REVIEW ARTICLE

Platelet-Rich Plasma in Dermatology

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In the last few years, the field of regenerative medicine has given a lot of attention to the use of platelet-rich plasma (PRP). In 1970, Matras for the first time used fibrin glues to improve skin wound healing in a rat model. (1) Later the work of Whitman in 1997 and Marx et al. in 1998 popularized the concept of platelet growth factors (GF) in oral and maxillofacial surgery for regenerative medicine. (2,3) Recently, PRP has been used with variable success for the treatment in specialties of dermatology, plastic surgery and aesthetics, ear-nose-throat surgery, orthopedics and sports medicine, gynecology and ophthalmology. (4)

Meaning of PRP

PRP has been defined as the portion of the plasma fraction of blood, having a platelet concentration above the baseline value. In a healthy individual normal platelet count in whole blood is between 1.5-4.5 × 105/μL (5). For the limited research data, platelet count in PRP has not been yet optimized, but for therapeutic effectiveness, platelet count of 4-5 times above the baseline should be present in the concentrate (6).

This is a novel research and therapeutic modality that contains abundant autologous growth factors and proteins, which on activation are involved in different phases of the tissue healing like collagen synthesis, tissue granulation and angiogenesis. This promotes the rate and quality of tissue restoration and remodelling (6). Hence, PRP has emerged as an impotent therapeutic armamentarium in the field of dermatology and aesthetics.

Mechanism of action

Platelets are anucleated cytoplasmic fragments that contain different varieties of granules. The membrane bound α-granules are an important intracellular storage pool of growth factors including platelet-derived growth factor (PDGF), transforming growth factor (TGF-β) and insulin-like growth factor (IGF-I) that are vital to wound healing (5,7). On activation, thesea α-granules fuse with the platelet cell membrane and activate secretory proteins to a bio-active state. These secreted proteins then binds to their transmembrane receptors on the target cells like epidermal cells, mesenchymal stem cells, fibroblasts inducing an internal signal transduction pathway, thereby increasing expression of various gene sequences in cells like cell proliferation, collagen synthesis, antiapoptosis etc. (7, 8) Growth factors present in PRP are summarised in *Table 1*.

Preparation of PRP

After the proper consent & with all aseptic precautions, venous blood is withdrawn in a tube containing an anticoagulant citrate dextrose solution formula A or sodium citrate. This is followed by soft spin centrifugation to separate platelet-rich plasma from whole blood and then via heavy-spin centrifugation, platelets are concentrated by with removal of the supernatant plasma .(9) The PRP so obtained contains leukocytes and is called Leukocyte & Platelet Rich Plasma (L-PRP) and when it passes through a leukocyte filter we obtain Pure Platelet Rich Plasma (P-PRP). (10) PRP can be used either in nonactivated form or as activated PRP. Calcium chloride leads to the activation of the PRP while nonactivated form gets activated after coming in contact with collagen of the tissues. (11) Further, it has been demonstrated that concentration of platelets lower or higher concentrations than 1.5 million platelets/μL, inhibits the angiogenic potential in human endothelial cells thus, indicating its dose dependant nature. The yield of platelets itself is determined by temperature, size and shape of the container, rate and time of spin and type of anticoagulant used. (12,13) Recently many commercially available automated devices with varying standards have been developed to obtain various platelet concentrates but still they lack reproducibility.

Time Period or Viability

Irrespective of the method of activation the release of

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Table 1. Growth Factors Contained in Platelet Rich Plasma

Growth Factor	Function
Transforming GF β (TGF β)	Proliferation of undifferentiated mesenchymal cells; inhibition of lymphocyte and macrophage proliferation; Regulate: Endothelial, fibroblastic and osteoblastic mitogenesis; Collagen synthesis and secretion of collagenases; Mitogenous effect on other GF; Endothelial chemotaxis and angiogenesis.
Basic fibroblast GF (FGFb)	Stimulates mitogenesis, growth & differentiation of mesenchymal cell mitogenesis
Platelet derived GF (PDGF)	Stimulates mitogenesis of mesenchymal cells; mitogenesis & chemotaxis of fibroblastic, glial, smooth muscle linage cells; regulates collagenase secretion and stimulates epithelial mesenchymal mitogenesis
Vascular endothelial GF (VEGF)	Increases angiogenesis, vascular permeability & endothelial cell mitogenesis
Connective tissue GF (CTGF)	Promotes angiogenesis, chondral regeneration, fibrosis & platelet adhesion
Epidermal GF (EGF)	Stimulates endothelial chemotaxis & angiogenesis; regulates secretion of collagenases; stimulates mitogenesis of mesenchymal & epithelial cells

packed GFs starts within 10 minutes of clot initiation and more than 95 percent of secretion is completed within one hour. So, PRP must be applied within 10 minutes of activation. Tryptan blue staining confirms the viability of platelet concentrate in PRP. (5)

Safety of PRP

PRP is an autologous preparation, so is safe and tolerant on infiltration. It rarely produces mild local inflammatory reactions or postpuncture infection. It is free from risk of transmission of infections like Hepatitis B, Hepatitis C or HIV. It lacks action on nucleus, so is devoid of any mutagenic effects. (5,6)

Dermatological Indications: Major uses of PRP in the field of Dermatology and Aesthetics are:

Androgenetic Alopecia (AGA)

Androgenetic alopecia (AGA) is the most common form of hair loss but current treatment options are limited and moderately effective. Efforts are on to understand cellular pathways and molecular mechanisms involved in the pathophysiology of alopecia, so as to target potential treatment that not only stimulates hair growth, but induces formation of new hair follicles. (14)

EGF & FGF activates the proliferation & causes transdifferentiation of hair stem cells & produce new follicular units. (15) bFGF & beta-catenin, promotes the anagen phase of papilla cells & thereby plays a key role in elongating hair shaft. (16) The antiapoptotic regulators, Bcl-2 protein & Akt signaling, that are activated by these GFs, prolongs the survival of dermal papilla cells during the hair cycle. (17) Thus, the mitogenic & antiapoptotic effects, of PRP prolong survival of dermal papillae. PRP modulates angiogenesis and enhance blood flow around hair follicles, thus improving cutaneous ischemic conditions.

