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Original article

Comparison of microneedling and polydeoxyribonucleotide salmon 3% versus microneedling and platelet rich plasma in treating wrinkles and facial hyperpigmentation

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Abstract. *Background:* As we age, skin wrinkles and facial hyperpigmentation are likely to appear. Microneedling (MN), a minimally invasive procedure, has gained popularity for its efficacy in addressing various concerns on the appearance of the skin. Combining it with additional agents enhances its therapeutic benefits. Polydeoxyribonucleotide (PDRN) Salmon 3% and Platelet-Rich Plasma (PRP) are two promising agents for skin rejuvenation. *Objective:* This study aims to compare MN combined with PDRN Salmon 3% versus PRP in treating wrinkles and facial hyperpigmentation. *Methods:* A randomized, controlled trial was executed involving 24 women, aged 30-50, with moderate wrinkles and hyperpigmentation. Participants were divided randomly into two experimental sets: Group 1 (MN + PDRN Salmon 3%) or Group 2 (MN + PRP). Both treatments were administered in two sessions, three weeks apart. Assessments were performed at baseline and six weeks after baseline. The outcome was measured using the Lemperle score for wrinkles, and Skin Hyperpigmentation Index (SHI) score for facial hyperpigmentation. *Results:* Both groups demonstrated significant reductions in wrinkles and facial hyperpigmentation. Notably, the PDRN group showed a significantly greater reduction in Lemperle scores (p=0.021), while no significant difference was observed in SHI scores between the groups (p=0.758). Adverse effects were minimal and similar between the groups. *Conclusion:* MN with PDRN 3% or MN with PRP is an effective therapy in treating mild to moderate wrinkles and hyperpigmentation. While both treatments are effective, MN with PDRN 3% demonstrated a more significant reduction in wrinkle scores compared to MN with PRP. Further research is needed to confirm these findings.

Key words: microneedling, PRP, salmon, skin aging, rejuvenation

Introduction

Aging is a progressive physiological decline that becomes apparent after the age of 30[1], including changes in the skin. Skin aging is influenced by both endogenous (genetic predispositions and hormonal fluctuations) and exogenous elements (environmental stressors like ultraviolet radiation and pollution)[2]. Studies have shown that the manifestations of photodamage in Asians are primarily seen in wrinkles, laxity, and hyperpigmentation, which increase with age[3]. A study carried out by Du et al. in 2022 in Indonesia discovered that 91% of aging concerns centered around wrinkles and hyperpigmentation[4].

Microneedling (MN) is a method comprising the use of tiny needles to form micro-wounds in the skin. These micro-wounds arouse collagen synthesis and tissue repair by releasing growth factors (GFs), collagen, and elastin[5,6]. Its applications include skin rejuvenation, acne scars, wrinkles, post operative scars, managing dyschromia and melasma, minimizing enlarged pores, and facilitating

transdermal drug delivery (TDD) through the formation of pores in the corneous layer and supporting neocollagenesis[7,8].

MN is appropriate for every skin type with a lower exposure of photosensitivity, infection, and pigment alterations[9]. Several studies have shown that MN treatments for skin rejuvenation yield positive results, with an increased synthesis of collagen and elastin, and improved wrinkle appearance[10–13]. Despite the availability of numerous skin rejuvenation treatments, MN procedures remain popular due to their minimally invasive nature, overall skin improvement, accessibility, and affordability.

Polydeoxyribonucleotide (PDRN) is a patented drug with tissue restoration, anti-hypoxic, and anti-inflammatory properties[14]. PDRN, extracted from trout or salmon sperm, has the advantage of accelerating skin wound healing and inducing neocollagenesis in photoaged skin[15]. PDRN has various physiological roles that control melanin synthesis and skin ageing[14].

Platelet-rich plasma (PRP) is described as a solution with a platelet concentration exceeding that found in native blood. It is derived from unfractionated centrifuged blood PRP[16], which is rich in GFs, has been utilized to accelerate tissue repair and revitalization, and is now being studied for its application in skin rejuvenation[17].

