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Platelet Rich Plasma: A Potential Treatment Option in Hyper Pigmentation of Skin

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Abstract

Melasma is characterized by symmetrical hyper pigmented macules and patches on the sun exposed area of the face, commonly on forehead, cheeks, lips and nose especially in women. It is an acquired pigmentary disorder. Its pathogenesis is not yet fully understood but the common risk factors for melasma include pregnancy, oral contraceptives, genetic factor, Ultraviolet exposure. Most recently data supported that pathogenesis of melasma involves vascular growth factors, Wnt pathway modulator genes and inducible Nitric Oxide Synthase (iNOS) expression and down regulation of H19 genes with a still unresolved pathogenesis. A wide variety of treatments include hydroquinone, tretinoin, kojic acid, and tranexamic acid, azelaic acid, glycolic acid, laser, broad spectrum sunscreen and sun avoidance. Though it is effective treatment, adverse effects have also been identified. In recent times, Platelet Rich Plasma (PRP) is fetching attention in aesthetic medicine. Interestedly, this study aimed to assess the effectiveness of PRP injection intradermally. It demonstrated that PRP injection resulted in the reduced hyper pigmented lesions in melasma with fewer side effects. Hence, PRP could be a promising treatment and hope for new safe and effective treatment options.

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Introduction

Hyper pigmentation disorders corresponding intracellular signaling cascades that lead to the stimulation of melanogenesis it include Ultraviolet B (UVB) hyper pigmentation and melasma [1]. Use of anti-pigmenting agents developed so far can inhibit melanogenesis partially. However, topical agents used for hyper pigmented skin area are potent anti-melanogenic agents capable of suppressing constitutive pigmentation and this may lead to hypo pigmentation in surrounding areas [2]. From this viewpoint, controlling the activation of melanogenesis would be an appropriate approach to develop new potent anti-pigmenting agents without the risk of hypo pigmentation. With this approach, we have been looking for unique growth factors that have the potential to resolute hyper pigmentation.

Platelet-Rich Plasma (PRP), platelet-rich concentrate, autologous platelet gel or platelet releasate all refer to one concept which is an autologous concentration of human platelets contained in a small volume of plasma. It is known for a long time that fibrin clot and platelets have haemostatic and tissue repairing effect [3,4]. In 1975, an article was published with the concept of platelet gel under the title of 'use of platelet-fibrinogen-thrombin mixture as a corneal adhesive. An exciting report was published in 1979 about the usage of gel foam in suture less nerve anastomosis. After a few years an animal model showed that platelets and fibrin initiate a process consist of cell migration, collagen synthesis, fibroplasia and angiogenesis which helps the lesion healing. The real application of platelet releasate in treating wounds has begun in the mid-1980s after publication of Kingthon in 1986. In 1997 another important reports was published about the maxillofacial surgery and platelet gels. The usages of platelet gel became more popular in late 1990s, after the publication (1998) of a paper about the effectiveness of the Platelet-Rich Plasma (PRP) in bone regeneration in the field of dental care. There are several growth factors in α-granules of platelets, secreted after the activation of platelets by aggregation initiators. These factors including Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor (TGF), Vascular Endothelial Growth Factor (VEGF) and Insulin-like Growth Factor (IGF) regulate cell migration and attachment (Figure 1) [5].

Some studies indicate that platelets have anti-inflammatory and analgesic effects and secrete antimicrobial peptides, thus have antibiotic effects [6,7]. More than 800 proteins are secreted in

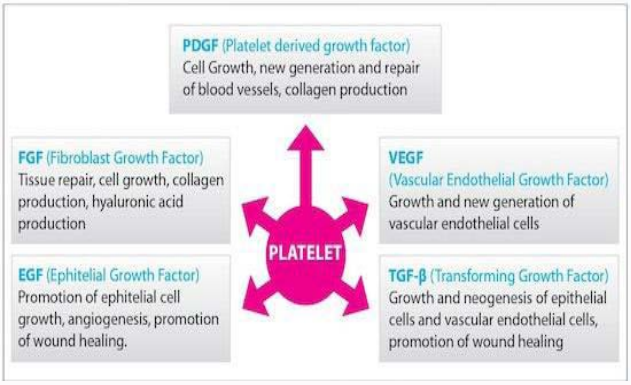

Figure 1: A variety of growth factor released from PRP.

