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Case report

Efficacy of microneedling with PDRN salmon 3% to reduce facial hyperpigmentation: Skin hyperpigmentation index (SHI) analysis

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Abstract *Aim:* The study aimed to assess the safety and efficacy of microneedling (MN) combined with Polydeoxyribonucleotide (PDRN) Salmon 3% for treating facial hyperpigmentation. *Methods:* Two patients, aged 40 and 50, underwent two MN sessions combined with PDRN 3%, spaced 3 weeks apart. Photos were taken before and after each visit, as well as at the final visit (6 weeks after baseline). *Results:* Photos were analyzed through a Skin Hyperpigmentation Index (SHI) analysis. Both patients showed improved skin quality, brighter facial skin, and reduced facial hyperpigmentation based on SHI scores. No side effects were noted during or after treatment. *Conclusion:* Combined therapy of MN and PDRN 3% shows promising outcomes in improving skin quality and hyperpigmentation. To the best of the author's knowledge, these are the first reported cases of MN combined with PDRN 3% for reducing hyperpigmentation.

Key words: microneedling, PDRN salmon, hyperpigmentation, skin hyperpigmentation index

Introduction

Skin pigmentation disorders, such as melasma, are common in the general population, affecting a wide range from 1.5% to 33%. They predominantly affect women with darker skin phototypes[1]. Based on a study conducted by Y. Du et al.[2] involving 419 Indonesian women to assess facial skin characteristics and issues, the main problems identified were uneven skin pigmentation (91%), reduced skin elasticity, fine lines, and wrinkles associated with aging. Asians and individuals with dark skin have a lower incidence of wrinkles compared to Caucasians but are more susceptible to pigmentary disorders[3,4].

Microneedling (MN) is a method that utilizes fine needles to make controlled micro-injuries. These tiny punctures stimulate collagen production and skin repair by releasing growth factors (GF), collagen, and elastin[5,6]. MN is suitable for all skin types and carries a lower risk of photosensitivity, infection, and pigmentary changes[7]. It can be useful for skin rejuvenation, acne scars, wrinkles, post operative scars, managing dyschromia and melasma, minimizing enlarged pores, and facilitating transdermal drug delivery (TDD) by forming pores in the stratum corneum and promoting neocollagenesis[8,9]. As opposed to other skin rejuvenation methods like lasers, peels, and dermabrasion, MN carries minimal risk of hyperpigmentation, hypopigmentation, and depigmentation[10].

Polydeoxyribonucleotide (PDRN), is a deoxyribonucleotide polymer that is widely utilized to accelerate skin wound healing and trigger photoaging skin neocollogenesis. PDRN is extracted from trout or salmon sperm[11]. PDRN has various biological functions that regulate melanogenesis and skin aging[12]. Polynucleotide (PN) comes from salmon testes and has a longer nucleotide chain. PN demonstrates enhancements in multiple skin parameters, including pore size, skin thickness, tone, melanin content, wrinkles, and sagging[13].

A novel, practical, unbiased and automated quantitative method has been developed to evaluate skin

hyperpigmentation. This new analysis, known as the Skin Hyperpigmentation Index (SHI), opens new possibilities for advancing objective clinical image analysis by quantifying optical density in proportion to the level of hyperpigmentation[14].

Combating aging remains a significant challenge in this century, particularly when seeking minimally invasive facial skin rejuvenation treatments. Given the diverse functions of PDRN in addressing photoaging complaints, its use is increasingly popular. Minimally invasive procedures like MN, which enhance PDRN absorption, offer promising treatment options for facial skin rejuvenation. However, no research has thoroughly examined the effectiveness of MN combined with PDRN in reducing skin hyperpigmentation using the SHI.