The use of PRP mesotherapy either alone or as an adjunct to surgical procedures in the patients of androgenic alopecia thus holds promising results. (18) PRP can be injected as inter-follicular injection as 0.1 ml/cm^2, in a retrograde fashion from deep to superficial, at every centimeter, throughout the treated site while in mesotherapy the microneedle roller of 1-mm fine needles is rolled over scalp followed by interfollicular injection of PRP over the treated area.

It is also used as an adjunct to hair transplantation to increase the survival rate after implantation. The pretreatment of follicular units with PRP before transplantation has resulted in improved hair growth and density. The hair follicle is dipped into PRP for 15 minutes, before implantation and after transplant PRP is injected into both the donor and recipient area of scalp to minimize bleeding, stimulate wound healing & to reduce scarring . (19) Though, PRP is a promising newer technique in a dermatosurgeon's armamentarium but it is yet to show consistency in results.

Skin Rejuvenation

Skin ageing is an unpreventable, irreversible process that is influenced by both intrinsic and extrinsic factors. The intrinsic factors like the reactive oxygen species along with matrix metalloproteinases (MMP) reflect different physiological and pathological processes involved in skin

ageing. There is accumulation of fragmented collagen fibrils that prevents neocollagenesis and causes further degradation of the extracellular matrix (ECM). Conventional anti-aging strategies, including lasers and topical treatments, increases ECM synthesis through the activation of fibroblasts. (20)

Different GFs including PDGF, TGF, VEGF and IGF present in PRP stimulates human dermal fibroblasts (HDF). There is an overall increase in collagen type-1levels after PRP with increase in expression of MMP-1 & MMP-3 protein. MMP-1 induction in photo aged skin leads to removal of damaged collagen fragments, thus facilitating deposition of new collagen. (21) Topical application of PRP or its direct injection into the skin produces ECM remodelling and induces the synthesis of new collagen by fibroblasts. More recently microneedles and lasers have been tried for increasing skin remodelling by inducing mild inflammatory reactions. However, results of PRP are better on the face and neck revitalization . (22,23)

Scars and Contour Defects

The presence of facial scars has both cosmetic as well as psychological effects. Techniques like dermabrasion, chemical peeling, lasers, fat grafting and fillers have been tried but with limited success. PRP effectiveness in wound healing has prompted its use in the treatment of depressed facial scars, along with the available treatment modalities. The use of fractional laser or light-emitting diode (LED) phototherapy along with PRP has led to substantial improvement with good cosmetic results and skin rejuvenation. (22, 24) Platelet-rich fibrin (PRF), the second generation of platelet concentrate has been used with success as filler to correct deep nasolabial folds. (25) PRP also has an adjuvant role in autologous fat transfer procedures as it has booster effect on fat grafts, along with its rejuvenation capacity per se. Growth factors present in PRP promotes recovery of laser-damaged skin & accelerates tissue remodelling with the increased synthesis of collagen. (26,27) So, PRP holds a promising role in soft tissue augmentation.

Acute and Chronic Ulcers

The treatment of diabetic foot ulcer is very challenging. Success of recombinant PDGF– ββ (becaplermin) gel in the treatment of diabetic ulcers has prompted use of PRP in these ulcers. (28) PRP is used either as topical spray or as perilesional injections. Platelet-rich fibrin matrix (PRFM), a viscous fibrin meshwork rich in GFs, resulted in faster healing and augments reepithelization. (29,30) The use of PRP thus, results in faster healing in diabetic foot ulcers. However, because of the limited available data, there is no clear evidence to recommend its role for treating chronic wounds.

Striae Distensae

Striae distensae (striae alba) is a challenging cosmetic problem for which present treatment modalities have limited results. Kim *et al*. injected PRP along with higher energy fluencies using radiofrequency (RF) device directly to the dermis. The thermal energy generated by bipolar RF, denatures the elastic fibers and collagen bundles while PRP stimulates wound healing, thus providing synergistic benefits and good cosmetic results. (31,32)

Other Dermatological Conditions

Alopecia areata is a common autoimmune condition, causing inflammatory hair loss with limited treatment possibilities. PRP has been found to benefit in hair growth in alopecia areata. (33) Since, these patients invariably show spontaneous remissions it requires planned studies to correlate regrowth of hair to PRP.

Isolated case reports highlight the unexplored but promising role of PRP in treatment refractory conditions of the skin like refractory lipodermato-sclerosis and lichen sclerosus of vulva. (34, 35)

Conclusion

For the limited clinical trials of proven effectiveness and concerns about its long term efficacy and safety data, caution is advised for the use of PRP. Still, because of its therapeutic usefulness and autologous nature with limited side effects profile PRP holds a promising future as treatment modality in the field of dermatology and aesthetics. The low evidence of the research data requires that good quality clinical trials be conducted to produce guidelines from collection to activation of PRP, so that appropriate dose & dosage forms can be established for effective patient management and safety.

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