

## Regeneration Through Platelet Rich Plasma – A Cell Therapy with a Path Full of Milestones, Controversies and Cautions!

Regenerative medicine is currently one of the fastest-growing branches of intervention dermatology and trichology with platelet-rich plasma (PRP) therapy forming its core component. Platelets are the body's autologous powerhouse of growth factors and cytokines that have remarkable healing abilities when used in specific concentrations. Their use is being explored in both the "diseased" and "desired" dermatology. PRP as a cell and tissue engineering therapy has contributed immensely. It is picking up the pace for difficult to treat conditions including non-healing ulcers, scarring alopecia, and post-burn scars.<sup>[1-3]</sup> With encouraging results being reported from the scientific community globally, PRP and its new generations have generated great interest amongst dermatologists, plastic surgeons, orthopedicians, orodental surgeons, faciomaxillary surgeons alike.

PRP primarily acts through growth factors and cytokines on the circulating hematopoietic stem cells as well as endothelial progenitor cells to facilitate revascularization which in turn, improves the supply of oxygen and essential nutrients to the regenerating cells. In addition, PRP also contributes to tissue regeneration due to the presence of fibrin.<sup>[4]</sup> PRP requires a conducive environment with balanced nutrition and correction of the underlying deficiencies to work to its full potential.<sup>[2,3]</sup>

This interesting supplement is coming up with the prestigious "IADVL PRP taskforce guidelines" for the use of PRP in different areas of dermatology and trichology. There is still a lot of confusion regarding the heterogeneity in PRP formulations, inconsistencies in nomenclature, and the poor standardization of evidence-based guidelines. With tremendous hard work, the IADVL task force has succeeded in establishing consensus guidelines to address the widespread disparity and non-uniformity in various gray areas pertaining to PRP, including method of preparation, single spin versus double spin, the type of centrifuge, desired platelet concentration, and contemplating the rationale of activator, besides addressing the various other burning topics in this field.

As far as the current literature goes, the evidence is still divided regarding the efficacy of PRP in various disorders including androgenetic alopecia. A recent publication from Harvard Medical School mentions that PRP lacks scientific evidence and only marginally benefits the patients of androgenetic alopecia, as indicated by a slight positive shift on the bell curve.<sup>[5]</sup> On the contrary, few other authors have proved the regenerative potential of PRP in their studies and have compared it to an "elixir"<sup>[6]</sup> which is further endorsed in recent publications.<sup>[7-9]</sup>

The IADVL-PRP task force has come a long way and the critical evaluation of the role of PRP in androgenetic alopecia as presented in these guidelines is based on the GRADE (Grading of Recommendation, Assessment, Development and Evaluation) framework. The task force has provided a clear and positive consensus on the use of PRP in androgenetic alopecia, with recommendations regarding the number of sessions, duration in-between the two sessions, and the quantity of PRP to be injected, with an attempt to address the prevailing confusion regarding these practical aspects. In contrast, the role of PRP in cosmetic and interventional dermatology may be regarded as a "prodigy in infancy," which still has to prove its mettle in the field with randomized controlled studies. The task force also aims to discuss the evidence of the role of PRP in various indications of cosmetic dermatology such as scar revision, pigmentation, skin rejuvenation, and anti-aging, which has been critically evaluated based on the current literature.

Various burning issues have been resolved by the unparalleled efforts of the task force, yet the path is still full of upheavals and various other factors need to be determined. An interesting point of discussion is regarding the use of simple vials versus commercial kits. Interestingly, most of the large-scale studies in PRP are published from medical colleges and institutes where resources permit the use of the more cost-effective manual methods. In contrast, there is a paucity of unbiased literature with the use of commercial kits that are commonly being used by private practitioners, and unfortunately, majority of the them are unable to publish their experience. Also, the focus of PRP has been to attain a high platelet concentration (1–1.5 million/mL) and reach the so-called magic number. However, the double spin method, aimed at attaining this higher concentration, increases the *ex vivo* time considerably, which may impact the platelet morphology, the effects of which can only be studied by electron microscopy and have remain underestimated. The effect on the final platelet degranulation capacity to unleash the efficient growth factors also needs to be studied, with well-conducted molecular studies. The role of cold centrifuge again holds considerable meaning under the same circumstances. Another interesting point of contention could be whether the "magic number" of platelets is actually magical or overhyped! This question becomes all the more relevant in the current times, where new generations of PRP such as i-PRF (injectable platelet-rich fibrin), A-PRF (advanced platelet-rich fibrin), and PRFM (platelet-rich fibrin matrix) are gaining importance in terms of efficacy and added benefits of plasma proteins. These therapies are technically less concentrated in terms of platelet count in comparison

