Review Article

Role of Platelet-rich Plasma in Treatment of Non-Scaring Alopecia

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DOI:10.37821/ruhsjhs.5.4.2020.339

ABSTRACT

Alopecia (baldness) refers to loss of hair from part of head (scalp) or whole body and can be temporary or permanent. It can be genetic, result of hormonal imbalance, medical diseases, auto-immune conditions, chemotherapy or a normal part of aging. Anybody can lose hair on their head, but it is more common in men.

Androgenetic alopecia (AGA), alopecia areata (AA), and telogen effluvium are the primary non-scarring alopecias found in clinical practice. Androgenetic alopecia and alopecia areata are common hair loss disorders affecting both men and women. AGA is the most common type of alopecia and is due to androgen hormone related problem and the major cause of AA is autoimmune disorder. Telogen effluvium is a common, transient form of hair loss that can be due to medication, pregnancy, hypothyroidism, or some type of physical or psychological stressor such as surgery or a severe illness. The focus of this review is on the potential therapeutic role of platelet-rich plasma in non-scarring alopecia. In addition to the available therapeutic options, search for new and more effective treatment is constant. In our review, 21 articles matched our criteria, including two articles for PRP biology and it's preparation, one article for PRP classification, two articles for non-scarring alopecia, three articles for AGA, two articles for AA, and remaining articles were related to PRP application in dermatology. PRP is used as a potential useful therapeutic tool for alopecia without any considerable adverse effects. Notwithstanding, due to the small number of conducted trials, further studies are enforced to investigate PRP's efficacy.

Keywords: Autologous therapy, Non-scaring hair loss, Plasma, Platelet-rich plasma.

INTRODUCTION

Platelet-rich plasma (PRP) is now used in distinctive medical areas. The interest in the application of PRP in dermatology has increased just a while ago. It is being used manifold in various applications as in tissue regeneration, wound healing, scar revision, skin rejuvenating effects, and alopecia. PRP is a biological product defined as a portion of the plasma fraction of autologous blood with a platelet concentration above the baseline.

The concept and characterization of PRP was initiated in the field of hematology.[1] Hematologists established the term PRP in 1970s in order to describe plasma with a platelet count above that of peripheral blood, which was initially used as a transfusion product to treat patients with thrombocytopenia.[2] Ten years later, PRP started to be used in maxillofacial surgery as pure platelet-rich fibrin (PPRF). Fibrin had the very likely adherence and homeostatic properties and PRP with its anti-inflammatory characteristics stimulated cell proliferation.[3] Subsequently, some of the world's most elite athletes used PRP predominantly in the musculoskeletal field for wound healing in sports injuries. With its use in professional sports persons, it has attracted widespread attention in the media and has been extensively used in this field.[4]

In dermatology, the application of PRP in tissue regeneration, wound healing, scar revision, skin rejuvenating effects, and alopecia has increased.[1,5,6,7] In cosmetic dermatology, an in-vitro study manifested that PRP can accelerate human dermal fibroblast proliferation and increase type I collagen synthesis.[8] Attributively, based on histological evidence, PRP injected in human deep dermis and immediate sub dermis induces soft tissue augmentation, activation of fibroblasts, and new collagen

deposition in conjunction with new blood vessels and adipose tissue construction.[9,10]

In 2006, PRP was instituted to express a likely beneficial mechanism for promoting hair growth and has been postulated as a new therapy for alopecia, in both androgenetic alopecia and alopecia areata. A recent meta-analysis suggested the lack of randomized controlled trials.[11] Asserted by the authors, controlled clinical trials are considered the choice to contribute scientific evidence for treatment and avoid potential bias when assessing efficacy.[12]

Definition of PRP: Platelet-rich plasma (PRP), also known as autologous conditioned plasma, is a concentrate of platelet-rich plasma protein derived from whole blood before centrifugation. After centrifugation and according to their different density gradients, the separation of blood components (RBCs, PRP, and platelet-poor plasma [PPP]) supervenes.

By itself, PRP includes not only a high level of platelets but also the full complement of clotting factors, typically remaining at their normal physiologic levels.[13] It is enriched by a range of growth factors (GF), chemokines, cytokines, and other plasma proteins.[4] A growth factor is a naturally occurring substance capable of stimulating cell proliferation, wound healing, and occasionally cellular differentiation.[14] Usually it is a secreted protein or a steroid hormone. Growth factors are important for regulating a variety of cellular processes. It typically acts as signalling molecule between cells. PRP helps in progressing the hair regrowth in last stages of hair loss when medical treatments have no significant role to play. So, the scales for hair loss measurement in both men and women should also be known.