Anti-aging treatments, especially minimally invasive facial rejuvenation, are in high demand. PDRN and PRP, known to stimulate collagen and elastin, reduce wrinkles, and inhibit hyperpigmentation, are progressively more used in this field. MN, often combined with PRP, is a common approach. However, evidence on MN with PDRN and direct comparisons between PRP and PDRN treatments is scarce. This study aims to determine which serum (PDRN or PRP) provides superior results in addressing wrinkles and hyperpigmentation when used with MN. Wrinkle assessment will utilize the Lemperle scoring method, while skin pigmentation will be evaluated using the Skin Hyperpigmentation Index (SHI). Notably, no prior studies have examined the effectiveness of MN with PDRN or directly compared MN with PRP to MN with PDRN, particularly using SHI to analyse hyperpigmentation scores.

Material and Methods

The clinical trial was executed though a single-center study, involving 24 female participants, which were divided into two groups of 12. Subsequently obtaining certification from the institutional review board of the Faculty of Medicine at Universitas Udayana and the ethical committee of the Faculty of Medicine at Universitas Trisakti, a consent form was acquired from every participant.

The inclusion criteria for participants in the study were as follows: women of age 30-50 years with moderate wrinkles and facial hyperpigmentation, Fitzpatrick III or IV, and willing to undergo 2 treatment sessions of MN combined with PDRN or PRP. The exclusion criteria included: participants who have undergone Botox or filler treatments, had facial surgery or depigmentation cream within the past 6 months, allergic to PDRN, pregnant or breastfeeding, using hormonal contraception, participants with bleeding disorders/ acute facial infections/ tendency to form keloids, participants with comorbid diseases, and ones who had participated in similar studies within 6 months.

Participants underwent baseline assessments including a general examination, a dermatological evaluation, and photography. Subsequently, 12 participants received MN with PDRN (Group 1) and 12 received MN with PRP (Group 2). Lemperle scoring and SHI analysis were performed to assess wrinkle severity and facial hyperpigmentation at baseline and 6 weeks post-treatment. An anesthetic cream was applied to the face 1 hour prior to treatment in both groups. The topical anesthetic used was Emla (lidocaine 2.5%, prilocaine 2.5%). The needle depth used was 1.5 mm, appropriate to achieve superficial bleeding that stimulates a wound healing cascade without scarring. Right after MN, PDRN or PRP were topically applied.

PDRN Salmon 3% (1.5 mL) was drawn into a sterile 23 gauge, 3 mL syringe and topically applied post-MN. The PDRN used in this procedure is PDRN 3% (Dr. Innoderm® PDRN 3% Ampoule, Innoderm, Korea) with high purity, which is extracted from salmon semen and has received permission from the Indonesian Food and Drug Supervisory Agency (BPOM) under registration number NA26220100037.

To prepare platelet-rich plasma (PRP), 4mL of the participant's unfractionated blood were harvested in a sodium citrate tube (blue tube). This blood sample was then centrifuged at 4000 rpm for 15 minutes to separate the PRP layer, which was subsequently transferred to a plain tube (red tube). A second centrifugation step, performed under the same conditions, was carried out to isolate the PRP for topical application. 1,5 mL of PRP was prepared using a 3-mL syringe to be applied topically after MN.

Results

Group 1 (MN with PDRN) included participants aged 45.58±5.62 years (34–50 yo). Group 2 (MN with PRP) included participants aged 45.58±4.12 years (37–50 yo). Both groups included 12 female participants with Fitzpatrick skin phototype III or IV. As seen in the following demographic data (Table 1), both groups were well-matched in terms of age, skin type, wrinkle and facial hyperpigmentation severity. A comparison of the two groups exhibited no statistically significant differences.

