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Platelet-rich plasma in dermatology: Boon or a bane?

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Abstract

There has been a recent spurt in application of platelet-rich plasma (PRP) in dermatology and aesthetic medicine. However, the details regarding use of PRP in various dermatological indications ranging from hair restoration to chronic ulcers are dispersed in literature, herein we have tried to focus all under one heading. Overall, PRP seems to be a promising therapeutic modality but the level of evidence as of now, from the available published data is low. This review will also stimulate readers to carry out well designed, larger population based trials, so as to validate its use in dermatology practice.

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Full Text

Introduction

Platelet-rich plasma (PRP) (syn. autologous platelet gel, plasma-rich growth factors and platelet-concentrated plasma) means "abundant platelets that are concentrated into a small volume of plasma." [1] The pivotal discovery of platelet-derived growth factor (PDGF) in promoting wound healing, angiogenesis and tissue remodelling threw light on this novel autologous therapeutic modality. The documented success of PRP in dentistry and surgery as shown by Marx and co-workers, [1] have fuelled research on its role in other specialities like dermatology and aesthetics. [2] Takakura et al., [3] revealed that PDGF signals in cell interactions are required for hair canal formation and growth of dermal mesenchyme, thereby opening newer perspectives for PRP in hair restoration. [3] Data regarding application of PRP in dermatology and aesthetics is dispersed in literature, hence in this write-up we have tried to focus all under one heading, which will provide the reader a comprehensive information regarding PRP.

What is PRP?

PRP is an effective concentration of multiple fundamental growth factors (GFs) by virtue of platelets alone (stored as α -granules in platelets) as enumerated in [Table 1] and plasma proteins, namely fibrin, fibronectin and vitronectin. This cocktail of GFs is pivotal in modulation of tissue repair and regeneration, [4] whereas the plasma proteins act as a scaffold for the bone, connective tissue and epithelial migration. {Table 1}

Degranulation of the pre-packaged GFs in platelets occurs upon "activation" i.e., on coming in contact with coagulation triggers. The secreted GFs in turn bind to their respective transmembrane receptors expressed over adult mesenchymal stem cells, osteoblasts, fibroblasts, endothelial cells, and epidermal cells. [5] This further induces an internal signal-transduction pathway, unlocking the expression of a normal gene sequence of a cell like cellular proliferation, matrix formation, osteoid production, collagen synthesis, etc., thereby augmenting the natural wound-healing process. [6]

Preparation of 'Activated PRP'

PRP is prepared either manually or by the use of automated devices, in a day care setting just prior to the procedure. The process must be carried out under strict aseptic conditions as well as optimum temperature regulations i.e., 20-22°C. In order to inhibit platelet aggregation, it is prepared with an anticoagulant, commonly using anticoagulant citrate dextrose solution formula A (ACD-A) or sodium citrate. The platelets need to be sequestered in high concentrations, enough for achieving therapeutic benefit and in a viable state at the same time, so that they can actively secrete their GFs.

Manual double spin method

The American Association of Blood Banks technical manual, [7] states that "platelet-rich plasma is separated from whole blood by 'light-spin' centrifugation and subsequently the platelets are concentrated by 'heavy-spin' centrifugation with removal of the supernatant plasma." The basic principle behind the PRP separation procedure is as follows.

The centrifugation process separates blood components owing to their different specific gravities, i.e., RBCs being the heaviest, followed by WBCs, whereas platelets are the lightest. The first centrifugation is slow to avoid spinning down platelets and to isolate plasma. Platelets are mostly concentrated right on top of the buffy coat layer. Subsequent centrifugation is faster, so that platelets are spun down and separate as a pellet at the bottom of the tube from platelet-poor plasma (PPP) above. The final platelet concentration depends on the volume reduction of PPP. Approximately 3/4 of the supernatant is discarded and the platelet-rich pellet is resuspended in remaining amount of plasma. The resulting suspension is used as PRP. Calcium chloride (CaCl_2) or thrombin can be used as an "activator" to trigger coagulation and hence degranulation of GFs to yield "activated PRP". The procedure has been illustrated in a simplified flowchart in [Figure 1]. {Figure 1}

The platelet yield depends mainly on conditional parameters like size and shape of the container used, rate and time of spin and anticoagulant used. There has been a gross lack of comparative studies to standardize the PRP procedural parameters. However, in our institution, we have adopted the centrifugation parameters used by Gonshor et al, [8] (as also mentioned in [Figure 1]) to obtain a desired platelet concentration of four to seven times that of whole blood. The viability of the platelets is assured by carrying out the process in a refrigerated centrifuge at 20°C. Trypan blue staining can confirm the viable state of the platelet concentrate obtained by the above method, as shown in [Figure 2]. {Figure 2}

