PRP when combined with hydroquinone in the overall cohort.

Subgroup analyses demonstrated consistent melanin index reductions across disease severity (mild, moderate, severe) and prior PRP exposure status (PRP-naïve vs PRP-experienced). In patients with mild to moderate disease, earlier improvement was observed on the PRP-treated side; however, between side differences remained small and non-significant (effect sizes ranging from d = 0.18 to 0.35). In severe disease, improvement was delayed on both sides, with comparable outcomes by week 20 (between-side effect size d = 0.12).

Among PRP-naïve patients, the PRP + HQ side showed earlier reductions in melanin index beginning at week 2, whereas significant improvement on the HQ-only side emerged later. Nevertheless, the final between-side difference at week 20 remained non-significant with a small effect size (d = 0.28). In PRP-experienced patients, both sides improved similarly, with a negligible between-side effect size (d = 0.10). A consolidated summary of subgroup outcomes, including mean changes, 95% confidence intervals, and effect sizes, is presented in Table 3. Given the small sample size, these subgroups findings should be interpreted as exploratory.

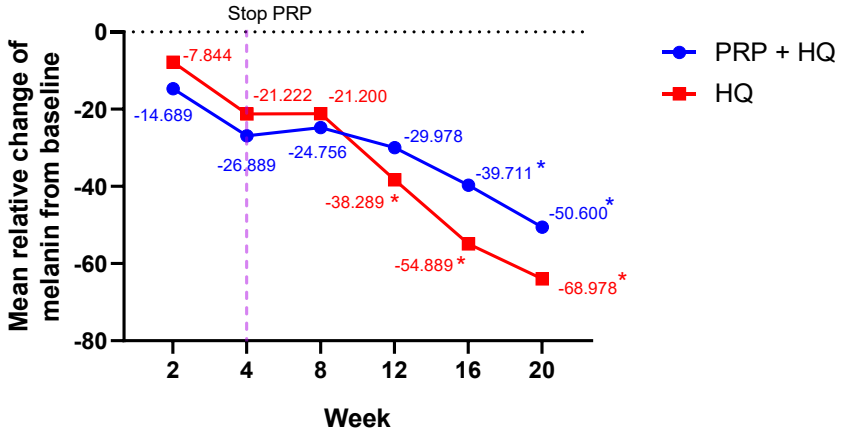

Figure 2 Mean Mexameter®-assessed relative melanin index change between baseline and weeks 2, 4, 8, 12, 16, and 20 in the PRP + HQ and HQ-only groups. (*Significant change from baseline where $p < 0.05$)

Table 3 Summary of Melanin Index Changes, 95% Confidence Intervals, and Between-Side Effect Sizes

Subgroup	N	Mean Δ Melanin Index (PRP + HQ)	Mean Δ Melanin Index (HQ only)	Between-side mean difference	Effect size (Paired Cohen's d)
Overall cohort	15	−50.6 (−82.4, −18.8)	−64.0 (−98.7, −29.3)	−13.4 (−38.9, 12.1)	0.22 (small)
Mild LPP	6	−80.0 (−125.6, −34.4)	−63.2 (−112.9, −13.5)	16.8 (−21.4, 55.0)	0.35 (small-moderate)
Moderate LPP	4	−76.5 (−118.3, −34.7)	−81.0 (−126.7, −35.3)	−4.5 (−39.2, 30.2)	0.18 (small)
Severe LPP	5	−69.2 (−103.7, −34.7)	−123.6 (−169.8, −77.4)	−54.4 (−96.5, -12.3)	0.12 (negligible)
PRP-naïve	6	−77.5 (−121.8, −33.2)	−84.8 (−130.4, −39.2)	−7.3 (−41.6, 27.0)	0.28 (small)
PRP-experienced	9	−74.1 (−108.6, −39.6)	−90.2 (−128.7, −51.7)	−16.1 (−43.9, 11.7)	0.10 (negligible)

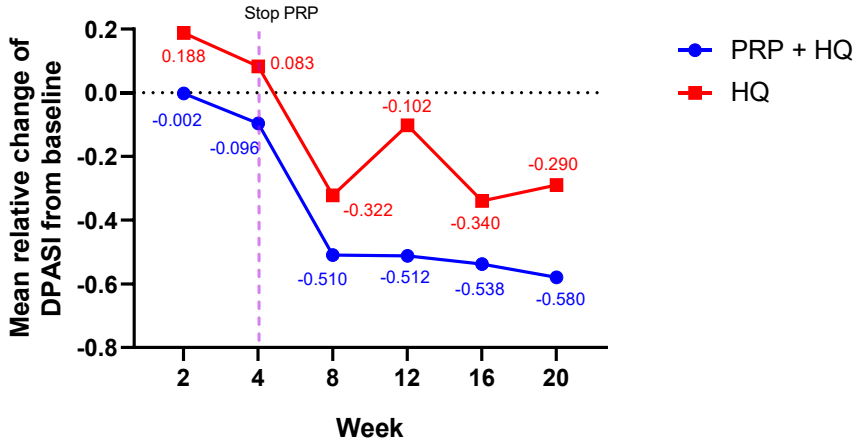

Figure 3 Mean DPASI relative score change between baseline and weeks 2, 4, 8, 12, 16, and 20 in the PRP + HQ and HQ-only groups. (There was no significant change from baseline in both groups.)

