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Outcome of intra-operative injected platelet-rich plasma therapy during follicular unit extraction hair transplant: A prospective randomised study in forty patients

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India**Abstract**

Context: Platelet-rich plasma (PRP) therapy is finding importance in aesthetic medicine. **Aim:** The objective of this study was to study efficacy of PRP therapy in follicular unit extraction (FUE) hair transplant. **Materials and Methods:** It is a single-blind, prospective randomised study on 40 FUE hair transplant subjects, allocated in two groups (PRP and non-PRP) alternately. PRP was injected intra-operatively immediately after creating slits over the recipient area in PRP group; and normal saline in non-PRP group. Two groups were evaluated at 2, 4 and 8 weeks, 3 and 6 months of the procedure. **Statistical Analysis:** It was done using Chi-square test and test of significance was set as $P < 0.05$. **Results:** In PRP group, all subjects had >75% hair regrowth at 6 months, density of >75% grafts was noticed in 12 patients at 4 weeks meaning reduced fall of transplanted hair during catagen phase. New hair growth started at 8 weeks in 16 patients and redness over recipient area completely disappeared in 19 patients at 3 months of surgery and activity in dormant follicles as fine thread like hair was noticed besides the thick transplanted hair in all subjects. In non-PRP group, four patients had >75% hair regrowth at 6 months; none showed >75% graft density at 4 weeks, and 13 subjects showed dormant follicle activity at 4 months. The number of patients having lengthier hairs was significantly more in PRP group. **Conclusion:** Intra-operative PRP therapy is beneficial in giving faster density, reducing the catagen loss of transplanted hair, recovering the skin faster and activating dormant follicles in FUE transplant subjects.

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Available from: <http://www.jcasonline.com.proxy.bib.uottawa.ca/text.asp?2016/9/3/157/191657>**Full Text****Introduction**

Alopecia is a hereditary and androgen-dependent progressive thinning of scalp hair. In hair follicles, reduction in the anagen phase of hair cycle leads to the entry of hair earlier into the telogen phase.[1],[2] Platelet-rich plasma (PRP) helps in tissue augmentation by activating platelets and releasing large amounts of platelet-derived growth factors (PDGFs) which act on stem cells of the follicles, stimulating the development of new follicles and promoting neovascularisation.[3],[4],[5] By taking this clinical significance of PRP, this study was planned for evaluation of PRP in growing and healing hair after follicular unit extraction (FUE) hair transplant.

Materials and Methods**Selection and description of participants**

A total of forty patients were randomised alternately into two groups of twenty patients each which were enrolled on the basis of inclusion and exclusion criteria.

Inclusion criteria

Male patients in the age group of 20–55 years willing to give informed consent Patients with androgenetic alopecia (AGA) Stage III–VII Hamilton–Norwood classification Patients who had not taken any form of treatment for AGA, at least in the past 3 months.

Exclusion criteria

Patients on anticoagulant medications-aspirin, warfarin, heparin Patients with alopecia other than AGA such as alopecia areata, alopecia totalis, telogen effluvium and acquired cicatricial alopecia Patients with history of bleeding disorders, autoimmune disorders, psoriasis or lichen planus Patients with infection at the local site Patients who were known to be HIV, hepatitis B or C positive or otherwise immunocompromised.

Technical information

While conducting study treatment, one arm of the two groups received injectable PRP during the transplantation just after the slitting process, and other arm of the subjects received

normal saline in place of PRP.[6]

Preparation with platelet-rich plasma and its application procedure

The process of PRP harvesting was standardised before the start of study and uniformly followed in all the subjects with the same kit and methodology. PRP therapy was given to the enrolled subjects using YCELL BIO PRP kit.[7]

We collected 20 ml of whole blood from antecubital vein. We used two PRP kits in each patient containing 1.5 ml ACD-A anticoagulant solution which was mixed with 10 ml blood [Figure 1] and processed in a centrifuge. First spin was done at 3200 rpm for 4 min followed by 1 min second spin at the same revolutions per minute for a better demarcation of buffy coat. Of 10 ml of blood in each PRP kit, 1.5 ml of PRP along with buffy coat was harvested [Figure 1]. Thus, a total of 3 ml PRP was collected from 20 ml of blood.[Figure 1]

This process of PRP preparation was standardised and followed in each of study subjects as it revealed five to seven times increase in the concentration of platelets from the baseline value. Considering an average platelet count of $200,000 \pm 75,000/\mu\text{L}$, the final platelet concentration in PRP was expected to be around 10–14,00,000/ μL .

