

Systematic Review

Platelet-rich plasma in the treatment of alopecia

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ABSTRACT

Platelet rich plasma (PRP) is a promising treatment choice for patients with thinning hair. Despite excellent clinical safety and low cost, its clinical standing is still weak. The effectiveness of this method depends on its dosage, number of sessions, their intervals and technique of injection incorporated. PRP can produce particularly some phenomenal effects when applied in cosmetic dermatology. The therapeutic value of PRP is equivalent to stem cells and considered as one of the promising therapeutic agents in regenerative medicine. Harvesting of PRP plays a significant role, which is obtained from the patient's blood after centrifugation of the sample i.e., the platelet concentrates above the baseline which is the plasma fraction of the autologous blood. There are many applications of PRP in the medical field and has an incredibly significant role in dermatologic conditions e.g., tissue regeneration, wound healing, scar revision, skin rejuvenation and alopecia. In this review, we will be analyzing the authenticity of the use of PRP in the treatment of alopecia. PRP, in current scenario, is considered as a novel treatment modality. The efficacy of PRP therapy carries some deficiencies, which include lacking standard in preparation and concentration of platelets in PRP.

Keywords: PRP, Androgenic alopecia, Alopecia areata, Topical corticosteroids in alopecia, Scarring and non-scarring alopecia

INTRODUCTION

Platelet rich plasma (PRP), is biologically defined as a part of the plasma fraction of autologous blood plasma that has a platelet concentration above the basal concentration (150,000-350,000 μ /L).¹ PRP or platelet-rich growth factors (PRGF), platelet-rich fibrin (PRF) matrix, PRF and platelet concentrate. The start of PRP and the concept of its use took place in the 1970s, earlier used as transfusion products for the treatment of patients with hematologic disorders.² Later their use was explored in the treatment of various surgical procedures.³ It all happened because of the characteristic property i.e., potential adherence and hemostasis. With the start of PRP and their anti-inflammatory properties and stimulated cell proliferation, its use in alopecia was found to be significant, with quality subjective results within 10 months of follow up when used as mesotherapy followed by the added method of micro-needling.⁴

The biological aspect of platelets

Platelets develop from the bone marrow, they are nucleated, disc-shaped elements of cells having varied sizes and densities. Several secretory granules play a vital role in platelet function.⁵ The granules are of three types: dense granules, o-granules, and lysosomes. These granules manage aggregation and contribute to hemostasis by adhesion, activation, and aggregation. The growth factors and cytokines in the platelets affect the process of inflammation, angiogenesis, stem cell migration and cell proliferation. With the activation of platelets, the P-granules degranulate and release the growth factors and cytokines which change the pericellular microscopic environment. The important growth factors released by platelets in PRP include 1) Vascular endothelial growth factor, 2) Fibroblast growth factor (FGF), 3) Platelet-derived growth factors, 4) Epidermal growth factors (EGF) 5) Hepatocyte growth

factors, 6) Insulin-like growth factors 1,2 (IGF-1, IGF-2), 7) Matrix metalloproteinases 2, 9, and 8) Interleukin 8.⁶

METHODS

The study method includes the most up-to-date reviews published in the last ten years. The systematic review is oriented toward reviewing published studies of the highest level describing clinical use and biological aspect of PRP in the treatment of alopecia. This review is also aimed at evaluating the efficacy, safety of PRP as a therapeutic choice in treating several types of alopecia. A systematic search of the PubMed, EMBASE, Cochrane databases was performed, and reference lists of review articles were searched using medical subject headings (MeSH) with the following keywords: PRP, androgenic alopecia, alopecia areata, PRP, topical corticosteroids in alopecia, scarring and non-scarring alopecia. Five publications were found describing the clinical use of PRP in patients with alopecia.