to PRP.<sup>[10,11]</sup> Out of these new progenies of PRP, only C-PRF (concentrated platelet-rich fibrin) is known to have 10 times higher platelet concentration from the baseline, which is considerably higher than PRP.<sup>[12]</sup> Other new generations of PRP are delivering promising results in different fields, in spite of a lower concentration of platelets. In addition, a new form of regenerative therapy, the “growth factor concentrate (GFC),” which is gaining popularity, is based on the principle of degranulation of platelets, releasing growth factors mixed in the plasma *in vitro*.<sup>[13]</sup> Again, the “magic number” comes under the scanner, as based on preliminary literature, the same number of platelets releasing growth factors mixed in almost double the amount of plasma are yielding impressive results. This can lead to an extrapolation of the hypothesis that even half the platelet concentration *in vivo* might have delivered clinically good results with PRP. The other probability could be that *in vitro* released growth factors function better than *in vivo* degranulation or the latter are rapidly lost in the circulation and not fully utilized by the tissue of interest. The hypothesis needs rigorous evaluation in terms of significant differences in clinical outcomes with different platelet concentrations. Furthermore, head-to-head randomized controlled studies comparing the efficacy of PRP versus GFC should be performed to address the conundrum.

Moreover, to understand the effect of various concentrations, molecular studies have previously been performed using different PRP concentrations. Xiao *et al.*<sup>[14]</sup> demonstrated the competency of 5% activated PRP to enhance the hair-proliferative and hair-inductive properties of human and mouse dermal papillary cells (DPCs) *in vitro* and mouse DPCs in an *in vivo* mini-chamber assay. They observed that 5% concentration is more efficacious than the 10% concentration, citing the reason that higher concentration although helps in proliferation but interferes with differentiation of cells. A similar finding is further supported by Wang *et al.*<sup>[15]</sup> on human hair dermal papillary cells (HHDPCs) best documented with the use of 5% versus 10% PRP concentration, with a significant increase in alkaline phosphatase (ALP) and versican expression at both mRNA and protein levels in HHDPCs.

Regenerative medicine is an ever-evolving field, and PRP therapy along with its recently introduced new generations is refining the course of healing in various ailments. One must understand that, unlike conventional medicines, here the healing capacity is based on the positive environment created inside the body, which is chiefly regulated by available nutrients and the overall physical and emotional well-being. The healing signals may go wasted if the body is not supported in the right direction, thus explaining the variable outcomes in different settings, besides other technical reasons.

Another pertinent point that is required to be highlighted here is regarding the use of PRP therapy in the COVID-19 scenario. Of late, there is an increase in the number of anecdotal case reports of blindness with the use of PRP therapy.<sup>[16]</sup> The accidental intra-arterial injection of PRP could lead to detrimental effects, considering that a high concentration of platelets in the COVID-19 related hypercoagulable state<sup>[17]</sup> and few vaccines leading to prothrombotic thrombocytopenic events<sup>[18]</sup> may theoretically increase the risk leading to inadvertent arterial occlusion and subsequent complications. One must understand that although this is an autologous cell therapy, at the same time, it is armed with a high concentration of live platelets, growth factors, cytokines, and proteins that in due course of time might unleash their own paracrine, autocrine, and enzymatic effects. Hence, it is touted as our own “dragon warrior” to be used with the utmost caution, especially around periorbital, glabellar, and mid-face areas.<sup>[19]</sup>

Currently, based on its efficacy in different areas, there is a paradigm shift toward preventive and regenerative medicine. Molecular scientists, researchers, and clinicians toiling hard in this field should aim at structured, well-conducted, multicentric randomized trials to draw conclusive evidence in various gray areas.

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Dr Anuva Bansal MD, Dermatology Fellow, Aura Skin Institute, Chandigarh.