PRP was freshly prepared while slits were being created. No activator was used before usage of PRP to avoid any external chemical injury to newly implanted hair follicles. After harvesting and slitting were over, 0.2–0.3 ml PRP was injected through insulin syringe at a gap of 1 cm each to the depth of dermis and subcutis in freshly done slits over recipient area, and the blood oozing from these slits itself acted as stimulus for the degranulation of platelets. In comparison, non-PRP group received normal saline instead of PRP after slitting.

Efficacy evaluation criteria

Efficacy of PRP was evaluated in terms of change in hair density (percentage of number of grafts at a given time <25%, 25–50%, 50–75% and >75%), type of grafts, impact of healing process by appearance and recovery from scalp redness, length of shaft, texture and thickness of hair at the end of 2 weeks, 4 weeks, 8 weeks, 3 months and 6 months.

Each patient was photographed with clinical and video microscopic images, keeping identity confidential and data were evaluated independently.

Pre-operative evaluation

All the enrolled patients were evaluated for biochemistry parameters such as fasting plasma sugar, liver function test, renal function test, HbA1c, complete haemogram including platelet count, along with anti-HIV, anti-hepatitis C virus and anti-HBsAg before the initiation of transplant procedure.

Intra-operative methodology

All the patients were given detailed pre- and post-operative instructions. Only scalp hairs were harvested. Transaction rate during harvesting was 5–8%. While doing implantation, only the grafts with intact roots were implanted.

The follicles were kept moist in chilled normal saline and stored inside refrigerator at 2–8° centigrade till implantation. The follicles were implanted within 6 h of harvesting in both the groups and the roots were not fiddled with while implantation. The density of implantation was kept at 40–45 grafts/cm² in both groups using multipronged slitter [disposable 18G needles and wire holding forceps as shown in [Figure 2].{Figure 2}

Statistical analysis was done through Chi-square tests and test of significance were set as $P < 0.05$ significant and < 0.01 as highly significant.

Results

A total of forty male patients meeting the inclusion and exclusion criteria of the study were enrolled and evaluated. All the patients were suffering from male pattern of alopecia [Table 1].{Table 1}

None of the enrolled patients had undergone hair transplant previously or was on any kind of hair regrowth therapy for last 3 months. The impact of PRP treatment on follicle growth, type of grafts, length of hair shafts, activity of dormant follicles and redness on scalp were evaluated [Table 2].{Table 2}

Follicle growth

Follicle growth means percentage of grafts in actively growing phase at the time of inspection. Clinical images at 2 weeks post-transplant served as 100% reference density as the transplanted follicles were actively growing at 2 weeks. This is succeeded by catagen or dystrophic phase where there is fall of transplanted follicles leading to reduced density followed by gradual restoration of density over next few months. Various densities at interval of 4 weeks, 8 weeks, 3 months and 6 months were evaluated and compared clinically and using photographs with this 2 week baseline image and assessed as <25%, 25–50%, 50–75% and >75% accordingly. In PRP treated group, after 1 month 60% of the patients ($n = 12$) showed >75% density in comparison to none in non-PRP group. The difference was statistically highly significant with $P < 0.001$. After 6 months of hair transplant, all the patients ($n = 20$) had more than 75% follicle growth, wherein non-PRP group only 20% ($n = 4$) of patients showed more than 75% growth and rest 80% of the patients had follicle growth in the range on 50–75% [Figure 3] and [Figure 4]. PRP-treated group showed much denser and lengthier follicle growth as compared to non-PRP treated group, and difference was again statistically highly significant [Figure 5] and [Figure 6]. Activity in dormant follicles as fine vellus hair along the thick transplanted hair was seen as early as 3 months in PRP group in all twenty subjects as compared to non-PRP group where this activity was seen in 13 subjects at 4 months onwards.{Figure 3}{Figure 4}{Figure 5}{Figure 6}

Type of grafts

In PRP-treated group, the number of patients having multiple grafts was significantly higher as compared to non-PRP treated group.