The double spin method is preferred over the earlier prevalent single spin method, [9] as the therapeutic concentration of platelets was not achieved by the latter. [1] The active secretion of prepackaged GFs begins

within 10 minutes of clot initiation and 95% of the secretion is completed within 1 hour. [10] Hence, PRP must be used on the treated site within 10 minutes of activation. The concentrated platelets remain viable for up to 8 hours and sterile if placed on a sterile surgical table. [6]

Automated devices

Numerous commercial devices of varying standards are now available for the preparation of PRP, but their application has been confusing because each technique leads to a different product with potentially dissimilar biology and unknown relative efficacy. In the section below, various devices and kits have been classified according to the product formed. Although time saving, these adapted kits can be quite expensive as compared to the manual process. Also, commercial interests tend to obscure the true clinical benefits of various platelet concentrates. Easy reproducibility of the product is also not consistent with the devices/kits. However, a prudent clinician needs to ensure the viability, concentration and activation of platelets obtained by the device used. Various devices have been approved by US Food and Drug Association (FDA) e.g., Smart PReP® (Harvest Technologies Inc, Plymouth, MA), PCCS® (3i Implant Innovations Inc, West Palm Beach, FL), BioMet GPSII® etc.

'All PRP's are not the Same': Classification of Platelet Concentrates

The development of a wide range of preparation protocols, devices and centrifuges for varying indications have led to a number of different platelet concentrates, unfortunately all under the same name as PRP. Ehrenfest et al., [11] have proposed a classification of platelet concentrates into four categories depending upon their leucocyte and fibrin content as follows.

P-PRP (Pure platelet-rich plasma)

The P-PRP concentrate consists of an undetermined fraction of buffy coat, containing a large number of platelets, but most leucocytes are not collected. After the first slow spin centrifugation, only the superficial buffy coat layer is pipetted out and prepared for next centrifugation, as shown in [Figure 1]. E.g., Anitua's Plasma rich in growth factors (PRGF).

L-PRP (Leucocyte- and platelet-rich plasma)

L-PRP consists of most of the platelets, along with leucocytes and some residual RBCs, suspended in fibrin-rich plasma. It differs from P-PRP only on the means of buffy coat layer collection in which PPP along with the entire buffy coat layer and superficial 1-2 mm layer of RBCs are pipetted out [Figure 1]. E.g., Plateltex (Bratislava, Slovakia) and RegenACR® kit (Regen Laboratory, Mollens, Switzerland). These protocols employ gelifying agents or a separator gel within the centrifugation kit to enhance the complete collection of the buffy coat layer. Automated systems for L-PRP are PCCS and SmartPReP.

The manual PRP preparation process (as described above) is not clearly defined, it might randomly lead to P-PRP or L-PRP.

P-PRF (Pure platelet-rich fibrin)

The term PRF is used synonymously with platelet-rich fibrin matrix (PRFM). When P-PRP is mixed with activator and allowed to incubate for some time, a stable PRFM clot can be collected which has useful applications as described below. Very low amounts of leucocytes are collected owing to a specific separator gel used in the device. E.g., Fibrinet PRFM kit (Cascade Medical, NJ, USA).

L-PRF (Leucocyte- and platelet-rich fibrin)

Here, blood is collected without any anticoagulant and immediately centrifuged. A natural coagulation process then occurs and three layers are formed: the RBC base layer, acellular plasma top layer and L-PRF clot in the middle, which harvests platelet and leucocyte growth factors into the fibrin matrix. There is no biochemical modification of the blood, i.e. no anticoagulants, thrombin or CaCl₂ are required. When pressed between two gauzes, the PRF clot becomes a strong membrane which also has potential applications. E.g., Choukroun's PRF.

Concentration of PRP

The mean blood platelet level is $200,000 \pm 75,000/\mu\text{L}$. Although the PRP platelet count has not been optimized, a platelet concentration of more than 1 million/ μL (approximately four to seven times the mean levels) is generally regarded as the therapeutically effective concentration of PRP. [1],[12],[13] Further, a bell-shaped response curve indicating a dose dependant nature has been shown to be associated with PRP. [14] Giusti et al., [15] demonstrated that lower or higher concentrations than 1.5 million platelets/ μL , seemed to inhibit the angiogenic potential in human endothelial cells. In vitro studies on dermal papilla cells have also supported PRP at concentrations of five to ten times the mean levels. [12] All the FDA-cleared PRP separator devices have been shown to achieve this therapeutic concentration of PRP.