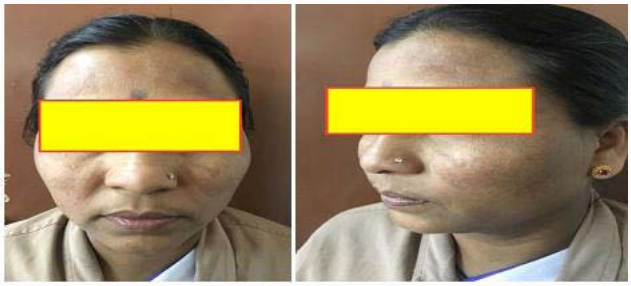

Figure 2: Melasma (acquired hypermelanosis).

this matrix affect on various cell types: osteoblasts chondrocytes fibroblasts, endothelial cells, mesenchymal stem cells from different origins, myocytes and tendon cells which lead to a wide range of surgical and clinical procedures and treatments which help the platelet concentrated products [8]. Nowadays, there are publications about the use of PRP in chronic wound treatment, soft tissue injuries, periodontal and oral surgery, maxillofacial surgery, orthopedic and trauma surgery, spinal surgery, heart bypass surgery, burns, cosmetic and plastic surgery, gastrointestinal surgeries. We want to summarize the use of PRP in dermatology especially in skin hyper pigmentation.

Disorders of Hyper Pigmentation

Melasma

Melasma is a common acquired hypermelanosis that occurs exclusively on sun-exposed areas, mostly on the face and occasionally on the neck and forearms (Figure 2). Melasma is a dermatological disease easily diagnosed by clinical examination, typically chronic with frequent recurrences with many unknown physiopathological aspects [9-11].

Epidemiology and etiology

Melasma is more common in women. Men have been reported to represent 10% of cases. Melasma is more apparent during and after periods of sun exposure. The exact cause of melasma remains elusive, but the one most important factor implicated in its etiopathogenesis is sunlight. Other factors in criminated in the pathogenesis of melasma include pregnancy and exogenous hormones (i.e. oral contraceptives and hormone replacement therapy), thyroid dysfunction, cosmetics, phototoxic and antiseizure drugs [12-15].

Clinical Features and Classification

The number of hyper pigmented patches may range from one

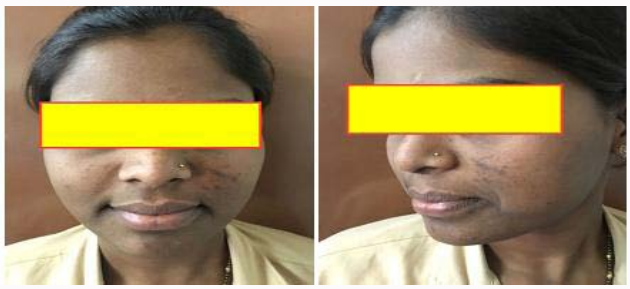

Figure 3: Erythema DyschromicumPerstans (EDP) or ashy dermatosis.

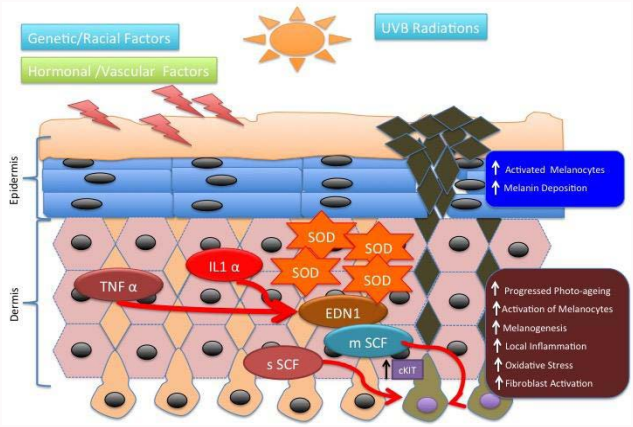

Figure 4: Mechanism of Hyperpigmentation.

single lesion to multiple patches located usually symmetrically on the face and occasionally cheeks and both sides of nose. The lesions have serrated, irregular, and geographic borders. According to the distribution of lesions, the following three clinical patterns of melasma are recognized [16-19].

- The centrofacial pattern: This is the most common pattern. It involves the forehead, cheeks, upper lip, nose and chin.
- The malar pattern: This involves the cheeks and nose.
- The mandibular pattern: This involves the ramus of the mandible.

Melasma can be classified into four histologic types [20,21].

- Epidermal type: The pigmentation is intensified under Wood's light examination. It is the most common type of melasma. Melanin is increased in all epidermal layers. Only a few scattered melanophages can be observed in the papillary dermis.
- Dermal type: The pigmentation is not increased under Wood light examination. Many melanophages are throughout the entire dermis.
- Mixed type: Under Wood's light examination, the pigmentation becomes more apparent only in some areas, whereas in others there is no change. Melanin is increased in the epidermis, and there are many dermal melanophages.
- Indeterminate type: Wood's light examination is of no benefit in individuals with skin type VI.