After 3 months of hair transplant, in PRP group, all the twenty patients had multiple grafts erupting out in areas compared to the ones at 2 weeks baseline images. Whereas in non-PRP group, only 60% of patients had multiple grafts which increased to 80% at 6 months when compared with 2 weeks baseline images. The difference at 3 months was statistically highly significant ($P = 0.001$) [Figure 5].

Length of shafts

The length of hair mentioned is not the length of longest hair but of the erupting hair recorded in video microscopic images. The cut-off value of 10 mm was selected as this is the maximum length supported by video microscopic images. While more than 10 mm length is being mentioned, many of these would be much more than 10 mm in actual length as is visible in clinical images.

After 6 months of hair transplant, in PRP-treated group 65% ($n = 13$) of the patient had more than 10 mm hair shaft length. While in non-PRP treated group, only 10% ($n = 2$) of the patient had more than 10 mm shaft length [Figure 6]. Remaining 35% ($n = 7$) in PRP group showed the follicle length of 6–10 mm whereas in non-PRP group 65% ($n = 13$) showed 6–10 mm length at 6 month. The difference was statistically highly significant ($P < 0.001$). Transplanted hair grow at a slower pace as compared to normal hair (1.25 cm/month for normal hair) and it is a common observation that many clients do not need a frequent hair trimming over transplanted area as compared to donor area which requires regular trimming.

Impact on scalp redness

At 4 weeks, all the patients in PRP group showed scalp redness over recipient area in comparison to 70% in non-PRP group. In PRP-treated group, after 3 months of hair transplant, only 5% of patients had scalp redness whereas, in non-PRP treated group, 30% of patient had scalp redness [Figure 7].{Figure 7}

After 6 months, in PRP-treated group, no patient had scalp redness whereas, in the case of non-PRP group, 10% of patients still reported scalp redness. Comparative images over 9 months post transplant have been shown non PRP and PRP group in [Figure 8] and [Figure 9], respectively.{Figure 8}{Figure 9}

Discussion

Male androgenic alopecia is one of the most prevalent dermal disorders in males.[7] It is also referred to as male pattern baldness as it happens in specific pattern and it impacts adolescents as well as adults. Polygenic heredity is considered to be its cause; in addition male, hormone testosterone plays a major role. Hormone binds to androgenic receptor on hair follicle leading to early entry to telogen phase and inducing hair fall.[8] PRP is rich in many growth factors and proteins. It is very rich in PDGF, epidermal growth factor, transforming growth factor, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and various pro and anti-inflammatory cytokines such as interleukin 4 (IL-4), IL-8, IL-13, IL-17, tumour necrosis factor alpha and interferon alpha.[8] These growth factors may induce an internal signal-transduction pathway, unlocking the expression of a normal gene sequence of a cell thereby initiating and improving tissue regeneration process.[5],[6],[7],[8]

Data present in this manuscript clearly suggests that PRP treatment during the hair transplant plays a significant role in hair re-growth, and it remarkably improves density and quality of hair growth. As shown in [Figure 3] and [Figure 4], all patients in PRP-treated group had more than 75% follicle growth whereas in non-PRP treated group only 20% of the patient showed more than 75% follicle growth. The catagen loss in transplanted hair reduced significantly at 1 month interval though there was a delayed fall but not as severe as in non-PRP group.[5] The fall was noticed as breakage of hair strand just above skin surface rather than actual shedding of transplanted hair in these cases. This can be explained by the effect of growth factors on the newly transplanted hair. Furthermore, the new growth of follicles was noticed as early as 2 months in video microscopic images [Figure 10]. In contrast in the study by Uebel et al., new anagen hair started after 4 months of transplant. Only the length of newly growing follicles was studied in video microscopic images, so maximum length attained may not be commented upon. Since most of the clients that showed more than 10 mm length, even the trailing anagen hair got activated at around 4–5 months to sport a length of 10 mm or more. On the other hand in non-PRP group, 65% (No. 13) clients showed the length of follicles 6–10 mm at 6 months meaning most of these trailing follicles entered anagen phase more recently [Table 2]. The difference could be attributed to injected PRP therapy in our study compared to submersion of grafts in PRP in the above-mentioned study. The injected therapy could be better as there is less wastage, added benefit of faster recovery of skin, activity of dormant follicles and faster entry into the new anagen hair. [Figure 10] shows video microscope image at 2 months showing new anagen hair in centre and activity of dormant follicles in the periphery. It may be inferred that spontaneous apoptosis of 15–30% hairs mentioned by Uebel et al. can be reduced by injected PRP significantly with PRP induced new vessel formation and effect of growth factors on stem cells of bulge region and mesenchymal cells in dermal papillae. The combination of growth factors plays pivotal role in tissue repair, and regeneration and presence of plasma proteins act as a scaffold in epithelial migration. The effect may result into anagen hair growth as early as 2 months.{Figure 10}