Methods

Patient's selection

The inclusion criteria for this study are as follows: women aged 30-55 years with facial hyperpigmentation, willing to undergo two treatment sessions of MN combined with PDRN. The exclusion criteria include patients using depigmentation cream or undergoing depigmentation treatment, allergic to PDRN, pregnant or breastfeeding, using hormonal contraception, patients with bleeding disorders/acute facial infections/prone to keloid formation. Additionally, participants currently enrolled in other research studies and those who participated in similar studies within the last 6 months are excluded.

Treatment protocol

The treatment consisted of two sessions spaced 21 days apart, with a post-treatment evaluation conducted at 6 weeks from the baseline (3 weeks after last treatment). Photos were taken before and after each treatment session, as well as during the final visit (Figure 1). The Hyperpigmentation assessment involved uploading patient photos before and after treatment to calculate a hyperpigmentation score based on the Skin Hyperpigmentation Index (SHI) available at https://shi.skinimageanalysis.com.

Technique

A full-face microneedling (MN) treatment was performed, followed by the application of PDRN Salmon 3%. The necessary equipment and materials for the MN procedure included face wash soap, a MN tool (Dr. Pen®), a microneedle cartridge with 12 needles, topical anesthetic cream (EMLA®), sterile water, a 0.9% sodium chloride solution, topical antibiotic (gentamicin 0.1% ointment), medical gloves, napkins, and PDRN Salmon 3% in a 1cc syringe. Deeply cleanse and disinfect the face to prepare a clean face for the treatment. Apply numbing cream for 30-40 minutes. Disinfect the entire face using alcohol swabs. Adjust the needle depth (between 0.5mm to 1.5mm) based on the target area. PDRN Salmon 3% was applied to the skin surface. Glide the pen across the skin to create controlled micro-injuries and enhance serum absorption. During the PDRN application, pinpoint bleeding may still be

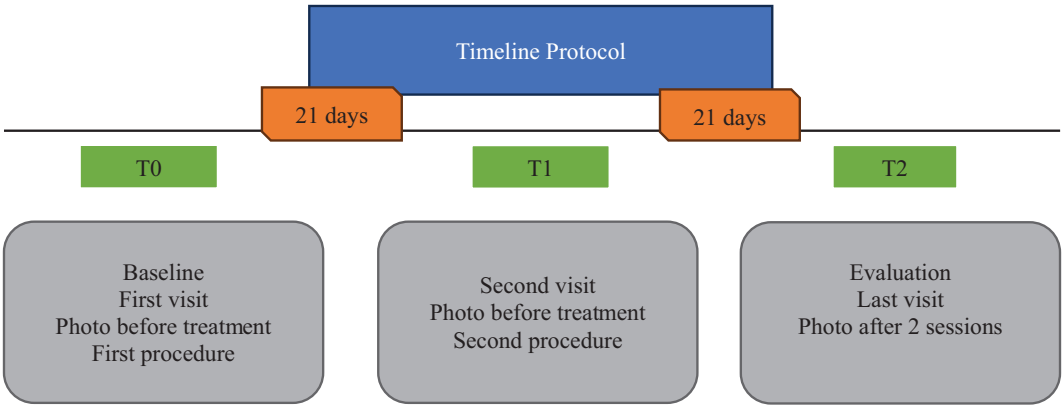

Figure 1. Treatment protocol timeline.

visible on the skin surface. Afterward, use sterile gauze soaked in a sodium chloride solution to compress the patient's face for 15 minutes, followed by cleaning with more sterile gauze. Finally, apply topical antibiotic and SPF 50 PA ++++ sunscreen to the entire facial surface.

After treatment care

After the procedure, the patient was advised to apply gentamicin 0.1% ointment twice daily for three days and apply SPF 50 PA ++++ sunscreen each morning. Additionally, the patient received maintenance instructions for facial hygiene, avoiding face rubbing during washing, refraining from using night cream, and protecting against direct sun exposure during outdoor activities (e.g., using an umbrella or hat).