Dermatological Indications

Data analysed from peer-reviewed journals demonstrates a wide range of dermatological indications ranging from hair restoration to acne scarring as enumerated in [Table 2].{Table 2}

Androgenetic alopecia (AGA)

AGA is associated with a significant amount of psychosocial distress both in men and women. Much research has been done to expand the available therapeutic armamentarium. Hair transplantation has proven to be a boon for patients consenting for surgical procedures. Minoxidil and finasteride have an established efficacy in AGA, also as an adjuvant to hair transplantation. The angiogenic role of PRP has recently caught the attention of dermatologists and plastic surgeons, to explore its usefulness as a hair growth modality.

Mechanism of action of PRP in AGA

Activated PRP stimulates proliferation and differentiation of stem cells in the hair follicle bulge area via multiple molecular mechanisms, [12] as mentioned in [Table 3].{Table 3}

Procedure

A proper informed consent, aseptic conditions and local anesthesia are important pre-requisites for the procedure. Patient must be free of anti-platelet drugs like aspirin or other non-steroidal anti-inflammatory drugs, for at least two weeks prior to the procedure. It has been used in a number of ways, based on personal preferences, both as an independent therapeutic modality or as an adjunct to hair transplantation to increase the survival of implanted grafts.

Various modes of PRP therapy for AGA are as follows:

Inter-follicular injection of PRP at the amount of 0.05-0.1 ml/cm², in a retrograde fashion from deep to superficial, at every centimetre, throughout the treated site. PRP mesotherapy: Scalp is punctured with microneedle roller of 1-mm fine needles followed by interfollicular injections of PRP (or by using mesogun) over the treated area and later, PRP is also sprayed on top of the scalp and left on overnight. It is usually done in 3 monthly sessions. PRP can be used as an adjunct to hair transplantation: The follicular grafts are dipped

into PRP for about 15 minutes, before implantation so as to increase their survival rate after implantation. PRP is injected into the recipient area of scalp prior to or just after implantation of grafts. PRP is injected at and around the donor strip excision line, in follicular unit transplantation (FUT), to minimize bleeding, stimulate wound healing and reduce scarring.

Evidence to support its use

There is presently limited published data for this most widely used application of PRP in dermatology as summarized in [Table 4]. Most of the studies are open label with low to intermediate quality of evidence. In 2006, Uebel et al., [16] were among the first to use PRP along with hair transplantation. They demonstrated an increase in the follicular density (range = 3-52%) after 7 months of FUT, by keeping follicular grafts in PRP for 15 minutes before implantation, with saline as the control. The increased survival of 2.4 follicular units per cm² implanted on the experimental side, can be extrapolated as 240 units (or 480 follicles, assuming two follicles per unit) over a bald area of 100cm² (10 × 10 cm). This methodology can be advantageous especially in those patients with very thin and sparse hair in the donor area, so as to ensure the highest survival yield in implanted grafts. However, this trial was non-blinded and evaluation was done by manual counting of hair grafts (digital imaging was done in only 1 patient).{Table 4}

PRP as an incubation medium in FUT was also analyzed in a recent double-blind randomized controlled trial (RCT) on 100 AGA patients. [17] The investigators found reduction in diffuse hair loss and stimulated hair growth, without any untoward effects for a follow-up period of 18 months. In vitro evaluation also revealed that PRP could prevent dermal papilla apoptosis and prolong anagen phase of hair cycle.

The molecular pathways involved in the mitogenic effects of PRP have been well illustrated by Li et al., [12] as mentioned in [Table 3]. In support to their in vitro data, authors demonstrated significant hair regrowth in treated mice, which further paved the way for its clinical application.

Kang et al., [18] suggested that the CD34+ hematopoietic stem cells mobilized in peripheral blood and further concentrated in PRP prepared using Smart PRP®, could have synergistic effects on PRP-induced angiogenesis in patients with pattern hair loss. Their hypothesis was based on the previous evidence of angiogenic role of autologous CD34+ hematopoietic stem cells in ischemic conditions. [19]

PRP used as mesotherapy in AGA patients has also shown promising results. Open label studies by Greco et al. [20] and Lopez et al., [21] observed a significant increase in hair diameter and hair density respectively, with this minimally invasive technique. An isolated report suggests the role of PRP therapy in patients intolerant to available medical therapies. [22]

Modification of PRP

The ever increasing literature has also seen modifications of PRP to increase its therapeutic results. Takikawa et al., [23] investigated a low-molecular weight heparin, as a carrier for PRP. Dalteparin/protamine (DP), in water soluble microparticles, acts as a biomaterial to adsorb, stabilize and gradually release the GFs in PRP, as almost all of them are known to be heparin binding. Results showed that DP in PRP could further improve the hair thickness as compared to PRP alone without any side effects, although effect of DP alone was not assessed as control.

