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Follicular unit extraction and Hair Transplantation in Cicatricial Alopecia using Platelet rich plasma

Samar Makarem Mohamed, Mohamed Hassan Mohamed Abd El-Aal , Ayman Fekry Mehana

Plastic, Reconstructive, Hand, Microsurgery Department, Faculty of Medicine, Zagazig University, Egypt

Email: Samar.makarem@gmail.com

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Abstract: Background: Disturbed self-perception and bad psychological conflict could be resulted from a disease or other conditions that cause hair loss e.g. cicatricial alopecia. Hair transplantation could be used for scar camouflage in hair bearing areas of the head and neck and can provide restoration not obtainable with other methods, and that could change the lives of patients and restore them to the premorbid condition. However, hair transplant in scarred tissues is challenging because of the degenerative changes and decreased vascularity of these areas, consequently may produce a lower survival rate of transplanted hair. Platelet rich plasma (PRP) is considered as an alternative way for delivering concentrated growth factors (GFs) to the healing site. This cocktail of GFs released from platelets is essential in modulation of tissue repair and regeneration. The PRP was used along with hair transplantation demonstrating an increase in the follicular density after 7 months of follicular unit transplantation (FUT), by keeping follicular grafts in PRP for 15 minutes before implantation, with saline as the control. The PRP with its action of tissue regeneration and remodeling with angiogenesis has the potential to revitalize the scarred tissue, improve its vascularity to make it more receptible for transplant and help increase the donor yield. Such PRP can serve as adjuvant to hair transplant in compromised recipient areas as seen in post burn alopecia.

Keywords: Follicular unit extraction, Hair Transplantation, Platelet rich plasma.

Introduction

Disturbed self-perception and bad psychological conflict could be resulted from a disease or other conditions that cause hair loss e.g. cicatricial alopecia **(1).**

Hair transplantation could be used for scar camouflage in hair bearing areas of the head and neck and can provide restoration not obtainable with other methods, and that could change the lives of patients and restore them to the premorbid condition **(2).**

Before considering hair transplantation in cicatricial alopecia cases, the condition have to be stationary, and the scarred tissue needs to be mature, ideally including some substance and pliability. Also, hypertrophic or keloid scars should be treated to provide a tissue bed that is at the same level as like the surrounding skin before transplantation **(2).**

However, hair transplant in scarred tissues is challenging because of the degenerative changes and decreased vascularity of these areas, consequently may produce a lower survival rate of transplanted hair **(2).**

Many investigators have observed that due to the fact of their small size and low metabolic requirements, hair grafts could grow well in scars even in large areas of burns and thin skin**;** however, care has to be taken to minimize further compromising blood supply **(*1*)**.

Special techniques include limiting the use of adrenaline in the recipient bed because it could reduce the blood supply and consequently the graft survival**.** The use of tumescence and or fat grafting before the placement of grafts into very thin skin or areas of skin grafts has been used by some surgeons who have observed that these techniques may help in proper placement and optimal growth of grafts in these attenuated tissues **(2).**

Many investigators recommended using topical minoxidil (2-5%) on the recipient cicatrized tissue for 2 weeks before, and at least for 5 weeks after hair transplantation process. Benefits of using minoxidil include enhancing the blood flow to the attenuated scarred tissues due to its vasodilatation effect, also long lasting the anagen phase and graft survival improvement **(3).**

Other investigators recommended to use Pentoxifylline 400 mg three times daily, for 2 weeks before the process with the aim of expanding oxygenation of the scalp tissue **(4).**

Also, thermal ablative lasers were reported to be helpful in obtaining esthetically accepted results, and faster wound healing. This could be explained by the new vascular formation, specific growth factors and cytokines occurring during the process of wound healing after using laser therapy **(4).**

Barrera has also noted an improved clinical appearance of the scar, including texture, thickness, and pliability, after transplanting hair grafts directly into scar tissue, and that could be explained by the presence of stem cells in the follicular units **(2).**