RESULTS

PRP in alopecia, its efficacy is of significance and carry excellent subjective results within 10 months of therapy when used in combination with mesotherapy and micro-needling. There is evidence of an increase in hair growth with regrowth. It has been found that there is a considerable reduction in hair dystrophy, burning and itching sensation with minimum side effects.²⁹ PRP has proven to be more effective than steroid therapy in resistant forms of alopecia including ophiasis. It has also

proven much effective than topical treatment with minoxidil 5% in the treatment of alopecia areata. As there is poor blood perfusion hence the cicatricial alopecia patches are found to be poor graft recipients. The quantity of grafted follicles that survive depend on the blood supply of the vascular bed. PRP is a rich source of anagen-maintaining factors, Insulin-like growth factor 1(IGF-1), basic fibroblast growth factor (bFGF) and VEGF, which improves the cutaneous vascular ischemic conditions following PRP injections, thereby improving the vascular supply around the hair follicles. Before graft implantation patch test is done by infiltration of 1ml PRP intradermally into the recipient site which helps in improving the efficacy as well as proves good in managing cicatricial lichen planus. It has been found that intraoperative PRP therapy along with FUE hair transplant, is highly effective in improving the density of hair.³⁰ After the PRP is obtained it is loaded in insulin syringes which is having calcium chloride, acting as activators, are injected over the recipient site. Nappage technique is incorporated in this process i.e., multiple small injections measuring a gap of one cm apart, in a linear pattern. All aseptic precautions are considered while doing this procedure in the minor operation theatre setting. In the first session, a total volume of 2-3 cc of PRP is injected. The second session and a total of four sessions are done at an interval of two weeks. In every visit, an account of hair growth is taken by hair counting over the treated area. An evaluation scale is used with worst marked as (1) and (10) as best. There is a complete evaluation of the subject after the completion of 12 weeks of therapy.³¹

Table 1: Classification of molecules present in platelet-rich plasma and their functions.

Category	Proteins	Function
Adhesive proteins	Von Willebrand factor, fibrinogen, fibronectin, vitronectin, laminin 8	Cell interaction, hemostasis, composition of extracellular matrix.
Associated proteins, coagulation factors	Factor-V/Va, multimerin, protein S, kininogen (HMW), antithrombin III, tissue factor pathway inhibitor.	Thrombin production and regulation.
Associated proteins, fibrinolytic factors	Plasminogen, -2 antiplasmin, histidine-rich glycoprotein, -2 macroglobulin.	Plasmin production, vascular remodeling.
Proteases and antiproteases	Tissue inhibitors of metalloproteases 1-4 (TIMP 1-4), metalloproteases 1, 2, 4, 9 and α 1 antitrypsin.	Angiogenesis, vascular modeling, coagulation regulation.
Growth factors	PDGF, TGT-1 and 2, EGF, IGF-1, VEGF, bFGF, HGF, BMP-2,4,6, CTGF.	Chemotaxis, cell proliferation and differentiation, angiogenesis.
Chemokines, cytokines, and others	IL8, FasL, endostatins, osteonectin, bone sialoprotein.	Regulation of angiogenesis, vascular modeling, cell interactions, bone formation.
Antimicrobial proteins	Thrombocidins	Bacterial and fungicidal properties.
Membrane glycoproteins	Most of the components of the plasma membrane	Platelet aggregation and adhesion, protein endocytosis, inflammation, thrombin generation, platelet-leukocyte interactions.
Others	Chondroitin 4 sulfate, albumin, immunoglobulins, semaphoring	Promote angiogenesis, cartilage regeneration, fibrin production and platelet adhesion.

DISCUSSION

PRP has gained acknowledgement in medicine among dermatologists, and plastic surgeons due to its acceptable role in wound healing.⁴ PRP is an autologous blood concentrate that is aimed at delivering biologically rich growth factors, cytokines, fibrin etc.,. Has gained acceptance in the greater number of various clinical applications. There are different growth factors, which include PDGF, transforming growth factor (TGF), vascular endothelial growth factor (VEGF), and insulin-like growth factors (IGF) secreted from the α -granules of concentrated platelets activated by aggregation inducers. These factors in turn regulate the process of cell migration, attachment, proliferation, and differentiation promoting extracellular matrix (ECM) accumulation by binding to specific cell surface receptors.⁷ Fibrin, fibronectin and vitronectin are some of the essential protein components which act to promote cell adhesion. They are essential to support cell migration, proliferation, and 3-dimensional growth of tissue.⁸ PRP does carry the property of direct relation with various growth factors and affects the stimulation, repair, and regeneration of the tissue. Activation of PRP can be obtained with various agents which include 10% calcium chloride and thrombin. The activation can be obtained within 10 minutes with the active secretion of growth factors which includes 95% of pre-synthesized growth factors within 1 hour.⁶ The more inactivated PRP may result in more physiologic activation by injected tissue. When PRP is used in soft tissue, it gets activated naturally with collagen.