Wrinkle and Facial Hyperpigmentation Scoring Method. All participants were assessed using the Lemperle scoring method to evaluate the severity of the wrinkles. Lemperle scores were recorded at both the baseline (before the first procedure) and at the final visit (6 weeks after baseline). Significant differences were observed between the scores prior and subsequent the treatment procedures ($p<0.05$). A Lemperle scoring system was employed to assess treatment outcomes. In Group 1 (MN with PDRN), the mean post treatment Lemperle score reduced from 2.33±0.49 to 1.00±0.43 and statistically significant differences were apparent ($p=0.001$). In Group 2 (MN with PRP), the mean post treatment Lemperle score reduced from 2.33±0.49 to 1.50±0.52 ($p=0.002$). Although both groups showed significant reduction, a significant inter-group difference was evident. The result showed a p-value of 0.021 ($p<0.05$), indicating that the treatments between Group 1 and Group 2 were statistically significantly different in the scores highlighting wrinkle reduction (Table 2). This means that Group 1 was likely more effective than the other in reducing wrinkles.

All participants were assessed using the SHI scoring method to evaluate the severity of facial hyperpigmentation. A statistically significant reduction in SHI scores was observed between baseline and the six-week follow-up ($p<0.05$) as shown in Table 3. In Group 1 (MN with PDRN), the mean post treatment SHI score reduced from 2.83±0.15 to 2.62±0.17 and statistically significant differences were apparent ($p=0.001$). In Group 2 (MN with PRP), the mean post treatment SHI score reduced from 2.76±0.17 to 2.60±0.16 ($p=0.001$). An independent t-test was conducted to

Table 1. Demographic data of the two groups

Variable	Group	Mean	SD	Median	Minimum	Maximum
Age	PDRN	45.58	5.62	47.5	34	50
	PRP	45.58	4.12	46.0	37	50
Fitzpatrick	PDRN	3.25	0.45	3	3	4
	PRP	3.67	0.49	4	3	4
SHI score (pre)	PDRN	2.83	0.15	2.86	2.48	3.00
	PRP	2.76	0.17	2.76	2.51	3.00
SHI score (post)	PDRN	2.62	0.17	2.63	2.23	2.81
	PRP	2.60	0.16	2.61	2.32	2.83
Lemperle (pre)	PDRN	2.33	0.49	2	2	3
	PRP	2.33	0.49	2	2	3
Lemperle (post)	PDRN	1	0.43	1	0	2
	PRP	1.5	0.52	1.5	1	2

Table 2. Mean difference in Lemperle scores among both groups

Group	n	Baseline	Evaluation	p
PDRN	12	2.33±0.49	1.00±0.43	0.001*
PRP	12	2.33±0.49	1.50±0.52	0.002*
p		p=1.00^	p=0.021^	

*Wilcoxon test; ^Mann Whitney test

Table 3. Mean difference in SHI scores among both groups

Group	n	Baseline	Evaluation	p
PDRN	12	2.83±0.15	2.62±0.17	0.001*
PRP	12	2.76±0.17	2.60±0.16	0.001*
p		p=0.310^	p=0.758^	

*paired t-test; ^ independent t-test

compare the effects of treatments in Group 1 and Group 2 on SHI scores. While both treatments reduced SHI scores, the difference between the two groups was not statistically significant (p=0.758).

Undesirable reactions. Thirteen participants reported no adverse effects, while the remaining participants experienced post-procedural complications such as swelling, pain, redness, itching, dryness, and skin peeling. These side effects typically resolved within 2-5 days and were attributed to the MN application method.

Participant-reported outcome. A participant self-assessment of wrinkle severity and facial hyperpigmentation revealed no statistically significant inter-group differences. Both groups demonstrated comparable levels of satisfaction, with all participants reporting high or very high satisfaction.

Discussion

Both endogenous and exogenous elements determine skin aging. Over time, intrinsic and extrinsic elements cause changes in the ECM, connective tissue deterioration, and a reduction in hyaluronic acid (HA) molecules[18]. Sun exposure is estimated to cause as high as 90% of apparent skin aging. The decrease in elastin and collagen types I and III is significantly greater in individuals exposed to sunlight[5,19,20].

The visible changes in aging skin are a result of decreased fibroblast proliferation, followed by a decline in new collagen production, as well as an increase in the production of matrix metalloproteinases (MMPs), especially MMP-1[21]. Ultraviolet (UV)-induced photoaging causes wrinkles, photoaging-associated mottled pigmentation (PMP), and a rough texture. Studies show that manifestations of photodamage in Asians are primarily seen in wrinkles, laxity, and hyperpigmentation, which increase with age[3]. Fighting aging has become a major challenge in this century, including finding minimally invasive facial rejuvenation treatments.