Results

Case 1

A 40-year-old patient with Fitzpatrick skin type IV, came with overall poor skin quality and facial hyperpigmentation, particularly in the under-eye area. She had not received any prior treatments. Treatment with MN combined with PDRN resulted in improved skin quality and reduced hyperpigmentation. Minimal side effects (such as redness) were observed, and recovery was quick. The treatment pain was rated as 3 out of 10. The SHI score decreased from 2.67 (before treatment) to 2.03 (final evaluation) as shown in Figure 2. In general, the appearance of facial skin is better between and after two treatment sessions, 3 weeks apart, as depicted in Figure 3.

Case 2

A 50-year-old patient with Fitzpatrick skin type IV, came with overall poor skin quality and facial hyperpigmentation. She had never had any treatments before. Treatment with MN combined with PDRN has led to an improvement in skin quality and reduced hyperpigmentation. Side effects were minimal (i.e., redness) and recovery was quick. The treatment pain was rated as 4 out of 10. The SHI score decreased from 2.95 (before treatment) to 2.79 (final evaluation), as shown in Figure 4. Overall, the appearance of facial hyperpigmentation is better between and after two treatment sessions, 3 weeks apart, as depicted in Figure 5.

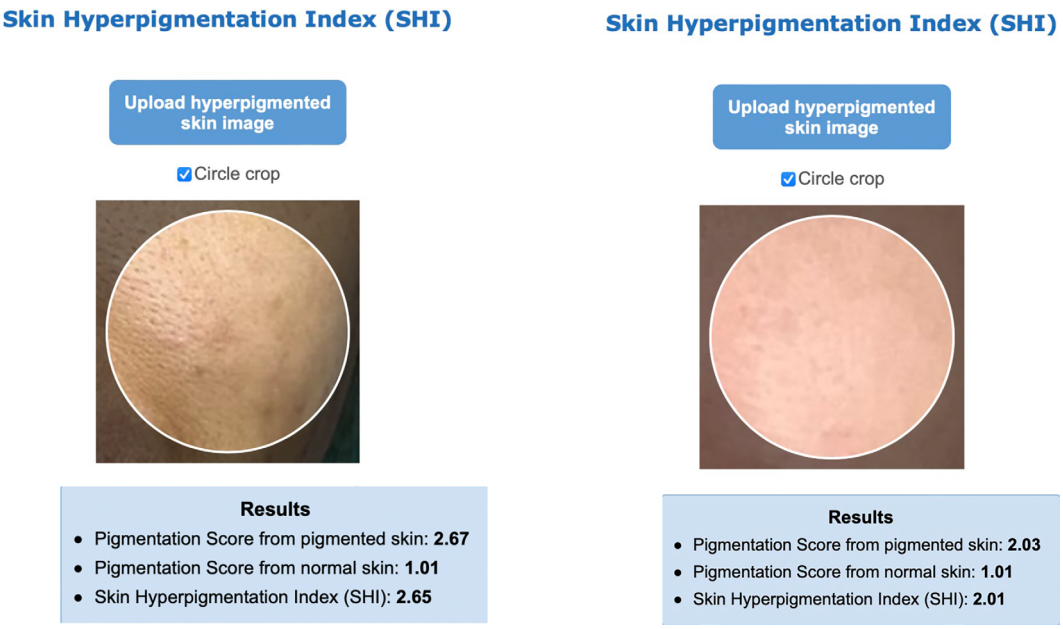

Figure 2. SHI before the treatment (baseline) and after 6 weeks, SHI score decreased from 2.67 to 2.03.

Discussion

Microneedling (MN) is a minimally invasive technique that includes creating small channels in the skin using microneedles. These microneedles typically have diameters in the micron range, between 250 μm to 2,000 μm. In 1995, Orenteich discovered MN as a method for scar treatment, involving subcision or dermal needling. This process stimulates collagen growth and dermal remodeling beneath scars. Later, Fernandes introduced MN as a novel technology to initiate post-trauma inflammation[15–18]. MN can synergize with intradermal or topical platelet-rich plasma (PRP) treatments[19]. Furthermore, it can enhance transdermal drug delivery (TDD) by forming pores in the stratum corneum[16,17]. Also referred as percutaneous collagen induction (PCI), MN was introduced in 1997 as a promising minimally invasive therapy for various skin conditions. It serves as a simple alternative for aging skin and scar treatment, stimulating collagen deposition without the risk of hyperpigmentation[15].