Erythema Dyschromicum Perstans

Erythema Dyschromicum Perstans (EDP) or ashy dermatosis

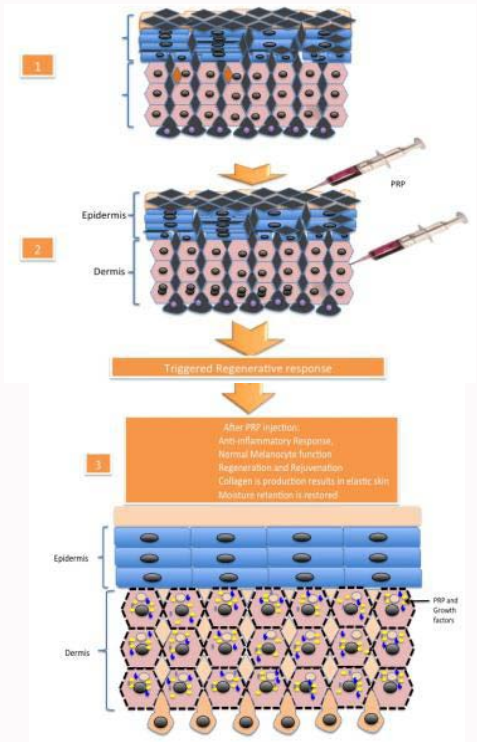

Figure 5: PRP treatment for Hyperpigmentation.

is an idiopathic, acquired, and chronic skin disorder characterized by hyper pigmented patches on the trunk, face, and extremities. Epidemiology and etiology most adult patients with EPD are of Hispanic origin but white adult patients have also been reported [22]. As far as children are concerned, there are more reports with white children than with Hispanic children. There appears to beno sexual predilection for EDP. The cause of EDP remains unknown. There is considerable evidence that an immunologic mechanism is involved in the pathogenesis of the disease. A variety of possible causative agents have been reported including ingestion of ammonium nitrate, orally administered X-ray contrast media, exposure to chlorothalonil, chronic hepatitis C infection, and exposure to environmental contaminants [23].

Clinical features

EDP is characterized by oval or round-shaped blue-gray patches over the face, trunk, and extremities. Early lesions may have a raised, erythematous border that disappears later, and usually it is not evident upon initial consultation. The lesions are occasionally pruritic, and their diameter may vary from a few millimeters to several centimeters. The trunk and proximal extremities are more usually affected, followed by the face and neck [24]. There seems to be no predilection for exposed or unexposed areas (Figure 3).

Histopathology

The histologic features of EDP are relatively non specific. The inflammatory border of the lesions may show vacuolization of the basal cell layer and occasional colloid bodies. There is also mononuclear infiltrate of the mid and upper dermis and pigment incontinence with many melanophages. In the inactive lesions, the incontinence of pigment prevails, whereas the vacuolization of the basal cell layer and the cellular infiltrate show different degrees of intensity [25].

Treatment and prognosis

Sun protection is of pivotal importance in the treatment of melasma. Without strict adherence, any treatment regimen will fail. Recurrence during the summer is very common in patients with melasma. The treatment of melasma includes topical formulations, chemical peels, lasers, and light sources. Combinations of treatments are often used to maximize results in difficult cases [26]. Topical treatment with combination of hydroquinone, tretinoin, and a steroid appears to be the most effective initial therapy. Glycolic acid peels may be a useful adjunct to topical treatment, especially after a patient's pre-treatment with hydroquinone for 2 weeks to minimize the risk for post procedure hyper pigmentation. Fractional laser therapy is the only laser treatment for melasma and it could be used as a third-line treatment in severe cases who have not responded toother treatments and who are willing to accept the risk for post procedure hyper pigmentation. There is no consistently effective therapy for EDP. In children, a high rate of spontaneous remission has been observed. Dapsone, Clofazimine, and narrow-band UVB phototherapy have been used with good results in small series [27].