Microneedling (MN), also known as percutaneous collagen induction (PCI), was introduced in 1997 as a favourable minimally invasive treatment for many skin changes, and an easy option to treat aging skin and scar treatments that stimulates collagen avoiding the risk of depigmentation[5,9,22]. This therapy has been clinically demonstrated to enhance the look of fine lines, skin dyspigmentation, wrinkles, melasma and facial scars[6]. MN is a non-thermal, non-destructive procedure, ensuring it suitable for every skin type and Fitzpatrick classification[6,22,23]. Benefits of MN include simplicity, a quick recovery, good tolerability, low risk of post-inflammatory hyperpigmentation (PIH), comfort, and affordability[5].

Treatments using a needle depth of 1.5 mm have been shown to initiate collagen synthesis without disrupting the participant's lifestyle. Increasing the needle depth to 3 mm demonstrated better results but with longer downtime and more severe bruising, swelling, and bleeding[9]. Possible side effects include post-procedural erythema (most common), contact dermatitis (irritant or allergic), lymphadenopathy, an allergic granuloma reaction, systemic hypersensitivity, nickel hypersensitivity, and hyperpigmentation[24].

MN utilizes a micro-needling technique to induce controlled micro-wounds in the skin, thereby stimulating the production of collagen and elastin, vital elements of skin rejuvenation. This procedure is often combined with other substances such as GF serum, PRP, PDRN, or other topical agents, to increase transdermal drug delivery and enhance its effectiveness. Given the various functions of PDRN and PRP

in addressing photoaging concerns, the use of these two substances has become increasingly popular.

PDRN, a purified DNA fragment obtained from the sperm cells of Oncorhynchus mykiss or Oncorhynchus keta, possesses a molecular weight ranging from 50 to 1,500 kDa. With a purity exceeding 95%, PDRN is highly biocompatible and exhibits a wide range of therapeutic effects, including anti-aging properties for the skin[14,25]. PDRN is safe and has good biocompatibility with minimal risks[26].

PDRN supresses MMP-1 and elastase, which are key players in skin aging and wrinkle formation[25]. Treatment with PDRN increases collagen synthesis through the binding of adenosine to the A2A receptor. Additionally, the increased synthesis of collagen and elastin is also due to the inhibition of MMP-1; a decrease in MMP activity results in increased collagen synthesis[27]. PDRN reduces melanin synthesis by downregulating melanogenic gene expression and suppressing tyrosinase enzyme activity[28]. Based on a study done by Noh et al. in 2016, PDRN injections demonstrated improvements in hyperpigmentation[15]. Other studies on polynucleotides (PN) by Lee et al. (2022), Park et al. (2016), and Rungsima et al. (2022) also demonstrated positive results in skin rejuvenation and wrinkle improvement[26,29,30]. As far as we know, no previous research has investigated the synergistic effects of MN and PDRN.

Platelet-rich plasma (PRP) is a self-derived serum enriched with platelets at concentrations exceeding $1\times10^6/\mu L$[31]. PRP proteins play a pivotal role in accelerating wound and tissue repair. Among all proteins present in PRP, the utmost crucial component are GFs[32]. There are more than 20 natural GFs in PRP; Platelet derived growth factor (PDGF), transforming growth factor (TGF)-β1, and epidermal growth factor (EGF) play the most significant roles[33]. PDGF and TGF-β enhance collagen synthesis by causing an increase in fibroblasts. As a result, they can clinically cause wrinkles to become more subtle, minimize scar severity, accelerate wound repair, reduce dyspigmentation, and comprehensive skin revitalization in various states[34,35]. EGF decreases melanogenesis by inhibiting prostaglandin (PG)E2 and tyrosinase[24].

