Evaluation of platelet-rich plasma as a treatment for androgenetic alopecia: A randomized controlled trial

Jerry Shapiro, MD,[a] Anthony Ho, MD,[a] Kumar Sukhdeo, MD, PhD,[b] Lu Yin, BA,[a] and Kristen Lo Sicco, MD[a]
New York, New York

Background: Platelet-rich plasma (PRP) shows promise as an androgenetic alopecia (AGA) treatment.

Objective: To conduct a randomized placebo-controlled split-scalp study to investigate the effects of PRP on hair regrowth and thickness.

Methods: Two 7.6-cm × 7.6-cm squares were tattooed on the scalps of 35 study participants with AGA. Areas were randomly assigned to intradermal injection with PRP or saline. Participants received 3 monthly treatment sessions with evaluation 3 months after the final treatment.

Results: Hair density in the PRP-treated area was significantly increased compared with baseline at all visits. At the final assessment, hair density in PRP-treated areas increased from 151 ± 39.82 hairs/cm^2 at baseline to 170.96 ± 37.14 hairs/cm^2, a mean increase of approximately 20 hairs/cm^2 ($P < .05$). However, hair density in placebo-treated areas also increased from 151.04 ± 41.99 hairs/cm^2 to 166.72 ± 37.13 hairs/cm^2 ($P < .05$). There was no significant difference in hair density change between the 2 groups ($P > .05$). No serious adverse events were reported.

Limitations: Possible PRP diffusion due to split-scalp study design as well as microinjections causing microinjury to both sides.

Conclusion: PRP may have benefit in increasing hair density. (J Am Acad Dermatol 2020;83:1298-303.)

Key words: androgenetic alopecia; female pattern hair loss; hair; male pattern hair loss; platelet-rich plasma; randomized controlled trial.

Androgenetic alopecia (AGA) is the most common type of progressive hair loss.[1,2] Androgens interact with receptors on dermal papilla cells to stimulate hair growth in certain body areas and suppress scalp hair by promoting hair miniaturization and decreased anagen phase length.[2] Dermal papilla cells serve in the regulation of the production of several paracrine growth factors, including insulin-like growth factor, basic fibroblast growth factor, and vascular endothelial growth factor, that stimulate hair growth. In AGA, hair becomes thinner and shorter, resulting in a bald appearance.[3]

Although AGA is highly prevalent, approved therapeutic options are limited, with potential adverse effects including teratogenicity. Finasteride is commonly used to treat male AGA and is used off-label for female AGA. Topical minoxidil is approved for both male and female AGA, and several double-

From the Ronald O. Perelman Department of Dermatology, New York University Grossman School of Medicine[a]; and Pilaris Dermatology.[b]

Funding sources: This study was funded by Regen Lab SA (Le Mont-sur-Lausanne, Switzerland).

Conflicts of interest: Dr Shapiro is a consultant for Aclaris Therapeutics, Incyte, and Replicel Life Sciences and is principal investigator for Regen Lab. Dr Lo Sicco is a coinvestigator for Regen Lab. Authors Ho, Sukhdeo, and Yin have no conflicts of interest to declare.

IRB approval status: The New York University Grossman School of Medicine Institutional Review Board reviewed and approved this study.

Accepted for publication July 4, 2020.

Reprints not available from the authors.

Correspondence to: Jerry Shapiro, MD, Ronald O. Perelman Department of Dermatology, New York University Grossman School of Medicine, 530 1st Ave, #7R, New York, NY 10016. E-mail: Jerry.Shapiro@nyulangone.org.

Published online July 9, 2020.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.07.006

blinded, randomized, placebo-controlled trials have established its efficacy.[1]

Because impaired cell signaling and altered growth factor and cytokine production contribute significantly to AGA, there is great interest in the use of platelet-rich plasma (PRP), a blood product rich in growth factors and other molecules, for AGA treatment. PRP is made by separating platelets and plasma from other blood components and is defined as the portion of the plasma having a greater platelet concentration than whole blood. The biologic activity of PRP is based on the ability of platelets to release numerous growth factors from α-granules, conferring regenerative properties.[4]

CAPSULE SUMMARY

- This double-blinded randomized controlled study adds rigorous evidence to existing literature on platelet-rich plasma treatment of androgenetic alopecia to elucidate its efficacy and optimal protocols.
- Hair density increased after platelet-rich plasma treatment, although not significantly greater than placebo. Treatment is potentially efficacious, although further studies comparing to placebo are necessary.

Several clinical studies have shown PRP improves hair density and hair thickness in the early stages of AGA, likely through modulation of the hair cycle signaling pathways.[5-7] Histologic changes in PRP-treated scalp, such as increases in the number of follicular bulge cells and follicles, epidermal thickening, improved vascularization, and a higher number of $Ki67^+$ keratinocytes, have been observed.[8-10] Though PRP seems to be most effective at the early stages of AGA,[11,12] PRP can be used in later stages as an adjunct to other therapies, such as follicular unit transplantation, to reduce inflammation and facilitate establishment of new follicles.[13,14]

An on-going issue regarding the use of PRP for AGA is that neither a standard dose nor protocol has been established. Treatment standardization is a challenge due to the varied PRP preparations and protocols currently used and to the different measures evaluating outcomes in studies. A recent review and meta-analysis of 23 studies revealed at most 4 used a common PRP preparation method, and even they differed in injection frequency, injection depth, and whether activated or nonactivated PRP was used.[15] Clarifying the optimal PRP protocol is of great importance, because it seems likely that different doses or concentrations of particular growth factors and other molecules may be required depending AGA stage.[16]

To address these issues, we have initiated controlled clinical trials to determine the optimal protocols for PRP treatment of AGA. Here we report the results of our first clinical study evaluating changes in hair density of patients with AGA treated with a standardized nonactivated PRP treatment compared with placebo in a split-head study. Secondary objectives included changes in hair diameter and treatment safety and tolerance.