Mechanism of Hyper Pigmentation

Depletion of the ozone layer results in greater potential exposure to UV-B Radiation (UVR). Single exposure to UVR results in increase in the size of melanocytes followed by an increase in tyrosinase activity. Repeated exposures to UVR lead to an increase in the number melanosomes transferred to keratinocytes, as well as an increase in the number of active melanocytes [28]. In melasma, the secretion of soluble SCF (sSCF) by dermal fibroblasts is up-regulated in the lesional dermis, probably due at least in part to the photo aging process. This leads to the penetration of sSCF into the epidermis through the basement membrane and then to the activation of epidermal melanocytes via the SCF signaling cascade, resulting in the stimulation of epidermal pigmentation. Based on the evidence that EDN1 and SCF are only the intrinsic melanogenic cytokines in hyper pigmentary disorders, it is strongly anticipated that substances able to interrupt the EDN1- or SCF-specific intracellular signaling pathways but do not directly inhibit tyrosinase activity, would be effective new anti-pigmenting agents. They would have the advantage that they do not affect normally pigmented skin where the intracellular signaling cascade is not activated, but would have distinct inhibitory effects on hyper pigmented areas of the skin with UVB-melanosis, solar lentigo and melasma (Figure 4). For such anti-pigmenting agents, there seems to be a low risk of eliciting hypo pigmentation because they have no direct inhibitory effect on tyrosinase activity and because there is no activated intracellular signaling cascade in normally pigmented skin [29,30].

PRP Treatment

Platelet-Rich Plasma (PRP) treatment is performed via the autologous injection of high concentration of platelets in a small volume of plasma. Platelet-rich plasma was obtained by spin method, followed by the collection of 10 ml of autologous whole-blood into tubes containing trisodium citrate as anticoagulant [31]. The collected blood was first centrifuged at 150 g to 200 g for 10 minutes at room temperature to separate the red blood cells at the bottom of the tube, the buffy coat (containing the white blood cells) in the middle and the plasma above (soft spin). Then, the upper plasma was pipetted above the buffy coat to undergo another centrifugation at 1500 g to 2000 g for 15 minutes (hard spin) to obtain a platelet pellet in the bottom of the tube (with a platelet count 4-4.5 times higher

than that of baseline), and a Platelet-Poor Plasma (PPP) in the upper part [32]. The PPP is partly removed and partly used to resuspend the platelets to finally produce 2 ml of PRP. Platelet-rich plasma was activated by adding 10% calcium chloride 0.1 ml per 0.9 ml plasma. Local anesthetic cream (eutectic mixture of lidocaine and prilocaine) was applied to the face for approximately 45 min to 60 min before the procedure. After sterilization of the face with alcohol, 0.1 to 0.3 ml PRP was injected intradermally into the atrophic scars using insulin syringe with a total of 1 ml PRP in each side of the face (Figure 5). Gentle massaging was performed after the procedure, followed by topical antibiotic for 3 days after treatment, but application of sunscreen was not required.

Discussion

Because of the prevalence of acne scarring and the strong negative emotions it causes in affected patients, dermatologists are frequently presented with the challenge of evaluating and providing treatment recommendations to patients with acne scars. The efficacy and the safety of PRP in the treatment of atrophic acne scars and hyper pigmentation is a today's cardinal treatment. To the best of our knowledge, we evaluated the efficacy and safety of PRP intradermal injection alone in the treatment of atrophic acne scars. Platelet-rich plasma is an autologous preparation of platelets in concentrated plasma. It has recently attracted much attention in various medical fields, including orthopaedic, plastic, and dental surgeries and dermatology for its wound-healing ability. Platelets release various cytokines and growth factors that promote angiogenesis, tissue remodeling, and wound healing. Platelet-rich plasma works by the degranulation of granules in platelets, which contain the synthesized and prepackaged growth factors. Many growth factors have short half-lives, therefore greatest effectiveness may result if they are activated at or just before injection. Fibroblasts accumulate at the site of injection and start to lay down collagen.

Activated platelets release several growth factors, cytokines, and chemokines, including vascular endothelial growth factor, platelet-derived growth factor, epidermal growth factor, fibroblast growth factor, transforming growth factor-b, insulin-like growth factor, IL-8, macrophage inflammatory protein-1a, and platelet factor- 4.9. Platelet-rich plasma separation involves centrifugation of the whole-blood by single-spin or double-spin method. The single-spin method separates the whole blood into 3 basic components: red blood cells (bottom of the tube), PRP (middle of the tube), and PPP (top of the tube). PRP with a single spin would not produce a true PRP. Instead, it would produce a mixture of PRP and PPP with low platelet counts. Regardless of the rate of centrifugation or the time of centrifugation, a single spin cannot adequately concentrate platelets because the red blood cells will interfere with the fine separation of the platelets. The device must use a double centrifugation technique. The first spin will separate the red blood cells from the plasma, which contains the platelets and the second spin will finely separate the platelets from the PPP. The second centrifugation produces a platelet pellet that can be easily resuspended with maximum platelet concentration and the least platelet loss in the above PPP. The produced PRP contains almost no blood-derived cell types other than platelets.

Leukocytes are absent in PRP prepared by this method as they should be avoided in PRP preparations because of their potential pro-inflammatory effect. PRP intradermal injections alone in the treatment of different types of acne scars were applied. Promising results have been achieved using this PRP method as compared with traditional methods.

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