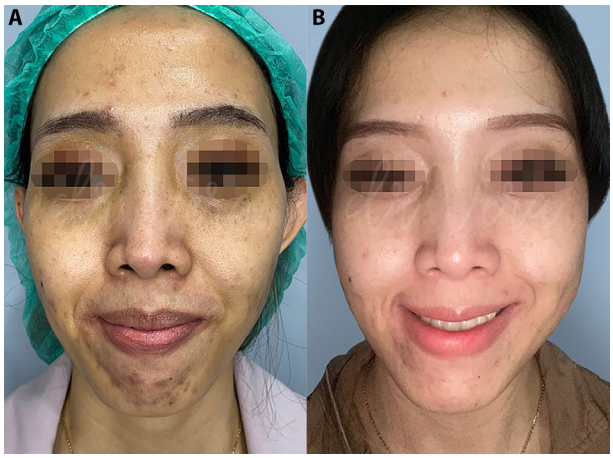

Figure 3. Comparison between before and after two sessions of treatment: (A) Before treatment (baseline). (B) 6 weeks after (final visit).

Microneedling (MN) has been employed to enhance various skin conditions, including acne scars, skin discoloration, melasma, fine lines, wrinkles, and facial scars[6]. Notably, 6 months after the MN treatment, there was a remarkable rise in collagen types I, III, VII and tropoelastin, contributing to skin rejuvenation and an improved appearance[15]. Histological research indicates that MN can enhance aging skin by tightening it and improve its appearance. The controlled needle penetration triggers a typical wound healing response, resulting in minimal epidermal damage. After several

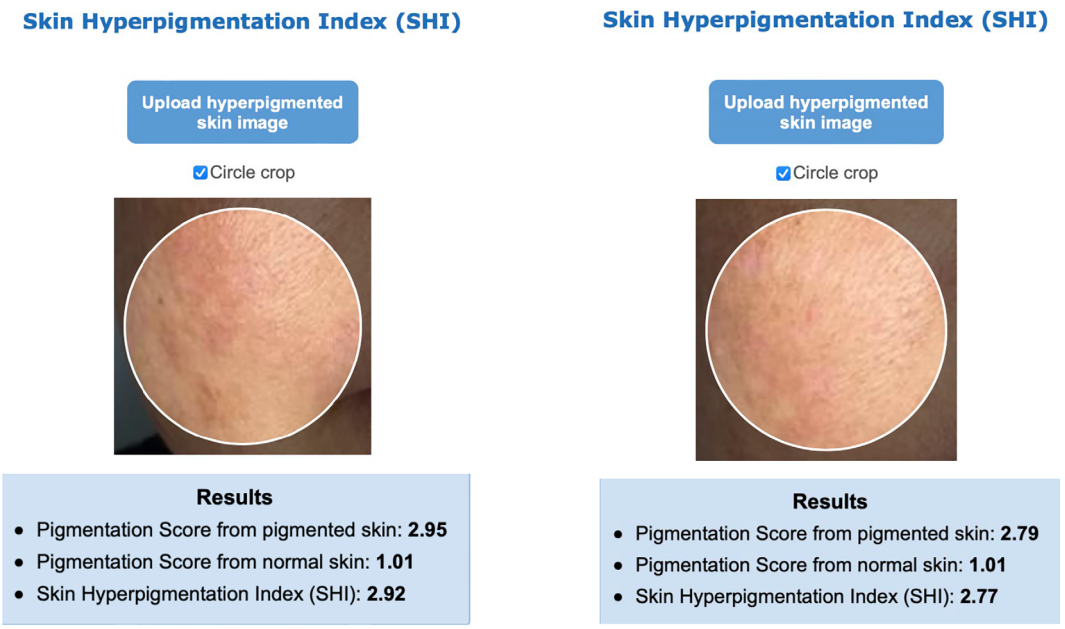

Figure 4. SHI before the treatment (baseline) and after 6 weeks, SHI score decreased from 2.95 to 2.79.