Many authors have reported the use of PRP as an adjuvant therapy with hair transplantation to improve the cutaneous ischemic conditions and increase the vascular structures around hair follicles **(5).**

PRP treatment together with hair transplant was reported to have a beneficial effect on quantity and quality of hair re-growth. It helps also to give better density, minimizing the catagen loss of transplanted follicles, early recovery of the skin, and earlier appearance of new anagen hair in FUE transplant subjects. Autologous fat grafting at the recipient scarred area was reported to be used in combination with hair transplantation by the FUE method minimizing scar size, improving its depression, and increasing quality and pliability of scar tissue **(5).**

In cicatricial alopecia cases, it is not easy to decide the number of incisions (grafts/cm2) to be created in the scarred recipient area. In non-cicatricial alopecia cases, its recommended to transplant up to 25- 30 Follicular Units (FU) per cm2. In scarred tissues, there is a diminished vascular supply, so it is important to transplant at a lesser density, e.g., 20 FU/cm2 **(1).**

Pathomvanich and Imagawa (1) have recommended to stage the reconstruction when dealing with large areas of alopecia, they advised to graft the most peripheral areas with the best blood supply first followed by the centermost regions at a second stage **(1).**

The transplanted hair density will be much lower than the surrounding hair bearing area, however, this outcome will still be fairly enough to camouflage the area of scarring **(1).** Usually, one to three sessions over the course of 6 to 18 months will be required to achieve optimal aesthetic results **(2).**

Diminished tissue perfusion in the scarred areas results in poor growth of the transplanted grafts, it could also cause ischemic injury to the recipient area; that may end with infection or necrosis **(6).**

It is necessary to make a decision whether the vascular supply of the recipient bed is good enough to allow for adequate perfusion to the transplanted grafts.

To test the blood supply of a large area, authors recommended anesthetizing part of that large area with a 2% lidocaine solution without use of adrenaline at first, Then to perform several incisions using a 19-G needle. There should be an evidence of bleeding when this is done. If not, it would be better for that area to be treated with surgical excision **(4).**

<u>Special considerations of hair transplantation according to the recipient site location</u>

The goal of hair transplantation is to mimic the natural hair pattern in the area of alopecia that aligns and blends into its surroundings **(7).**

1-The scalp

In scalp hair transplantation, it is better for the recipient sites to be created in such a way that the angle (the anterior-posterior direction of a recipient site) and the direction (the radial pointing either forward or laterally to one side of the recipient site) are done to mimic natural hair growth on the head **(7).**

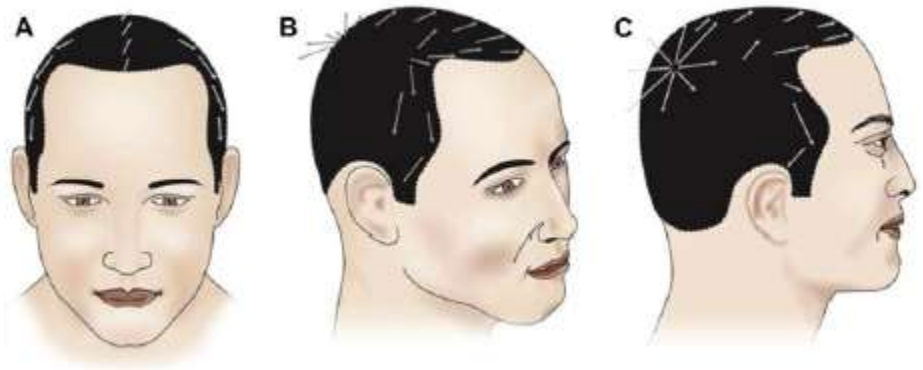

Figure 1: (A–C) How hair grows differently in the various regions of the scalp, which will dictate how recipient sites are created to ensure natural results (7).