The quality of hair was better in PRP-treated group as compared to non-PRP group. In PRP group, multiple erupting roots from the graft as early as 3 months besides lengthier shafts clearly suggest the role of growth factors in PRP in stimulating as well as nourishing transplanted follicular unit grafts [Figure 8] and [Figure 9]. However, we did not compare the exact diameter in the two groups, which is a limitation in this study.

PRP is the source of various growth and regulatory factors involved in cells growth and differentiation.[9],[10],[11] PRP not only induces growth but also improves cell survival by its anti-apoptotic activity. Activated PRP stimulates growth and differentiation of stem cells in hair follicle bulge along with activation of mesenchymal cells in dermal papilla. It stimulates transcriptional activity of b-catenin responsible for differentiation of stems cells to hair follicle cells. PRP is reported to stimulate Bcl-2 regulatory protein levels, which possess anti-apoptotic activity and prolongs survival of derma papilla cells.[11] This effect was clearly observed in vivo and in vitro study by Rinaldi et al. where they observed prolongation of the anagen and shortening of the catagen and telogen phase due to the effect of PRP released growth factors.[12] PRP is also reported to activate AKT and ERK signalling pathways to protective dermal papilla cells from apoptosis. PRP up-regulates FGF-7 growth factors, which are known to stimulate hair growth.[13] VEGFs and platelet-derived growth factors contribute in increasing peri-follicular vasculature thus, improving the blood supply and nourishment to the transplanted grafts.[14],[15],[16] This was also evident in our 1-month results where redness was more marked in PRP group due to new vessel formation but after 3 months, most of the patients had recovered from scalp redness whereas in non-PRP group 30% of the patient still reported scalp redness [Figure 11]. PRP has already been reported to augment tissue repair and regeneration process. Activity in dormant hair follicles was significantly high in PRP group which can again be explained by normalisation of scalp milieu with reduced fibrosis and neovascularisation secondary to the action of FGF and VEGF, which facilitated significantly higher activity in PRP group.{Figure 11}

Overall, PRP therapy improves the skin milieu of grafted area by cell growth and differentiation, anti-apoptotic activity and neovascularisation making grafted area more receptive and fertile for newly transplanted hair. It also helps in providing conducive environment for dormant hair follicles leading to their activity and appearance of new anagen hair as early as 2 months.

Our study is the first reported study observing various aspects of hair transplant from follicle growth and density, catagen loss of transplanted hair, re-growth of transplanted hair, type of graft, length of shafts, activity of dormant hair follicles and post-surgical healing over a period of 6 months.

Some researchers believe that the comparison between the two groups should be on half and half side of scalp rather than on different subjects. Since this study was based on injected PRP therapy, there will be a possibility of diffusion of plasma into the control side and thus confounding the outcome. Moreover, hair transplant is an aesthetic procedure and we as clinician need to understand the implications of attaining and justifying variable densities on two sides of the scalp. Hence, in the quest of achieving better results for our future clients, whether it is justified to give aesthetically unpleasant result to present ones is again debatable!

The limitation in the study is that exact hair count is not performed as can be done with more sophisticated equipment like cross-sectional trichogram, though we have taken serial video microscopic images. Future studies may be directed to achieve more objective evidence using these equipment.

Conclusion

This study clearly demonstrated impact of PRP treatment during and after hair transplant and its beneficial effect on quantity and quality of hair re-growth. Intra-operative injectable PRP therapy is beneficial in giving faster density, reducing the catagen loss of transplanted hair, early recovery of the skin, faster appearance of new anagen hair in FUE transplant subjects and also activating existing dormant follicles.

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Conflicts of interest

There are no conflicts of interest.

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