Scale for hair loss measurement: The Norwood scale (or Hamilton-Norwood scale)[15] is the leading classification system used to measure the extent of male pattern baldness. The Norwood scale has seven stages (Table 1). Each stage measures the severity and pattern of hair loss.

The Ludwig scale[16] is an approach of classifying female pattern baldness (androgenic alopecia) and ranges from stages I to III (Table 2).

Mechanism of action of PRP in alopecia: The growth factors (GFs) and the bioactive molecules present in PRP stimulates four main actions in the local environment namely, proliferation, migration, cell differentiation, and angiogenesis.[17-19] Various cytokines and GFs are involved in the regulation of hair morphogenesis and cycle hair growth.[20] The dermal papilla (DP) cells give outcome like GFs such as insulin like growth factor-1 (IGF-1), fibroblast growth factor-7 (FGF-7), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) that are responsible for maintaining the hair follicle in the anagen phase of the hair cycle. Consequently, a potential target would be to upregulate these GFs within the DP cells, which lengthen the anagen phase.[21]

Table 1: Characteristic features of alopecia (Norwood Scale)[15]

Stages	Characteristic features
1	No significant hair loss or recession of the hairline over the temples.
2	There is a slight recession of the hairline throughout the temples. This is also recognized as an adult or mature hairline.
3	The first signs of clinically significant balding appear. The hairline becomes deeply recessed at both temples, looking like English alphabets as M, U, or V shape. The recessed spots are completely exposed or quitely covered in hair. Then after the hairline stays at stage 2, but there is significant hair loss on the top of the scalp (the vertex).
4	The hairline recession is more severe than in stage 2, and there is sparse hair or no hair on the vertex. The two areas of hair loss are independently by a band of hair that connects to the hair remaining on the sides of the scalp.
5	The two areas of hair loss are larger than in stage 4. They are still distinct, but the band of hair between them is narrower and sparser.
6	The balding areas at the temples join with the other side of balding area at the vertex. The band of hair across the top of the head is gone or sparse.
7	The last and most severe stage of hair loss, only a band of hair going over the sides of the head remains. This hair is usually not dense and may be fine.

Table 2: Characteristic features of alopecia (Ludwig Scale)[16]

Stages	Characteristic features
I	Starts with thinning on the top of the head.
II	The scalp also begins to show.
III	All of the hair at the crown of the head may be lost.

Alongwith the GFs, the anagen phase is also activated by Wnt/β-catenin/T-cell factor lymphoid enhancer.[22] In the DP cells, the activation of Wnt will precede to an accumulation of β-catenin, which, in combination with the T-cell factor lymphoid enhancer, also acts as a co-activator of transcription and stimulates proliferation, survival, and angiogenesis. The DP cells then initiate the differentiation and therefore the transition from telogen to anagen phase.[18] β-catenin signalling is influential in human follicle development and for the hair growth cycle. The other pathway presented in DP is the activation of extracellular signal-regulated kinase (ERK) and protein kinase B (Akt) signalling that promotes cell survival and counter the apoptosis.[6]

The precise mechanism by which PRP promotes hair growth is not fully understood. To analyse the possible mechanisms involved, Li et al[6] performed a well-designed study to investigate the effects of PRP on hair growth using in-vitro and in-vivo models. In the in-vitro model, activated PRP was applied to human DP cells achieved from normal human scalp skin. The results show that PRP increased the proliferation of human DP cells by activating ERK and Akt signalling, leading to anti-apoptotic effects. PRP also increased the β-catenin activity and FGF-7 expression in dermal papillae cells. With reference to the in-vivo model, mice injected with activated PRP showed a faster telogen to anagen transition in comparison to the control group. Recently, Gupta et al[18] also proposed a mechanism for the action of PRP on the human follicles that includes the "elicitation of the Wnt/β-catenin, ERK, and Akt signalling pathways to harbour cell survival, proliferation, and differentiation." After GF binds with it's coincide growth factor receptor, the signalling mandatory for its expression initiates. This complex activates the expression of both Akt and ERK signalling.

The activation of Akt is impeded by two pathways through phosphorylation process: (1) the glycogen synthase kinase-3β which promotes degradation of β-catenin, and (2) Bcl-2-associated death promoter, that is liable for inducing apoptosis. According to the authors, PRP might increase vascularization, prevent apoptosis, and prolong the duration of the anagen phase.[23]

PRP Classification: The literature on PRP is noticeable but the published results are often incompatible. It is very challenging to sort and interpret the available data due to a large number of preparation techniques, terminologies, forms of these materials, and endless list of potential applications.