The combination with PRP is popular because it uses natural components from one's own body, thus minimizing the risk of allergies or other side effects. Natural autologous PRP offers an exceptional level of safety[36]. PRP enhances skin elasticity, HA and collagen synthesis, resulting in smoother and firmer skin[18,37]. Combining MN and PRP increases effectiveness, consistent with studies by Asif et al. (2016), Ibrahim et al. (2018), Ibrahim et al. (2017) which showed better results[38–40]. Although abundant proof exists regarding the efficacy of PRP in skin revitalization, there are still studies (da Silva et al., 2021) that show no improvement with PRP[41].

This study compared the effects of MN combined with PDRN and MN combined with PRP in treating facial wrinkles and hyperpigmentation. Wrinkle assessment was conducted employing a scoring method as described by Lemperle et al. (2001). The Lemperle scale was chosen because it is a photo-numeric scale that allows for reproducibility, compared to traditional descriptive scales, and has been correlated with measurements of wrinkle depth. A significant correlation of 87% was observed between the subjective assessment and objective wrinkle depth measurement using profilometry[10,42].

As for facial hyperpigmentation, we use a SHI analysis for the study. SHI is an objective and dependable method for quantitatively measuring skin hyperpigmentation[43]. The SHI scoring method has been validated as a tool for evaluating skin hyperpigmentation. Studies have shown that SHI has very good intra-rater and inter-rater reliability, meaning different raters can use it consistently to assess hyperpigmentation. This method has a good correlation with physician global assessment (PGA) scores. This validation demonstrates that SHI is a practical and objective method for evaluating skin hyperpigmentation[44].

Both study groups exhibited comparable demographic characteristics, including age, skin type, sun exposure, and the number of treatment sessions. The present study demonstrated a significant reduction from baseline to the 6-week follow-up in wrinkle severity and facial hyperpigmentation following MN with PDRN and MN with PRP treatments. Before treatment, both Group 1 and Group 2 had 8 participants with a wrinkle score of 2 and 4 with a score of 3. Post-treatment, wrinkle scores decreased, shifting from 2 and 3 to 0, 1, and 2. In Group 1, scores were

0 (1 participant), 1 (10 participants), and 2 (1 participant). Nine participants in Group 1 had a 1-point reduction, 2 had a 2-point reduction, and 1 had a 3-point reduction. Group 2 had 6 participants with a score of 1 and 6 with a score of 2. Two participants in Group 2 had no reduction, while 10 had a 1-point reduction.

Group 1 showed a significant 50% reduction in the mean Lemperle score from 2.33±0.49 to 1.00±0.43 ($p=0.002$), as evidenced by a statistically significant decrease ($p<0.05$) (Figure 1). Our results align with those of Rungsima et al. (2022) and Park et al. (2016), who found that polynucleotide (PN) treatments led to quicker wrinkle improvement without side effects[26,30]. In addition to increasing collagen production by binding adenosine to A2A receptors, PDRN prevents wrinkle formation by inhibiting the breakdown of collagen and elastin. By inhibiting the activity of MMP-1 and elastase, it helps maintain the skin's structural integrity[25,27].

In Group 2, a reduction in the mean Lemperle score from 2.33±0.49 to 1.50±0.52 ($p=0.001$) (Figure 2) was also observed. In line with previous studies (Cameli et al., 2017; Everts et al., 2019), this research found an increase in skin firmness, skin barrier function, elasticity, and a smoother skin texture[45,46]. Additionally, there was a decrease in pigmentation, wrinkles, and skin redness. The findings of this study align with those of Du and Lei (2020), indicating that PRP improves wrinkles, texture, and pore appearance[32]. PDGF and TGF-β increase collagen production by inducing fibroblast proliferation. These cellular effects can manifest clinically as smoother wrinkles, reduced pigmentation, and overall skin rejuvenation in various conditions[34,35].

Clinically, a significant improvement was observed in most subjects (91.7%) of both groups, as indicated by a decrease in scores. While both groups showed significant wrinkle reduction, the MN with PDRN group exhibited a more pronounced effect ($p=0.021$). This may be attributed to PDRN's ability to suppress elastase and enhance mitochondrial biogenesis. This study, with a 6-week evaluation, may not have fully captured PRP's long-term benefits, as PRP exhibits greater efficacy over extended durations. Both treatments likely benefited from the influence of GFs, either directly from PRP or indirectly stimulated by PDRN. Although preliminary findings indicate a potential benefit of PDRN in reducing fine wrinkles, further research with a larger sample size is required to rigorously assess its effectiveness and determine its efficacy definitively.