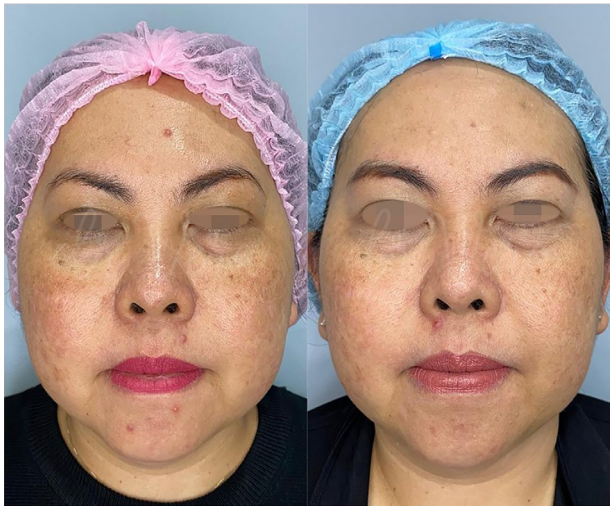

Figure 5. Comparison between before treatment (baseline) and after 6 weeks (evaluation at final visit).

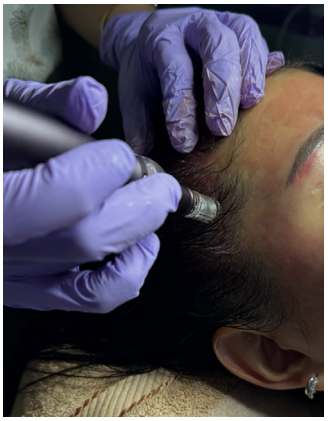

Figure 6. Microneedling pen.

MN sessions, there was a remarkable 400% rise in collagen and elastin. Notably, this procedure offers advantages such as simplicity, fast recovery, well tolerated, minimal risk of post-inflammatory hyperpigmentation, comfort, and cost effectiveness[5].

The basis of the MN procedure involves repetitively applying a tool with needles 0.5 – 1.5 mm long into the skin, in various directions, to create pores in the epidermis and dermis[10]. The needles in the MN device are very fine and can penetrate up to 3 mm deep. When using a needle length of 1.5 mm, it stimulates scarless healing by reaching the papillary and reticular dermis. Notably, the superficial bleeding confluence zone occurs at a depth of 500–600 μm. MN preserves the stratum corneum and barrier function of epidermis, resulting in reduced scarring. Importantly, MN is safe for all skin types and Fitzpatrick classifications because it doesn't cause thermal injury or necrosis[6,15,18]. Creating microchannels induces controlled injury with negligible harm to the epidermis, aiding the various stages of wound healing (inflammation, proliferation, and remodeling)[8].

Various tools are available for PCI techniques. Stamping tools are designed for treating smaller areas and localized scars, making them particularly useful for precise applications. Drum-shaped Rollers, which come in different needle materials (such as gold, titanium, etc.), lengths, diameters, and overall surface density, vary based on the manufacturer. While rollers work well for flat open surfaces like cheeks, they can be challenging in narrow channels (e.g., perioral or scalp areas) where hair might get entangled[7]. Electric Pens (depicted in Figure 6) offer advantages over drum rollers. They allow for the easy adjustment of speed and penetration depth. The treatment of larger areas becomes more efficient, and depth can be customized as needed. Single-use needles reduce the risk of infection and are particularly useful for difficult areas (e.g., above the lip or deep scars)[8]. Modern automated MN devices have replaced traditional dermal rollers[15].