The process known as differential centrifugation is incorporated in the preparation of PRP in which force of acceleration is adjusted to obtain sediments of some cellular constituents depending upon specific gravity. There are two techniques in the extraction of PRP that are classified as open technique: in which the product is exposed to the external environment and comes in close contact with various materials which are used in the production of PRP e.g., lab equipment; pipettes or product collection tubes. This technique requires a blood processing and non-contamination guarantee during microbiological handling.

Closed technique: This technique involves the use of devices with CE markings. In these devices, the product is not vulnerable or does not get exposed to the external environment or the working area and there is a guarantee of non-contamination of the blood processing during microbiological handling. Here the blood sample obtained in a tube carries an anticoagulant, the quality of the tube used is such that it can be used for any kind of centrifuge. The collected blood is stored in an anticoagulant having a tube. After centrifugation, the components of blood get separated from the plasma because of variable density phenomena. Composition of PRP: platelets of high quality and elevated level, complement of clotting factors enriched with growth

factors, chemokines, cytokines, and other plasma proteins. Depending on their densities, which is variable there is the separation of blood components follows i.e., red blood cells, PRP and platelet-poor plasma.⁹

Alopecia, in broad terms, is associated with hair loss, having various causes which are often treatable. Alopecia can be broadly categorised into non-cicatricial and cicatricial alopecia.¹⁰ The non-cicatricial alopecia includes androgenic alopecia, telogen effluvium, alopecia areata, trichotillomania, anagen effluvium etc. while cicatricial alopecia include lichen planopilaris, frontal fibrosing alopecia, folliculitis decalvans, cutaneous discoid lupus erythematosus etc.¹¹

Alopecia areata (AA) is found to be a chronic, non-scarring hair loss disease. This condition affects specific organs which include hair follicles and often nails. Epidemiologically, this disease is prevalent in 0.2% of the world's population.¹² Clinically it is characterized as small circular patches of hair which gradually turn into diffuse patches mostly affecting the scalp area.¹³ It is not clear about the etiological factor and pathology of alopecia areata; however, it is considered an autoimmune process through auto-reactivation of CD8 + T cells.¹⁴ There are many theories postulated in connection with the aetiology of alopecia areata, which include a) genetic theory, b) allergy (Atopy), c) neurophysiological and emotional disorders, d) endocrine disorders, e) infection and several other theories. During the last 30 years, quite a few researchers were able to coin autoimmune theories, which describes humoral and cellular immunity disruption.¹⁵ PRP therapy has been found to cause no allergic reaction when used in the treatment of alopecia areata. The growth factors produced with the use of PRP act on the stem cells present in hair follicles, which further stimulate the development of newer hair follicles and neovascularization. PRP carries anti-inflammatory properties, which reduces the production of cytokines thereby decreasing local tissue inflammation.^{16,17} PRP therapies have been found useful and considered as an adjuvant therapeutic choice in the treatment of alopecia totalis and universalis.¹⁸

Androgenetic alopecia affects about 50% of males and females, considered genetically disordered which is found to be predetermined following a pattern, due to excessive response to circulating androgens. Characterized by gradually progressive hair loss more of terminal hair of scalp after puberty, following a characteristic distribution, seen in males and females. The pattern of hair loss in males is mainly from the vertex and frontotemporal region. The pattern of hair loss seen in females is typically sparing the frontal hairline and involves the wider anterior part with apical hair loss in a diffuse pattern.¹⁹⁻²¹ In androgenetic alopecia, shortening of the anagen phase is observed in normal hair growth cycle with androgen receptor activation which leads to follicular miniaturization with progressive anagen phase