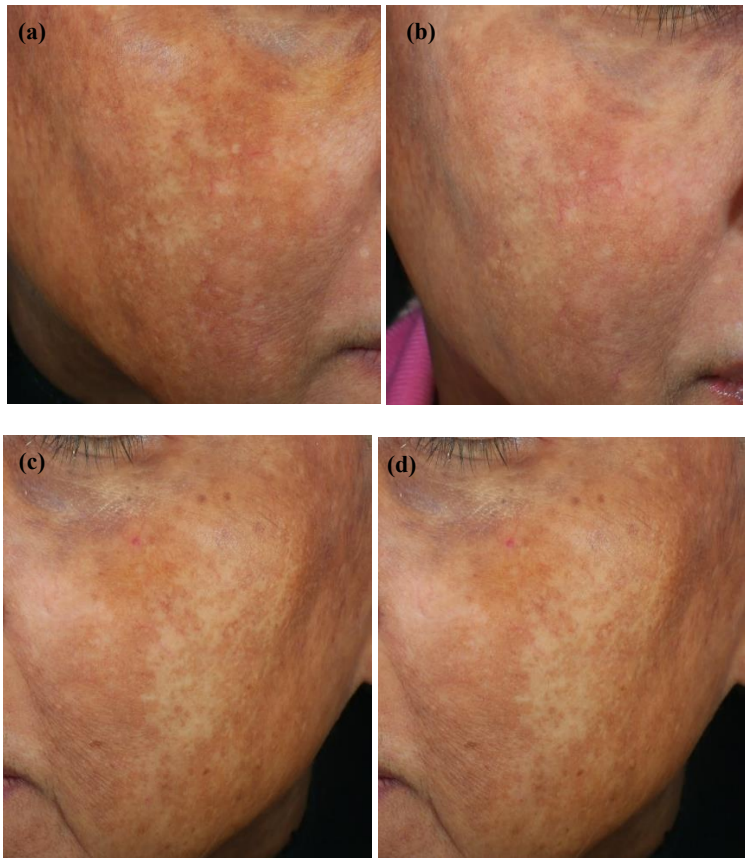

Figure 4 Clinical photographs of a patient. (a) baseline (HQ-only side); (b) week 20 (HQ-only side); (c) baseline (PRP + HQ side); (d) week 20 (PRP + HQ side).

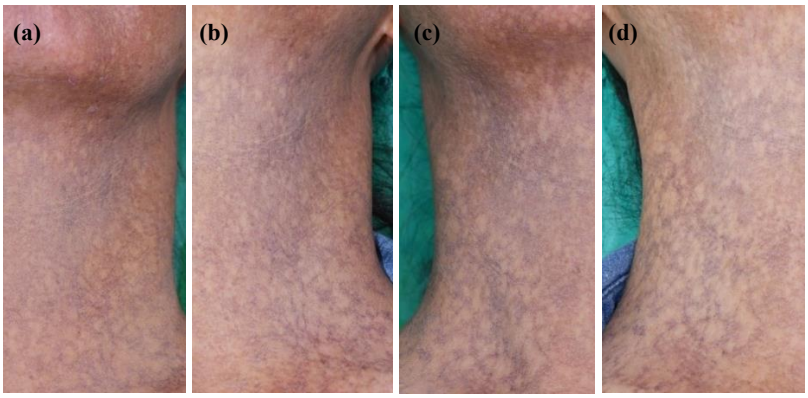

Figure 5 Clinical photographs of a patient's neck. (a) baseline (HQ-only side); (b) week 20 (HQ-only side); (c) baseline (PRP + HQ side); (d) week 20 (PRP + HQ side).

4.3 Clinical Assessment

Baseline hemi-modified DPASI scores were similar between the PRP + HQ and HQ-only sides (4.06 ± 2.84 vs. 4.14 ± 2.78). Both sides showed gradual numerical improvement over time; however, these changes did not reach statistical significance within or between groups at any time point. Between-side effect sizes for DPASI change were consistently negligible ($d < 0.20$). The mean relative change in DPASI from baseline is shown in Figure 3. Representative clinical photographs are shown in Figures 4 and 5.

4.4 Patient Satisfaction and Safety

At week 20, patient satisfaction scores favored the PRP + HQ side, with 12 patients reporting excellent improvement (75-100%) and 3 reporting marked improvement (50-75%). On the HQ-only side, 10 patients reported excellent improvement, 4 reported marked improvement, and 1 reported moderate improvement.

Treatment was well tolerated. The most commonly reported adverse effects were mild, transient edema and erythema at the injection sites, resolving spontaneously within one to three days. No infections, scarring, or post-inflammatory pigmentary alterations were observed.