A decrease in SHI score were also noted. In Group 1, the mean SHI score before the treatment was 2.83 ± 0.15, and after the treatment decreased to 2.62 ± 0.17 ($p=0.001$) (Figure 3). A previous study by Park et al. (2016) concluded that PDRN has the potential as an anti-melanogenesis agent and is effective in treating hyperpigmentation[26]. Additionally, Noh et al. (2016) found that PDRN injections resulted in improved hyperpigmentation[15]. These findings suggest that MN with PDRN may serve as an effective adjunctive therapy for addressing facial aging concerns. While PDRN inhibits MITF and tyrosinase activity, the exact mechanism underlying this inhibition remains to be fully elucidated[28].

Prior to the intervention, Group 2 (MN and PRP) exhibited a SHI score of 2.76 ± 0.15. Following

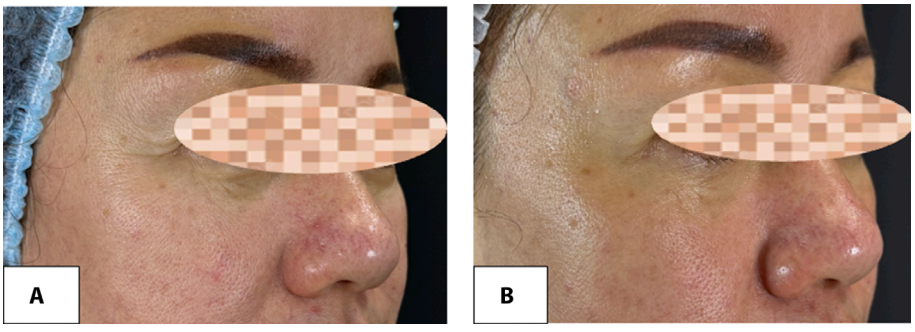

Figure 1. Female participant treated with MN followed by PDRN; A) Before treatment, Lemperle score: 3; B) After treatment, Lemperle score: 0.

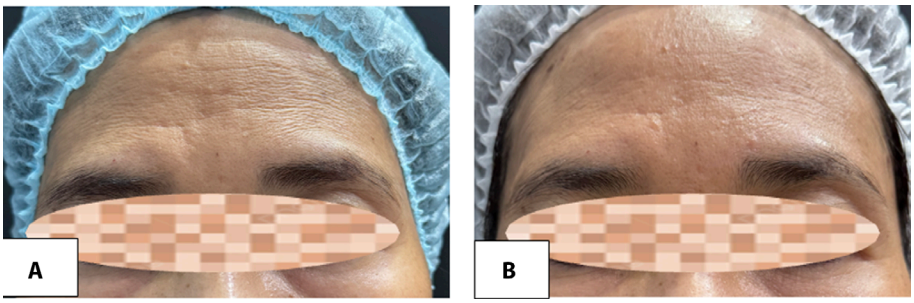

Figure 2. Female participant treated with MN followed by PRP. A) Before treatment, Lemperle score: 3; B) After treatment, Lemperle score: 2.

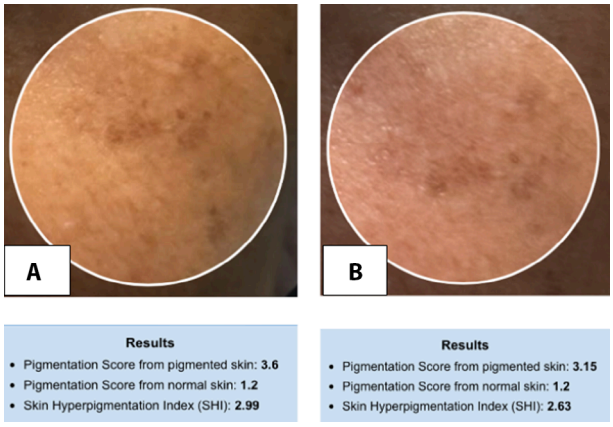

Figure 3. Female participant treated with MN followed by PDRN; A) Before treatment, SHI score: 2.99; B) After treatment, SHI score: 2.63.