shortening. There is the formation of shorter and thinner hair follicles that may not penetrate through the epidermis. While going through the pathological specimens, a decrease in anagen to telogen hair ratio is found to be 5:0, however, normal is 12:1.^{22,23} PRP is considered a newer advanced therapeutic modality in the treatment of androgenetic alopecia. PRP therapy is a therapeutic choice because of its autologous nature, minimal invasiveness, almost no side effects and cost-effectiveness when compared with other hair restoration surgeries, considered more affordable. There is minimal risk of infection and immunological rejection due to its autologous origin and minimally invasive collection technique. During the wound healing process, the activated platelets release growth factors and cytokines from alpha granules. Following injection of PRP in the scalp, it gets activated followed by the release of multiple growth factors which further promote hair growth. The released growth factors have a vital role in a) activation of fibroblast, b) collagen synthesis, c) stimulation of extracellular matrix and d) endogenous growth factors overexpression.²⁴ In summary, PRP stimulates hair growth by improving hair follicle vascularization, apoptosis inhibition and prolongation of anagen phase which is followed by a faster transition from telogen to anagen phase in dermal papillary cells.²⁵

Mechanism of action of PRP in alopecia

The four main actions as proliferation, migration, cell differentiation and angiogenesis, promoted by growth factors and bioactive molecules present in the PRP. There is consistent involvement of various cytokines and growth factors in the regulation of hair morphogenesis and hair growth cycle.²⁴ The growth factors e.g., IGF-1, FGF-7, hepatocyte growth factor and vascular endothelial growth factor produced by dermal papilla help to keep hair follicles during the anagen phase of the hair cycle. The accumulated β -catenin in the dermal papilla, in combination with the T-cell factor, functions as a co-activator in transcription, proliferation, survival and angiogenesis.²⁶

The dermal papilla initiate, differentiation, and transition from telogen to anagen phase after the initiation of differentiation and transition from telogen. Cell survival and prevention of apoptosis is increased by dermal papillary cell proliferation by activation of extracellular and signal-regulated kinase (ERK) and protein kinase B (Akt) which gradually leads to antiapoptotic effects. There is also an increase in β -catenin activity and expression of FGF-7 in dermal papillary cells. Akt inhibits 2 pathways through phosphorylation: 1) Glycogen synthase kinase-3 β , 2) Bcl-2-associated death promoter.²⁷ The PRP therapy may increase vascularization, prevent apoptosis, prolong the duration of the anagen phase.²⁵

Classification of PRP extraction techniques

Classification of 4 main families of preparations following 2 principal parameters. The two principal parameters which include the presence or absence of cell contents further includes leucocytes and fibrin. 1) Pure PRP: This is obtained without leucocytes and presents with a low-density fibrin network after activation. 2) PRP and leucocyte: This has leucocytes in which the fibrin network is in low-density after activation. 3) Leucocyte deficient PRF or pure PRF in which there is the complete absence of leucocytes and high-density fibrin network. Classification of DEPA based on 4 different components 1) Injected dose of platelets 2) Production efficiency (a) High efficiency of device (b) Medium efficiency of device (c) Low efficiency of device (d) Poor efficiency of device 3). PRP purity estimation (a) PRP very pure (b) PRP pure (c) PRP heterogeneous (d) PRP whole-blood 4. Activation process.²⁸

CONCLUSION

PRP is considered a new and advanced therapeutic choice for various pathological conditions and in dermatological conditions like wound healing, trichology, and cosmetic procedures. The standards of PRP depends on characteristics of the type of PRP used, which is extremely helpful in sorting and interpreting available data. With the use of PRP the rejuvenation of melanocytes, neurovascular bundle and dermal papilla can be obtained, which improves the environment and survival rate of hair regrowth, also supports the surrounding structure which causes reversal of miniaturization. PRP has proven to be a better, safe, and efficient option for the treatment of alopecia than with the use of minoxidil 5%, finasteride and persistently resistant cases of hair loss with the use of topical steroids. PRP is considered a safer procedure compared with other therapeutic options. PRP when used in combination therapy after FUE transplantation delivers excellent results.

There are quite a few complications reported following PRP therapy, which carry minor significance. These complications include pain at the site of injection, slight headache, heaviness in the head, swelling, redness, allergic reaction which can be in the form of an urticarial rash, skin discoloration which is temporary and often bruising etc. Although PRP, in current scenario, is considered as a novel treatment modality, however the efficacy of PRP therapy carries some deficiencies, which include lacking a standard in preparation and concentration of platelets in PRP.

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