Following the procedure, the treated area will exhibit redness and minimal bleeding. Typically, this redness subsides quickly, with most patients experiencing slight redness lasting 1 to 2 days. However, individuals with sensitive skin may have redness persisting for a longer duration[6]. The effectiveness of MN MN relies on its ability to stimulate neocollagenesis and wound healing processes in the upper dermis. Additionaly, MN creates a pathway for a better absorption of topical medication, including PDRN, into the upper skin layers. In these patients, MN was combined with topical PDRN to reduce facial hyperpigmentation.

Polydeoxyribonucleotide (PDRN) is a medication with multiple functions, including tissue repair, anti-ischemic effects, and anti-inflammatory properties[12]. In 1989, Bruroni et al. investigated the use of PDRN in patients with ectropion[20]. PDRN is composed of DNA fragments originating from sperm cells of Oncorhynchus mykiss (trout salmon) or Oncorhynchus

keta (chum salmon). Its chemical composition comprises DNA with a molecular weight spanning from 50 - 1.500 kDa[12,21]. Phosphodiester bonds linked these linear polymer chains of deoxyribonucleotides, creating a double-helix steric structure. The derivation and purification process of PDRN ensures over 95% purity, minimizing immunological reactions[21]. Spermatozoa are the preferred source for obtaining highly pure DNA[12]. PDRN shows therapeutic potential, including as an anti-aging skin agent[21]. The PDRN used in this procedure was PDRN 3% (Dr. Innoderm® PDRN 3% Ampoule, Innoderm, Korea), a high-purity formulation extracted from salmon semen. It has been approved by the Indonesian Food and Drug Supervisory Agency (BPOM) under registration number NA26220100037.

Polydeoxyribonucleotide (PDRN) stimulates adenosine A2A receptors, which are pivotal in controlling inflammation, oxygen utilization, ischemia, cell proliferation, and angiogenesis. By inhibiting nuclear factor - kappa B (NF-κB) signaling and mitogen-activated protein kinase (MAPK) pathways activated by reactive oxygen species (ROS), PDRN promotes tissue repair, inhibits pro-inflammatory cytokines, and increases collagen synthesis. Overall, A2A receptors are crucial for managing ROS-related disorders and supporting healing processes[12,21]. PDRN effectively reduces melanin synthesis in a dose-dependent way. Additionally, it decreases intracellular tyrosinase activity was in Mel-Ab, accompanied by reductions in microphtalmia-associated transcription factor (MITF) and tyrosinase-related protein 1 (TRP-1)[21]. In a separate study, PDRN immediately suppressed tyrosinase activity, resulting in a substantial decrease in cellular melanin content within B16-F10 melanocytes. Likewise, treatment with PDRN led to the reduced expression of MITF, TRP-1, and TRP-2 proteins[22]. The study by Noh et al. in 2016 explored the impact of PDRN on skin melanogenesis. Their findings revealed that PDRN led to a reduction in melanin, tyrosinase activity, MITF and TRP-1 and an increase in extracellular signal regulated kinase (ERK) and AKT (protein kinase B) in mouse melanocytes. In this study, PDRN injections were administered to 6 female patients over three sessions, resulting in improvements in mottled pigmentation associated with photoaging (PMP)[11].