In addition, all of the recipient sites must have a very low angle (i.e., low anteriorly), and that could be maintained by having the patient in a fully supine position, which will help the surgeon's hand to fall into a very low anterior angle for site creation **(7).** Furthermore, it's better for the recipient slits not to be created in a parallel fashion, but to be tightly interlocked; that is, each successive row of recipient sites should be staggered from the one in front of it. That would help to achieve a better visual density and also the grafts will appear to be arranged more tightly **(7).**

The graft must remain angled in a correct way during its insertion so that the natural curl of the hair faces forward and down. The curl refers to the fact that each graft curls as it exits the epidermis **(7).**

The right depth should be kept in consideration too, typically about 1 to 2 mm above the surrounding native tissue, because they will sink when the edema fades. It is important that the grafts do not sit flush to the skin because they will sink inward and cause pitting, which will appear as small depressions in the skin at the insertion site. If they sit more than 2 mm above the surrounding skin they can cause a cobblestoned appearance, or the graft may desiccate and die **(7).**

Another potentially mistake is to "piggy-back" one graft over another, which can cause buried grafts underneath and engender cysts **(7).**

2- The Eyebrow

Eyebrows are the most expressive feature and create a master line of the face **(8).** The eyebrows are divided into three sections. The head which is the inner most portion that lies mostly below the orbital margin with the hairs in this region vertically oriented. The body which is the central most dense and wide part that lies along the orbital margin with hairs oriented obliquely or horizontally. The tail which is the outer part that lies above the orbital margin **(8).**

Figure 2: Direction and angle of eyebrow hair (www.scottsdaleinstitute.net)

Aesthetic landmarks:

Westmore, 1975, described the most acceptable concept of the ideal brow **(9).**

The medial brow end should begin on the same vertical plane as the lateral extent of the ala and the inner canthus (A–B) **(9).**

The medial brow extends laterally (C) at an oblique line drawn from the most lateral point of the ala (A) through the lateral canthus **(9).**

The medial and lateral ends of the brow (B, C) lie approximately at the same horizontal level **(9).**

The apex lies on a vertical line (D–E) directly above the lateral limbus of the eye at approximately the junction between the medial 2/3 and the lateral 1/3 of the eyebrow **(9)**

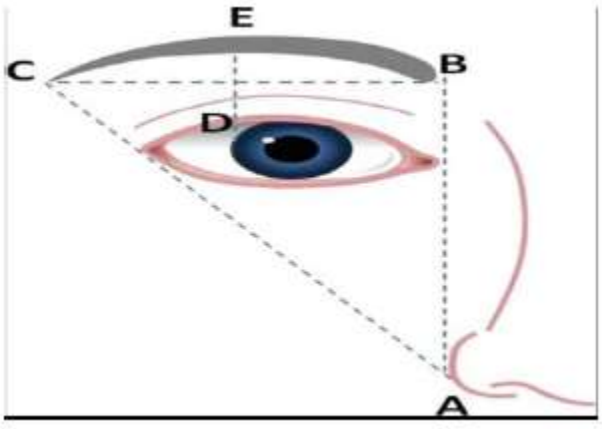

Figure 3: Ideal brow shape (9)

The ideal position of the eyebrow and its forms is different between females and males. The female eyebrow is more arched and rests above the superior orbital rim within slightly several millimeters with a club-shaped medial portion. The arch of female eyebrows peaks at its lateral portion. The male eyebrow is less arched and lies just over the superior orbital rim. It's heavier and thicker than the female eyebrow **(10).**

The hairs of the female eyebrow are fewer in number and more regular than those of the male eyebrow **(10).**

An average distance from top of the eyebrow to the mid-pupil is 2.5 cm (range of 2.3-2.9 cm) and the distance from the top of the brow to the anterior hair line is 4.8 cm (range from 4 to 6.2 cm). The distance between the upper lid crease and the lower edge of the brow is 15 mm described this distance as 1.6 cm **(11).**