According to the classification proposed by Dohan et al[24], four main families of preparations can be defined, depending on their cell content and fibrin architecture.

1. Pure platelet-rich plasma (PPRP) or leucocyte-poor PRP products are preparations without leucocytes and with a low-density fibrin network after activation.
2. Leucocyte- and PRP (LPRP) products are preparations with WBCs and with a low-density fibrin network after activation. It is the family in which largest number of commercial or experimental systems exists. Peculiarly, many automated protocols have been flourished in the last years, compelling the use of specific kits that allow minimum handling of the blood samples and maximum standardization of the preparations.
3. Pure platelet-rich fibrin (PPRF) or leucocyte-poor platelet-rich fibrin preparations are without WBCs and with a high-density fibrin network. These products only prevail in a strongly activated gel form and cannot be injected or used like traditional fibrin glues.
4. Leucocyte-and platelet-rich fibrin (LPRF) or second-generation PRP products are preparations with WBCs and with a high-density fibrin network.

PRP Preparation: At present, there is a great deliberation and no harmony regarding PRP preparation. PRP is prepared by a process known as differential centrifugation, in which acceleration force is composed to sediment assured cellular constituents based on different specific gravity.[25]

Table 3: Main functions of growth factors present in platelet rich plasma

Growth factors		Main functions
PDGF	-	Increases hair growth - Vascularization
	-	Blood vessel formation
	-	Mitogenesis for cells of mesenchymal origin, including fibroblasts, smooth muscle cells, and glial cells
TGF-β	-	Inhibits hair growth in vitro - Hair-cell proliferation and regeneration
	-	Immune and stem cell regulation and differentiation eg. cancer, autoimmune diseases
VEGF	-	Expressed in DP cells in the anagen phase - Probably regulates perifollicular angiogenesis (as such conditions ischemia, inflammation, wound healing, and cancer)
	-	Vasculogenesis and Lymphogenesis in embryonic development of myocardial tissue
	-	Chemotactic for macrophage and granulocytes
	-	Increases perifollicular vessel size during the anagen growth phase
EGF	-	Stimulates the process of angiogenesis
	-	Hair-cell proliferation and regeneration
	-	Maintenance of oro-esophageal and gastric tissue integrity
HGF	-	Increases hair growth by inducing the anagen phase of HF - Promotes DP cell proliferation
	-	Embryonic organ development, specifically in myogenesis, in adult organ regeneration, and in wound healing.
FGF	-	Increases the HF size in mice - Angiogenesis stimulators
	-	Promotion of endothelial cell proliferation
IGF-1	-	Maintains HF growth in vitro - Angiogenesis stimulator
	-	Stimulates systemic body growth

PDGF: platelet derived growth factor; TGF: transforming growth factor; VEGF: vascular endothelial growth factor; DP: dermal papilla; EGF: epidermal growth factor; HGF: hepatocyte growth factor; FGF: fibroblast growth factor; IGF-1: insulin-like growth factor 1; HF: human follicle(s).

PRP is accessed from a sample of patient's blood drawn at the time of treatment. A 30 cc venous blood draw will bring in 3-5 cc of PRP depending on the baseline platelet count of an individual, the device used, and the technique employed. The blood draw appears with the addition of an anticoagulant such as citrate dextrose A to prevent platelet activation proceeding to its use. The columnist handle is a specialized 'table top cold centrifuge' device.

Principles of PRP Preparation: PRP is prepared by a process acknowledged as differential centrifugation. In differential centrifugation, acceleration force is accommodated to sediment satisfied cellular constituents based on different specific gravity. There are various ways of formulating the PRP. It can be prepared by two methods: (a) PRP method[26] or (b) buffy-coat method.[27]

In the PRP method, an introductory centrifugation of isolated red blood corpuscle (RBC) is followed by a second centrifugation to concentrate platelets which are hung down in the smallest final plasma volume. The flow chart (Figure) describes a double centrifugation process of PRP. Whole blood is initially collected in tubes which contain anticoagulants.

The first spin step is performed at constant acceleration to separate red blood cells from the remaining whole blood volume. After the first spin step, the whole blood separates into three layers: an upper layer that contains mostly platelets and leukocytes, an intermediate thin layer that is recognized as the buffy coat and that is rich in leukocytes, and a bottom layer that is enriched of RBCs. For the origination of pure PRP (PPRP), upper layer and superficial buffy coat are transferred to an empty sterile tube. For the production of leucocyte rich PRP (LPRP), the entire layer of buffy coat and few red blood cells are shifted.