In view of the overall limited level of evidence of available literature, better designed, larger and long term trials are awaited. The question still remains, whether the clinical benefit achieved by PRP either as monotherapy or as an adjunct to surgical procedures, is worth the added resources and processing. Also, head to head comparative studies need to be performed between PRP and already established medical adjuvants. In view of relapse of pattern hair loss seen with early discontinuance of medical therapies, whether PRP can prove to be of any advantage is still a concern.

Other alopecias: Alopecia areata, telogen effluvium

There is a clear paucity of published data in support of this application in alopecia areata and telogen effluvium. Greco et al., [20] tried it in a single patient of alopecia areata as mesotherapy, with good subjective results at 10-months follow-up. Recently a randomized double blind, placebo and active controlled, half-head study evaluated PRP in 45 patients of alopecia areata. Monthly regimen for three sessions resulted in significant increase in hair regrowth and decrease in hair dystrophy and burning/itching sensation at 1-year follow-up, when compared with intralesional triamcinolone acetate or placebo. [24]

However, patients with alopecia areata and telogen effluvium, usually tend to have spontaneous remissions and respond well to commonly used medications, so it is difficult to attribute the regrowth of hair to PRP.

Skin rejuvenation

A fresh PRP has been an emerging area of interest in aesthetic medicine. PRP has been reported to augment dermal elasticity by stimulating the removal of photodamaged extracellular matrix (ECM) components and inducing the synthesis of new collagen by dermal fibroblasts via various molecular mechanisms, [25],[26] illustrated in [Table 5].{Table 5}

Procedure

Various methods have been tested for clinical use of PRP in skin rejuvenation, but a clearly defined method is unavailable.

Topical application under occlusion
Direct intradermal injections
As an adjuvant to lasers or microneedling. It is usually done once in every 4-6 months for 1 year and then yearly as maintenance therapy. [27]

Evidence to support its use

Monthly intradermal injections of PRP in 3 sessions have shown satisfactory results in face and neck rejuvenation and scar attenuation. [28] Shin et al., [29] showed that a combination of fractional non-ablative (erbium glass) laser therapy with topical application of PRP, resulted in objective improvement in skin elasticity, a lower erythema index and an increase in collagen density as well. Histological examination showed an increase in length of dermoepidermal junction, amount of collagen and fibroblasts in the treated skin.

PRP in combination with fractional ablative lasers (carbon dioxide) for deep wrinkles and severe photodamaged skin, has also been shown to reduce commonly encountered, transient adverse effects and decrease the downtime. [30] In a split face blinded trial, PRP injections given monthly for 3 months, have shown good results for infraorbital rejuvenation as well, without any obvious side effects. [31]

As varied number of products are available nowadays for skin rejuvenation like mesotherapy solutions, adipose derived stem cells etc., whether PRP can be used in combination with them to boost the aesthetic results, needs further clinical trials. Also, comparative studies are lacking to contrast PRP with other treatments like topical cosmeceutical preparations of growth factors, to be used after fractional laser resurfacing.

Scars and contour defects

PRP has become a promising modality among soft tissue augmentation techniques. PRFM has been used as a filler to correct deep nasolabial folds without any adverse effects. [32] As an adjuvant, it has been studied with autologous fat transfer procedures. An in vitro pilot study, revealed that fat grafts when mixed with PRP resulted in greater vascularity, fewer cysts and vacuoles, less fibrosis and overall improved survival and quality of fat grafts as compared to saline. [33] This novel regimen was found to maintain fat graft survival in a patient with facial contour defect for upto 2 years. [34] Data suggests that fat grafts can be admixed with PRP in treating traumatic scars, and further can be followed by fractional laser resurfacing to give best results. [35] PRP injections in combination with fractional carbon dioxide resurfacing have shown good results in acne scar

resurfacing also, apart from skin rejuvenation. [36]

Acute and chronic ulcers

The success of recombinant PDGF- $\beta\beta$ (becaplermin) gel in the treatment of diabetic neuropathic and other chronic wound ulcers, [37] has been translated into the potential use of PRP in the same. It can either be used as topical spray or as perilesional injections. PRFM, a viscous fibrin meshwork rich in GFs, has shown promising results when applied topically to the non-healing ulcers, to augment re-epithelialization.