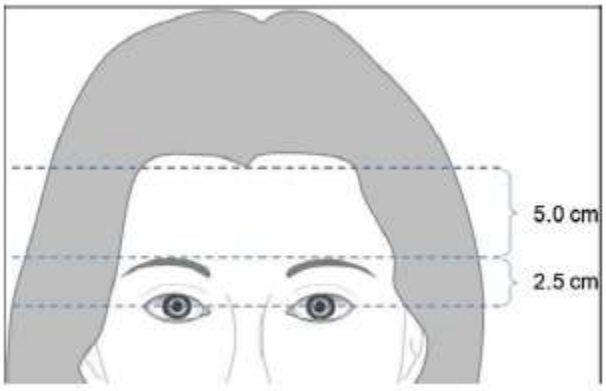

Figure 4: The distance from midpupil to the top of the brow (12)

3- Beard and moustache transplantation

In the beard and moustache, the direction of growth is essentially caudal, somewhat anterior along the upper cheek region with an angle closely parallel to the skin **(12)**

The hair on the face does not grow in follicular units, and single hair grafts should be used when transplanting the beard, while two to three hair grafts may be used toward the center of the moustache to improve density **(2).**

Although variations occur, generally the angle the hairs make with the skin is as shallow as possible and the direction of growth is directly downward. On the mustache, the hairs will grow slightly laterally, which usually continues as the mustache extends downward along the lateral aspect of the mouth, where it then becomes the lateral goatee along the jowl region **(13).**

One of the most important keys to achieve a natural appearing result is angling the recipient sites so that the transplanted hairs grow as flat as possible to the facial skin to avoid them sticking out from the face.

This goal is best achieved by the use of the smallest possible recipient site blades, which minimizes the rotational movement of the grafts with healing, thus keeping them at the intended angulation. It is imperative to keep the blade handle at this shallow angle to the facial skin, especially in the mustache, where the lip border often slightly protrudes because of the normal shape of the lip, which can undesirably push up on the blade handle **(13).**

Because the immediate results are very close to what will be the final result, this allows the patient to assess the shape and density of transplanted areas, permitting feedback and making desired alterations before the procedure is complete **(13).**

Platelet rich plasma

Platelet rich plasma (PRP) is considered as an alternative way for delivering concentrated growth factors (GFs) to the healing site. This cocktail of GFs released from platelets is essential in modulation of tissue repair and regeneration **(14).**

Alfa granules of the platelet are considered as a rich source of anagen-maintaining factors such as platelet derived growth factors (PDGF (AA, BB, and AB)), fibroblast growth factors (FGF), transforming growth factors TGF (b1 and b2), insulin-like growth factor (IGF)-1, vascular endothelial GF (VEGF), epithelial GF (EGF), hepatocyte growth factor and a mixture of the other fundamental GFs. Other substances identified in the secretion of alpha granules include osteonectin, von willebrand factor and proaccelerin **(15).**

On platelet activation, the pre-packed GFs becomes degranulated, secreted and attached to their transmembrane receptors expressed over adult osteoblasts, fibroblasts, MSCs, epidermal cells and endothelial cells **(14).**

This further enhances an internal signal transduction pathway, unlocking the expression of a normal gene sequence of a cell like cellular proliferation, matrix formation, osteoid and collagen synthesis **(14).**