After the first spin is completed, the second spin step is then performed. 'g' for second spin should be just satisfactory to aid in formation of soft pellets (erythrocyte-platelet) at the bottom of the tube. The upper portion of the volume that is possessed predominately of PPP (platelet-poor plasma) is removed. Pellets are condensed in lower 1/3rd (5 ml of plasma) to create the PRP (platelet-rich plasma).

In the Buffy coat method, preparation of PRP is prepared by following steps-

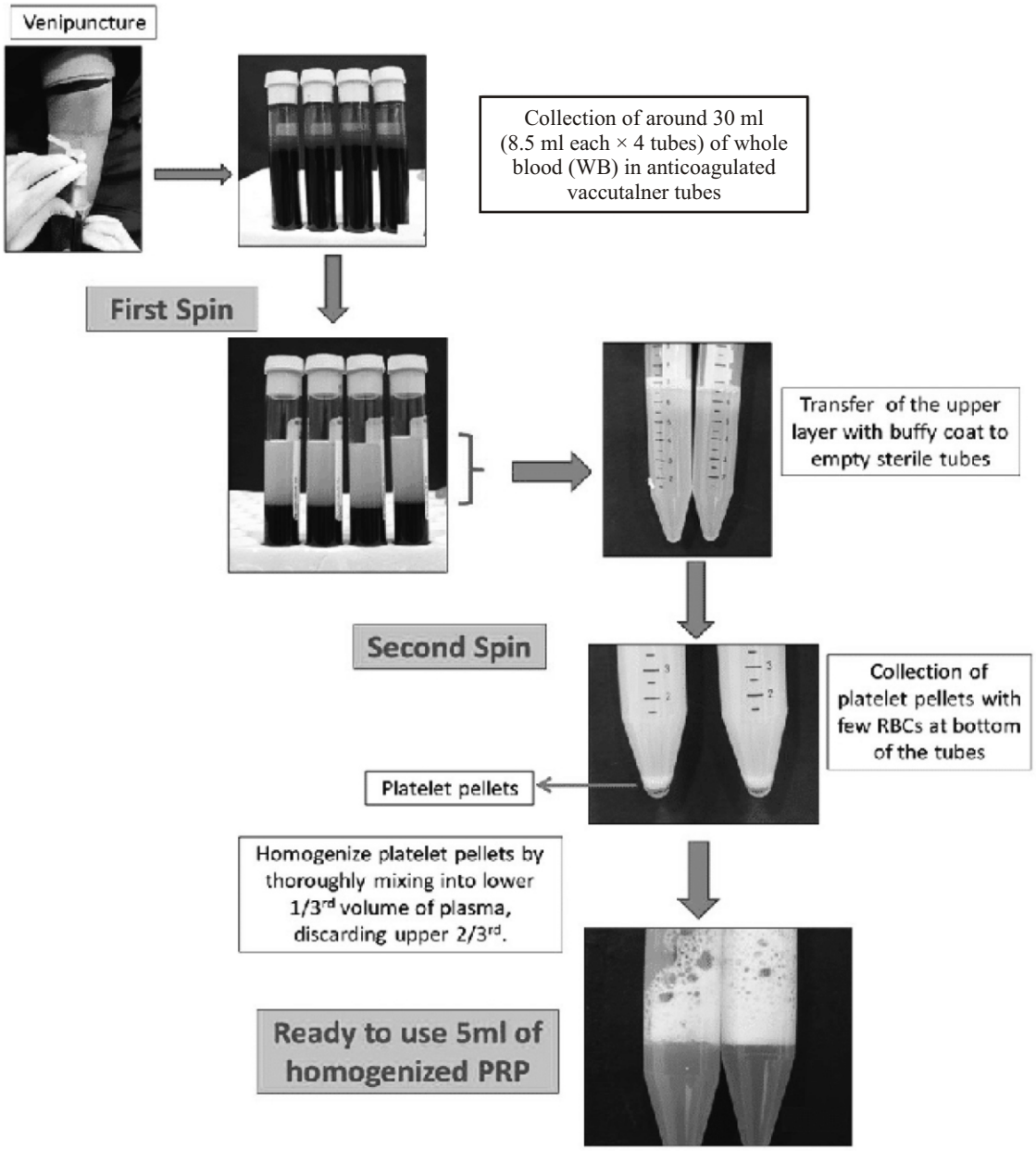

Figure: Flowchart describing preparation of PRP.