Kim et al., [38] treated 16 patients affected by various acute and chronic ulcers including stasis ulcers, diabetic ulcers, livedoid vasculitis, claw foot and traumatic ulcers with PRP. Topical application of PRP significantly accelerated the re-epithelialisation process, shown to be through the upregulation of cell cycle regulatory proteins like cyclin A and CDK4. Even dermatomyositis associated elbow ulcers have been successfully treated with PRP. [39]

However, in view of a small number of randomized controlled trials, most of which being either at high or unclear risk of bias, a recent review concluded that there is no current evidence to recommend the role of PRP for treating chronic wounds. [40]

Striae distensae

The wound healing properties of PRP has also been applied in treating striae distensae Kim et al., [41]

treated 19 patients of striae, by employing an intradermal radiofrequency (RF) device, capable of delivering higher energy fluencies directly to the dermis, along with injecting PRP as a filler through its needle electrode. The thermal energy generated by bipolar RF, denatures the elastic fibres and collagen bundles and PRP stimulates wound healing, thereby providing synergistic benefits and good results. Transepidermal delivery of PRP using ultrasound has also been combined with fractional RF for treating striae with post inflammatory pigmentation as the only reported side effect. [42]

Lipodermatosclerosis

In an isolated case report, refractory lipodermato-sclerosis was treated with intralesional subcutaneous injections of PRP in five sessions (fortnightly) that led to complete re-epithelialization of venous ulcer and marked improvement in hyperpigmentation and induration at the treated site. [43]

Lichen sclerosus

Although the evidence is anecdotal, multilayer PRP injections used along with autologous fat transfer, deserves a special mention as a novel technique in the management of lichen sclerosus of vulva. [44]

SAFETY OF PRP

True PRP is definitely autologous. Homologous platelets such as lyophilised donor platelets have no place in this field as they are antigenic by virtue of the abundance of cell membranes. [6]

The mitogenic effects of PRP are only limited to augmentation of the normal healing process and is theoretically not mutagenic, as the GFs released do not enter the cell or its nucleus, but only bind to the membrane receptors and induce signal transduction mechanisms. [45]

Being an autologous preparation, PRP is devoid of any serious adverse effects, apart from local injection site reactions like pain or secondary infection, which can be avoided with proper precautions. PRP has no issues regarding transmission of infections such as hepatitis-B, C or HIV. However, safety concerns with bovine thrombin have been raised about the potential transmission of Cruetzfeld-Jacob disease (mad-cow disease).

These have been refuted by some stating that the prion vector has been found only in the neural tissues of cattle, whereas thrombin is solely isolated from the blood and is also further processed by heating. [6] Furthermore, reports of post-operative bleeding due to bovine thrombin-induced factor-V deficiency, [46] have made it an unpopular choice. On the other hand, use of CaCl₂ as an activator, automatically eliminates the above risks. Newer alternatives like human recombinant thrombin, thrombin receptor agonist peptide (TRAP), [47] autologous thrombin (prepared simultaneously with some of the available kits) or type-I collagen [48] have been explored.

Future Trends

The next generation of autologous PRP is the addition of ECM and independent studies conclude that GF-ECM complexes may well be the most effective method to stimulate cell proliferation as well as tissue healing or regeneration. This GF-ECM complex has demonstrated a synergistic effect in both human and equine wounds and has future scope in hair research techniques. [49]

The role of PRP in addressing infection concerns in healing injuries is being widely investigated and holds promise, as reports of antibacterial nature of PRP are pouring in the literature. [50] Its bacteriostatic properties have been attributed to the antimicrobial proteins secreted by the platelets. The inclusion of leucocytes in PRP as in L-PRP with a potential benefit to combat infection and regulate immune function, is a matter of present debate. [11],[50] Also, leucocytes produce large amounts of additional angiogenic factor VEGF, which is of crucial importance to the GF cocktail. [51] More studies are awaited to apply this novel concept to clinical practice.

Conclusions

The potential role of PRP in dermatology and aesthetic medicine is an exciting frontier that may eventually lead to superior therapies in the near future, however according to the evidence based medicine, the level of evidence from the available published data is low. There are no double blind, randomized, placebo controlled trials conducted on a large sample size to constitute a good quality of evidence. Hence, a healthy amount of caution should be exercised by the treating physician in its preparation and use during procedures. Further research is awaited to unfold its long term efficacy and safety.

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