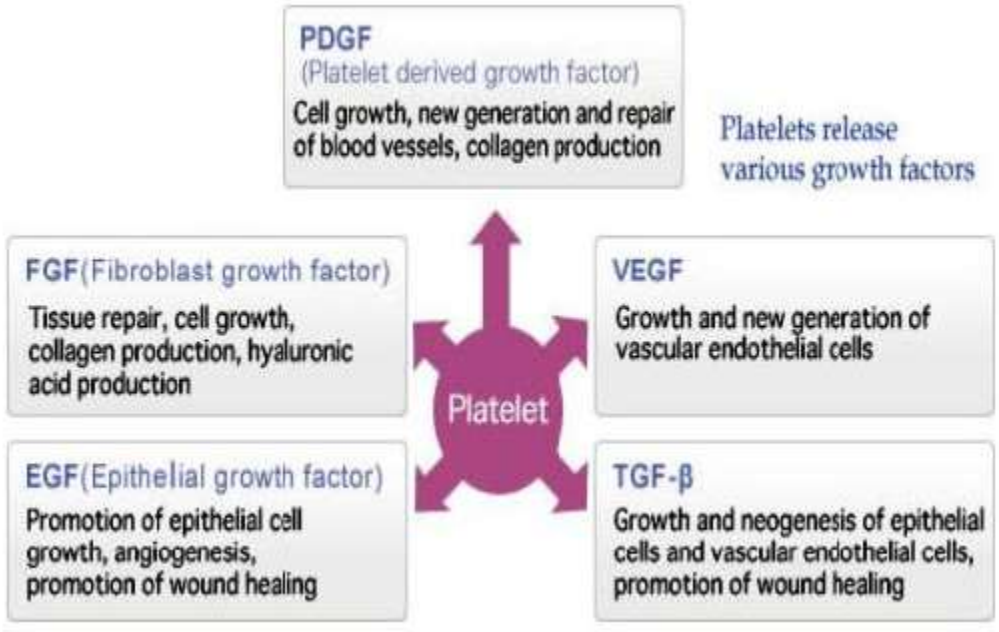

Figure 5: Growth factors by the platelets and their different effects (16)

It has been demonstrated that the application of active platelet gel to surgical sites reduces erythema, crusting, and swelling. Furthermore the Vascular endothelial growth factor 8 (VEGF8) and platelet derived growth factor 4 (PDGF4) found in PRP are known to facilitate angiogenesis around the hair follicle, and this may be one mechanism underlying observations that PRP can foster robust hair growth **(17).**

The PRP has been used either as a graft holding solution or injected into the recipient bed and donor area. In researching the effects of PRP in hair transplantation, Uebel found a significant benefit to graft survival, and Greco observed enhanced healing and earlier hair growth **(18).**

<u>Preparation of activated PRP:</u>

Platelet rich plasma is prepared either manually or by the use of automated devices. The process must be carried out under strict aseptic conditions and optimum temperature i.e., 20-22°C. Briefly, venous blood is collected from the patient shortly before starting the injection procedure. 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. Storage of the blood should be avoided for the fear of loss of platelet activity. 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 **(18).**

The manual method:

The PRP was made with using a two-step centrifugation process on at room temperature. Venous blood was obtained from the patient then put in the PRP tube containing anticoagulant like sodium citrate. Centrifugation is done at 1000 rpm for 10 minutes. The whole plasma, the buffy coat and the superficial RBCs are aspirated from all the tubes in a 5ml syringe then redistributed into 2 plain tubes. Re-centrifugation at 2000 rpm for another 10 minutes is done. The lower 1/4 of plasma is withdrawn into 1 ml syringes and becomes ready for injection **(10).**

Three protocols were analyzed for preparing PRP samples with variable compositions: a reduced both platelet and WBC concentration with 1 spin step at 1500 rpm lasting for 5 min (10 mL whole blood); a high both platelet and WBC process with 1 spin step at 3200 rpm lasting for 15 min (27 mL whole blood); ahigh platelet and low WBC concentration with a double-spin process (1500 rpm for 5 min and 6300 rpm for 20 min) **(10).**

The active secretion of prepackaged GFs begins within 10 minutes of clot initiation and 95% of the secretion is completed within 1 hour **(18).**

Hence, PRP must be used on the treated site within 10 minutes of activation. The concentrated platelets remain viable for up to eight hours and sterile if placed on a sterile surgical table**.**It's proved that double spin process shows higher platelets concentration than the single spin process do **(11).**

The American Association of Blood Banks technical manual in 1999 stated that PRP 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 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, in order to make the platelets to be spun down and separated as a pellet at the bottom of the tube from platelet-poor plasma (PPP) above **(8).**