1. Whole blood should be stored at 20°C to 24°C before centrifugation.
2. Centrifuge whole blood at a 'high' speed.
3. Three layers are formed because of its density: The bottom layer consisting of red blood cells, the middle layer consisting of platelets and leukocytes, and the top platelet poor plasma layer.
4. Supernatant plasma removed from the top of the container.
5. Shift the buffycoat layer to other sterile tube.
6. Centrifuge at low speed to separate leukocytes or use leukocyte filtration filter.

There is no concurrence on whether or not platelets must be already activated preceding their application and with which agonist. Some columnist activate platelets with thrombin or calcium, whereas others apply platelets without being already activated, disputing that better results are obtained.[28]

Market Available PRP Kits: There are various PRP systems available in market which promotes the preparation of ready to apply platelet-rich suspensions in a

reproducible manner. All operate on a small volume of drawn blood (20-60 mL) and on the principle of centrifugation. These systems alter widely in their ability to collect and concentrate platelets depending on the method and time of its centrifugation. As a result, suspensions of different concentration of platelets and WBC's are obtained. Differences in the concentrations in platelets and WBCs influence the diversity of growth factors concentration. It is troublesome to assess which kit for PRP preparation is better and which is worse. PRP devices can be consistently broken down into lower (2.5-3 times baseline concentration) and higher (5-9 times baseline concentration) systems.

Other Clinical Importance: Advantage of PRP is mixed, with some evidence for use in believing conditions and some against use in other conditions.[29] It has been explored for chronic tendinitis,[30] osteoarthritis,[31] in oral surgery,[32] and in plastic surgery.[33] A 2019 meta-analysis found that PRP might be more effective in reducing pain and enhance function than hyaluronic acid in knee osteoarthritis.[34] As an adjuvant to other conservative treatments for non-surgical orthopaedic illnesses (e.g. steroid injection for plantar fasciitis), evidence does not support the use of PRP as a conservative treatment.[35] The use of PRP in sinus lifts during dental implant placement found no evidence of benefit in Cochrane review of 2010.[32]

Literature Review Resources: This study used multiple searching engine/database in medical sciences, through PubMed/MEDLINE, ClinicalTrials.gov, Scopus, Cochrane Central Register of Controlled Trials, and Google Scholar/Web of Science databases. This review article information sources are apart from different articles that are published in International Journal of Trichology, skin appendage disorder related articles that are published by Department of Dermatology, University of International Catalunya, Barcelona, Spain, and Wikipedia of PRP. We considered conference papers whenever available, but we excluded them since the information was not sufficiently accurate to evaluate the quality measurement. Most of the controlled trials and the case report included a placebo group either of subjects or of the half head scalp of subjects treated with normal saline and some article explains the mechanisms of activated PRP on hair growth, we evaluated signaling pathways. Kang et al[36] used as placebo placental extract while both treatment and control groups were simultaneously treated with Finasteride per os.

Critical Discussion: Inspite of the growing interest in regenerative medicine, few trials investigating PRP's efficacy on hair growth have been published. Some articles give information regarding PRP's clinical uses apart from alopecia like chronic tendonitis and dental procedures and give classification of PRP preparations. Most of the reviewed studies had important methodological deficiencies. Main faults included lack of approved scientific devices for PRP preparation, lack of a reference protocol regarding the frequency of applications as well as the injected amount of PRP, heterogeneity in application modes, lack of controls, small sample size, scientifically ambiguous uses of PRP, lack of detailed reports in patients' characteristics, and used statistical methods. Further, few studies referred to the safety profile of PRP.

Randomized controlled trials are gold standard for proving the efficacy of a treatment and bypass potential bias in the efficacy assessment. The use of blind or double-blind study designs and placebo are other strategies that improve the quality of the trials. For these reasons, the acceptance of high-quality trial design, that is, placebo-controlled double-blind studies with randomization or intra-patient design strictly strengthen the testing of efficacy of PRP on alopecia. The most important obstacles in trials evaluating hair growth are the absence of standard, reliable, and objective non-invasive methods to evaluate hair loss as well as the results after PRP treatment. Nonetheless, a sufficient means of measuring hair growth in the clinic over time in a reproducible, economical, and non-invasive manner is not available and all the above methods give a highlighted assessment of the results after treatment. In all these trials, the safety profile of PRP should be reported with the description of adverse effects, even if they are negligible.

CONCLUSION

PRP is being used as a modern therapeutic preference for contrasting pathologies in the field of dermatology such as trichology, wound healing, dental procedures, orthopaedic minor procedures, and cosmetic medicine. We hope that this review serves as a basis for further research on the use of PRP by understanding mechanism of action.

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