5. Discussion

This randomized, split-face, single-blind controlled study evaluated whether intradermal autologous PRP provides additive benefit when combined with topical 4% hydroquinone (HQ) in the treatment of lichen planus pigmentosus (LPP). All participants received HQ on both sides of the face and neck, while PRP was administered to one randomly selected side during the initial 4-week treatment phase, followed by extended follow-up through week 20.

Overall, both treatment arms demonstrated statistically significant reductions in melanin index from baseline to week 20, indicating that HQ remains an effective depigmenting therapy in LPP. However, no statistically significant between-side differences were observed at any time point, and between-side effect sizes were consistently small or negligible, supporting the conclusion that PRP did not confer a strong additional depigmenting effect beyond HQ alone.

Subgroup analyses suggested that patients with mild disease and PRP-naïve individuals experienced earlier reductions in melanin index on the PRP-treated side, particularly during the first 4-8 weeks. Nevertheless, these early advantages were not sustained through week 20, and pigmentation levels ultimately converged between the two sides. In moderate and severe disease, the HQ-only side demonstrated comparable or greater late improvement. Given the small subgroup sizes and overlapping confidence intervals, these findings should be interpreted as exploratory rather than confirmatory.

Although DPASI scores showed a general downward trend over time in both groups, no statistically significant changes or between-side differences were detected. This apparent discordance between instrumental (melanin index) and clinical (DPASI) outcomes likely reflects methodological differences. The Mexameter® provides highly sensitive, point-based measurements at predefined injection sites, whereas DPASI captures global visual improvement across the entire face and neck. Because PRP was injected only at selected sites and HQ was applied uniformly, localized pigment changes detected instrumentally may not have translated into perceptible global improvement. Variability in PRP volume and injection coverage may have further contributed to this discrepancy.

Patient satisfaction tended to favor the PRP-treated side, particularly after week 8, despite minimal objective between-side differences. This finding may reflect subjective improvements in texture, brightness, or overall skin quality rather than measurable pigment reduction. PRP was well tolerated, with only mild and transient local adverse effects, supporting its safety as an adjunctive intervention.

Although PRP contains multiple bioactive components such as transforming growth factor-β1, platelet-derived growth factor, and mediators that enhance macrophage-mediated melanin clearance, its clinical impact in this study appeared modest when combined with a potent depigmenting agent such as hydroquinone. The early reductions in melanin index observed on the PRP-treated side, particularly in mild disease and PRP-naïve patients, are biologically plausible and may reflect transient modulation of melanocyte activity and dermal inflammation. These mechanisms, however, remain hypothetical in LPP and were not directly assessed in the present study. However, these effects were not sustained over time and did not translate into statistically significant between-side differences or clinically meaningful superiority when evaluated using global clinical assessment tools. The consistently small effect sizes further indicate that PRP's contribution was incremental rather than dominant.

Importantly, the small sample size limits statistical power, particularly for subgroup analyses, which should therefore be interpreted as exploratory. The split-face design, concurrent hydroquinone use on both sides, and the localized PRP injection strategy may have further attenuated detectable between-group differences. Larger studies with a standardized PRP protocol, broader treatment coverage, and longer follow-up are required to clarify whether PRP can provide sustained mechanistic and clinical benefit beyond conventional depigmenting therapy in LPP.

6. Conclusion

In this split-face randomized controlled study, both PRP combined with 4% hydroquinone and hydroquinone monotherapy produced significant reductions in pigmentation in patients with lichen planus pigmentosus over 20 weeks. No significant between-side differences were observed, and between-side effect sizes were small, indicating that PRP did not provide a robust additive depigmenting effect beyond HQ alone.

PRP may offer early, modest benefit in selected patients, particularly those with mild disease or no prior PRP exposure, but these effects were not consistently sustained. Clinical severity scores (DPASI) and instrumental melanin measurements showed divergent patterns, underscoring the influence of assessment methodology and the dominant global effect of hydroquinone.

Overall, PRP was well tolerated, with only mild and transient adverse effects, and patient satisfaction tended to favor the PRP-treated side. This subjective benefit may reflect perceived improvements in skin quality rather than measurable pigment reduction. Collectively, these findings suggest that PRP may serve as a safe adjunctive option for selected patients with LPP but does not demonstrate consistent clinical superiority over HQ monotherapy.

7. Acknowledgements

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8. Abbreviations

Abbreviation	Full Term
ADMH	Acquired Dermal Macular Hyperpigmentation
DPASI	Dermal Pigmentation Area and Severity Index
EGF	Epidermal Growth Factor
HQ	Hydroquinone
IRB	Institutional Review Board
LPP	Lichen Planus Pigmentosus
PDGF	Platelet-Derived Growth Factor
PRP	Platelet-Rich Plasma
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
TCTR	Thai Clinical Trials Registry
TGF-β	Transforming Growth Factor Beta
VEGF	Vascular Endothelial Growth Factor

9. CRediT Statement

Polpatt Jitpakdee: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization
Chanisa Kiatsurayanon: Conceptualization, Methodology, Resources, Supervision, Project Administration, Funding Acquisition, Writing – Review & Editing

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