Studies conducted in mice to investigate the adverse consequences resulting from multiple instances of administering PDRN systemically did not reveal any toxicity to the brain, heart, muscle, liver, or lungs[21]. Research conducted by Kim et al. in 2020 demonstrated that the HA-PN filler combination is more effective in stimulating collagen and fibroblast synthesis, as well as promoting skin regeneration[23]. PDRN significantly suppresses melanogenesis by inhibiting melanogenic gene expression and tyrosinase enzyme activity. As a depigmentation medication, PDRN holds a crucial role in skin lightening. It represses MITF and its target genes amidst melanogenesis. Additionally, PDRN actively suppresses tyrosinase activity, an enzyme that limits melanogenesis. The precise mechanism of this inhibition remains an area of ongoing research. Further investigations are needed to fully elucidate this process[22]. PDRN has diverse biological functions related to melanogenesis and aging of the skin. PDRN acts as a hypopigmentation material by inhibiting the activity of the tyrosinase enzyme. It achieves this inhibition by repressing MITF and the expression of its target genes in melanogenesis. PDRN combats skin aging by inhibiting elastase activity and matrix metalloproteinase-1 (MMP-1) expression. Ultimately, it stimulates mitochondrial biogenesis in fibroblasts and melanocytes, promoting ideal skin function[22].

Until recently, no reliable objective method existed to quantitatively measure skin hyperpigmentation. However, a novel practical, objective, and programmed quantitative method has been developed. The adoption of modern digital image processing systems like Image J (NIH, Bethesda, MD), has streamlined the intricate implementation of clinical images. The SHI is a novel analysis that assigns scores ranging from 1 to 4 based on a combination of 4 areas. It provides exciting opportunities for advancing objective clinical image analysis by quantifying optical density in proportion to the level of hyperpigmentation. When using this method, it is important to be aware that the scores can indeed vary based on skin type and photo settings. Interpretation of SHI score: 1 (without hyperpigmentation) to 4 (utmost hyperpigmentation). Scores 1 and 2 are described as mild hyperpigmentation, scores 2-3 as moderate hyperpigmentation, and scores 3-4 as severe hyperpigmentation. To facilitate

this quantification, the free online SHI calculator can be used by all practitioners via the link https://shi.skinimageanalysis.com/[14,24].

The mechanisms of microneedling and PDRN are different. Microneedling works by creating micro-injuries that stimulate collagen and elastin production. PDRN promotes tissue repair and regeneration at the cellular level, leading to improvements in pigmentation. We did not perform a split-face treatment because, in Indonesia, most patients would not opt for microneedling alone. By implementing MN therapy, transdermal drug delivery from PDRN is enhanced, leading to an increase in activity. The combination of these two approaches demonstrates a beneficial effect in reducing facial hyperpigmentation, as evidenced by decreased hyperpigmentation scores based on the reduced SHI before and after treatment. The choice of using the SHI score for analysis is advantageous due to its objectivity and ease of assessment. In both cases, the SHI score exhibited a reduction: in case 1, it decreased from 2.67 to 2.03, and in case 2, it decreased from 2.95 to 2.79. While both cases showed promising results, a definitive conclusion regarding the benefits of combining MN and PDRN cannot be drawn yet because of insufficient studies regarding this therapy. Further research is needed to establish whether the combination of MN and PDRN is likely to effectively reduce facial hyperpigmentation.

Conclusion

Until now, no studies have specifically investigated the effectiveness of MN combined with PDRN in reducing hyperpigmentation scores using a SHI analysis. Nevertheless, it is noted that PDRN notably suppresses melanin synthesis by repressing melanogenesis. It achieves this by repressing melanogenic gene expression and reducing tyrosinase enzyme activity. PDRN directly inhibits tyrosinase, an enzyme involved in melanogenesis. It is considered safe and exhibits good biocompatibility with minimal risks. Temporary side effects, such as redness, swelling, or bruising, may occur due to the application method. In both cases, greater skin quality and brighter skin were achieved with MN and PDRN therapy. Additionally, the hyperpigmentation score, as assessed by the SHI, was reduced. The importance of these cases lies in the fact that, as far as the author knows, there have been no published cases of MN combined with PDRN. These are the first cases reported in Indonesia. The study's primary limitation lies in its assessment of skin outcomes solely at a macroscopic-visual level. Without an evaluation at the tissue-cellular level, we can only infer that the clinical outcomes indicate an overall improvement in hyperpigmentation. Furthermore, the SHI analysis may yield varying scores depending on skin type and photo settings.

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