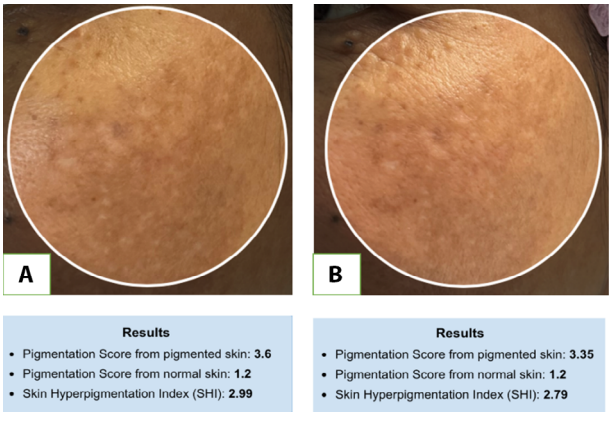

Figure 4. Female participant treated with MN followed by PRP; A) Before treatment, SHI score: 2.99; B) After treatment, SHI score: 2.79.

the treatment, the SHI score significantly decreased to 2.60 ± 0.16 (p=0.001) (Figure 4). These findings align with a meta-analysis by Zhao et al. (2021), which indicated that the combination of MN and PRP may be the most effective treatment for melasma compared to PRP alone or in combination with intradermal injections[47]. PRP enriched with GFs like TGF-β, PDGF, TGF-β1, and EGF, stimulates collagen and ECM synthesis, enhancing skin volume and reducing pigmentation. These GFs also inhibit melanogenesis through various mechanisms, including TGF-β1 and EGF's suppression of tyrosinase and MITF, and TGF-β's inhibition of paired box homeotic gene 3 (PAX3) gene expression[24].

While both treatments led to a reduction in SHI scores, no statistically significant difference was observed between the groups (p=0.758). Although both groups demonstrated a reduction in facial hyperpigmentation, the clinical significance was limited, as the scores remained within the same SHI category (e.g., moderate hyperpigmentation) in both groups. This lack of significant inter-group difference can be attributed to the similar mechanisms of action of PDRN and PRP, both of which stimulate cell regeneration, collagen production, and inhibit tyrosinase, resulting in comparable effects on skin tissue repair. Furthermore, the study did not assess key factors such as pigmentation depth or growth factor concentration within PRP, which could have contributed to the observed results. Finally, the influence of uncontrolled confounding variables, such as sun exposure and hormonal fluctuations, cannot be ruled out.

This comparative analysis revealed that MN combined with either PDRN or PRP effectively mitigated signs of skin aging, with both modalities significantly improving Lemperle and SHI scores. While both groups showed improvement, the PDRN group exhibited a more pronounced reduction in wrinkle severity. Both groups reported similar satisfaction levels and minimal complications. Notably, this study is the first to directly compare MN with PDRN versus MN with PRP. Further research is warranted to definitively determine the most effective treatment modality.

Limitations

Limitations of our study included relying solely on a photographic visual assessment, without any histological examination. Additionally, the results may yield varying scores depending on skin type and photo settings. Furthermore, factors like skin tone evenness and wrinkle improvement typically require time, and noticeable clinical improvements might take several months to appear. Additionally, some participants might not have fully complied with sun exposure limitations. Carrying out a final evaluation l months post-study could provide further insights into the long-term efficacy of the treatments.

Conclusion

This study is the first to directly compare the efficacy of MN combined with PDRN versus PRP for wrinkle and hyperpigmentation reduction. Both PDRN and PRP stimulate collagen/elastin production, inhibit melanin synthesis, and are generally safe. While both therapies reduced wrinkles and hyperpigmentation, MN with PDRN demonstrated greater wrinkle reduction. Limitations included reliance on visual assessment and potential variability in SHI scores. Future research may benefit from a histological analysis.

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