Calcium chloride ($CaCl_2$), thrombin or fibrinogen can be used as an "activator" to trigger coagulation and hence degranulation of GFs to yield "activated PRP" **(8).**

Use of these activators needs supervision and control to avoid cardiac arrhythmias and thrombosis **(14).**

Delivery of PRP without an activator is feasible because platelets are triggered to release growth factors and cytokines by exposure to derived collagen **(19).**

There is currently disagreement in the literature over whether the presence of WBC in PRP provides any benefit. Proponents of PRP containing high WBC concentrations believe that the presence of WBC provides natural protection against infections and allergic responses **(7).**

Other authors do not recommend the presence of high WBC concentration in PRP. The presence of neutrophils, which are 65% of WBC and more than 95% of granulocytes, may be harmful because they destroy surrounding tissue, even if the tissue is not injured. These neutrophils release nonselective and toxic reactive oxygen species (ROS) **(15).**

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. Although time saving, these adapted kits can be quite expensive as compared to the manual process. Various devices have been approved by 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. **(17).**

Concentration of PRP:

The mean blood platelet level is 200,000±75,000 /µL. 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 regarded as the therapeutically effective concentration of PRP **(15).**

PRP and hair transplantation:

PRP serves as an adjuvant to hair transplant in compromised recipient areas**.** Injection of PRP has been demonstrated to improve cutaneous ischemic conditions and to increase vascular structures around hair follicles **(5).**

In cicatritial alopecia, it was observed that the quality of scarred tissue improved after transplant, as in the skin atrophy appeared to have reduced in the alopecic patches. This can be possibly explained by the action of the PRP and additionally, the transplanted hair themselves cause neovascularization and dermal reorganization **(10).**

Activated PRP stimulates proliferation and differentiation of stem cells in the hair follicle bulge area via multiple molecular mechanisms: upregulation of transcriptional activity of beta-catenin leads to differentiation of stem cells into hair follicle cells, increased Bcl-2 levels (anti-apoptotic) prolongs survival of dermal papilla cells, activation of several signaling pathways that prolongs survival of dermal papilla cells, expression of FGF-7 in dermal papilla cells prolongs anagen phase of hair cycle and increased VEGF and PDGF increases peri-follicular vascular plexus **(5).**

The PRP was used along with hair transplantation demonstrating an increase in the follicular density after 7 months of follicular unit transplantation (FUT), by keeping follicular grafts in PRP for 15 minutes before implantation, with saline as the control **(20).**

During a study using PRP with hair transplant in 20 male hair pattern baldness patients, Uebel et al. found a considerably significant effect of platelet growth factors on the yield of follicular units over non PRP used conventional hair transplants **(20).**

It was suggested that the CD34+ hematopoietic stem cells mobilized in peripheral blood and further concentrated in PRP prepared using Smart PReP®, 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 **(20).**

The PRP with its action of tissue regeneration and remodeling with angiogenesis has the potential to revitalize the scarred tissue, improve its vascularity to make it more receptible for transplant and help increase the donor yield. Such PRP can serve as adjuvant to hair transplant in compromised recipient areas as seen in post burn alopecia **(21).**

Contraindications:

Absolute contraindications:

Platelet dysfunction syndrome, hemodynamic instability, critical thrombocytopenia, septicemia, local infection at the site of the procedure, pregnancy and active breastfeeding **(21).**

Relative contraindications:

Use of NSAIDs within 48 hours of procedure, corticosteroid injection at treatment site within 1 month, systemic use of corticosteroids within 2 weeks, tobacco use, recent fever, cancer-especially hematopoietic or of bone, hemoglobin <10 g/dL and platelet count <105/uL **(21).**

Safety of PRP:

Platelet rich plasma is devoid of any serious side effects for being an autologous preparation, apart from local injection site reactions e.g., pain or secondary infection, which could be avoided by adequate and proper precautions. PRP has no issues as regards transmission of infections e.g., hepatitis-B, C or HIV **(14).**

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