### Suruchi Garg

Department of Intervention Dermatology, Aura Skin Institute, Chandigarh, India

#### Address for correspondence:


Dr. Suruchi Garg,  
Department of Intervention Dermatology, Aura Skin Institute,  
Chandigarh, India.  
E-mail: gargsuruchi01@gmail.com

### References

1. Suthar M, Gupta S, Bukhari S, Ponemone V. Treatment of chronic non-healing ulcers using autologous platelet rich plasma: A case series. *J Biomed Sci* 2017;24:16.
2. Garg S, Pandya I, Bhatt S. Follicular unit extraction (FUE) hair transplantation in combination with platelet rich plasma for the treatment of scarring alopecia: A case series. *Arch Clin Med Case Rep* 2019;3:299-308.
3. Garg S, Badheka A, Singhal S. A pilot study of making new skin and appendages for post burn scars through a unique cocktail of platelet rich plasma, ablative pixel erbium: Yag laser and micro needling radiofrequency. *Stem Cell Res Int* 2018;2:1-4.
4. Kawase T, Okuda K, Saito Y, Yoshie H. *In vitro* evidence that the biological effects of platelet-rich plasma on periodontal ligament cells is not mediated solely by constituent transforming-growth factor-beta or platelet-derived growth factor. *J Periodontol* 2005;76:760-7.
5. Bigby M, Grimalt R. Platelet-rich plasma lacks evidence of clinically significant improvement in androgenetic alopecia.

- J Am Acad Dermatol 2021;84:1183-5.
6. Garg S, Manchanda S. Platelet-rich plasma—An ‘Elixir’ for treatment of alopecia: Personal experience on 117 patients with review of literature. *Stem Cell Investig* 2017;4:64.
  7. Elghblawi E. Platelet-rich plasma, the ultimate secret for youthful skin elixir and hair growth triggering. *J Cosmet Dermatol* 2018;17:423-30.
  8. Dhaniwala NS, Dasari V. Platelet-rich plasma as an ‘elixir’ for wound healing: An overview review. *JCR* 2020;7:1889-94.
  9. Kaushik A, Kumaran MS. Platelet-rich plasma: The journey so far! *Indian Dermatol Online J* 2020;11:685-92.
  10. Kobayashi E, Flückiger L, Fujioka-Kobayashi M, Sawada K, Sculean A, Schaller B, *et al.* Comparative release of growth factors from PRP, PRF, and advanced-PRF. *Clin Oral Investig* 2016;20:2353-60.
  11. Ghanaati S, Booms P, Orlowska A, Kubesch A, Lorenz J, Rutkowski J, *et al.* Advanced platelet-rich fibrin: A new concept for cell-based tissue engineering by means of inflammatory cells. *J Oral Implantol* 2014;40:679-89.
  12. Miron RJ, Chai J, Zhang P, Li Y, Wang Y, Mourão CF de AB, *et al.* A novel method for harvesting concentrated platelet-rich fibrin (C-PRF) with a 10-fold increase in platelet and leukocyte yields. *Clin Oral Investig* 2020;24:2819-28.
  13. Sthalekar B, Agarwal M, Sharma V, Patil CY, Desai M. Prospective study of growth factor concentrate therapy for treatment of melasma. *Indian Dermatol Online J* 2021;12:549-54.
  14. Xiao S-E, Miao Y, Wang J, Jiang W, Fan Z-X, Liu X-M, *et al.* As a carrier-transporter for hair follicle reconstitution, platelet-rich plasma promotes proliferation and induction of mouse dermal papilla cells. *Sci Rep* 2017;7:1125.
  15. Wang Y, Tang L, Zhu F, Jia M. Platelet-rich plasma promote s cell viability of human hair dermal papilla cells (HHDPCs) *in vitro*. *Int J Clin Exp Pathol* 2017;10:11703-9.
  16. Karam EZ, Gan A, Muci Mendoza R, Martinez E, Perez E. Visual loss after platelet-rich plasma Injection into the face. *Neuroophthalmology* 2020;44:371-8.
  17. Garg S, Garg M, Prabhakar N, Malhotra P, Agarwal R. Unraveling the mystery of Covid-19 cytokine storm: From skin to organ systems. *Dermatol Ther.* 2020;33:13859.
  18. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N Engl J Med* 2021;384:2092-2101.
  19. Garg S, Bansal A. Platelet-rich plasma in interventional dermatology and trichology: How far have we come? *Cosmoderma* 2021;1:12.

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