MATERIALS AND METHODS

Patient population

This study, conducted at New York University Langone Health, enrolled 35 individuals (17 women and 18 men) aged 18 to 58 years with Norwood-Hamilton stage 3 to 5 male AGA or Ludwig stage 1 or 2 female AGA. AGA was confirmed clinically by 2 board-certified dermatologists (K.L. and J.S.). The same dermatologists enrolled patients from August 2017 through December 2018, with the last follow-up visit in April 2019. Participants did not use any pharmacologic AGA treatment for 3 months before enrollment. Exclusion criteria were participants with a history of hair transplantation, facial cancer, hematologic/coagulation disorders, hemodynamic instability, participants who presented with an acute infection or autoimmune disease, pregnant or breastfeeding women, and participants undergoing chemotherapy or anticoagulant therapy. Participants taking aspirin or other nonsteroidal anti-inflamma-tory drugs were allowed to participate after discontinuing use 7 days before beginning treatment. Participants taking vitamin E supplements were also allowed to participate, provided use was discontinued 14 days before beginning treatment.

PRP preparation

Whole blood (10 mL) was taken from the antecubital vein using the Regen Blood Cell Therapy kit (Regan Lab, Le Mont-sur-Lausanne, Switzerland). The blood was centrifuged at 1500*g* for 5 minutes in a Drucker centrifuge (model 642VFD-PLUS; Drucker Diagnostics, Port Matilda, PA). The tubes contained a thixotropic gel allowing separation of the PRP portion from other blood components. The PRP is found above the separating gel with visible platelets as a cellular deposit that is resuspended in plasma by gently inverting the tube. PRP was collected using a transfer device connected to a 5-mL syringe for injection. Almost 5 mL of PRP was prepared from 10 mL of whole blood. To ensure investigator blinding, PRP and placebo products

Abbreviations used:

AGA: androgenetic alopecia
PRP: platelet-rich plasma

were prepared by a licensed physician or a certified phlebotomist in blinded syringes.

Treatment

On each side of the scalp, a 7.6-cm × 7.6-cm square was tattooed and designated A or B. We selected for areas with similarly thin hair positioned symmetrically on opposite sides of the affected scalp. Randomization assignments of scalp areas to PRP or placebo treatment were made sequentially according to a randomization table prepared by Regen Lab staff. Allocations were sealed in opaque envelopes. Participants and investigators were both blinded.

At the initial visit, specially trained study personnel otherwise unrelated to the study opened the envelope and prepared 2 blinded syringes labeled A and B according to randomization. The investigator then sequentially administered both treatments. Before the injection, the scalp was disinfected and anesthetized with topical lidocaine cream if the participant requested. The placebo and PRP were injected at a depth of 3 to 4 mm (angle, 35°-45°) at a quantity of 0.1 to 0.2 mL per injection/cm^2 of the treated area. Excess product was allowed to dry on the scalp. Participants were requested not to wash their hair for 4 hours after treatment. Participants received 3 treatment sessions at 1-month intervals, with a final follow-up visit 3 months after the last treatment (Fig 1).

Assessment criteria

Objective. Hair density and mean hair shaft diameter were assessed by Folliscope (Lead M, Seoul, South Korea). Photography was obtained at baseline and each subsequent visit. One investigator (A.H.) performed the quantitative measurements in a blinded manner.

Investigator assessment. Investigators used an Investigator Global Assessment questionnaire to compare photographs taken at baseline to photographs taken at the last visit.

Self-assessment. Quality of life was assessed using a quality of life questionnaire at baseline and each subsequent visit.

Patient satisfaction. Treatment tolerance was assessed globally using a 10-point visual analog scale. Efficacy, safety, and patient satisfaction were evaluated according to a 4-grade scale ("very satisfied," "somewhat satisfied," "somewhat dissatisfied," "very dissatisfied") at the final visit.

Statistical analysis

Statistical analyses were performed using SPSS 18 software (SPSS, Chicago, IL). Descriptive statistics or frequency tables, or both, were provided for all baseline variables, efficacy, tolerance, acceptability and safety variables, as appropriate. The Wilcoxon signed rank test, a nonparametric statistical hypothesis test, was used as an alternative to the paired Student *t* test when the population could not be assumed to be normally distributed. The McNemar test was used when the data were nominal.

Primary efficacy analyses

The primary efficacy analysis was performed using the Wilcoxon signed rank test. Data were compared between the PRP- and placebo-treated sides of the scalp to evaluate changes in hair density.

Secondary analyses

Changes of hair diameter in AGA scalp treated with PRP compared with placebo were evaluated with the paired Student *t* test.

Other analyses

The Wilcoxon signed rank test was used to analyze change in the subjective Investigator Global Assessment from baseline to the last visit. The mean score obtained with PRP treatment was compared with the score obtained with placebo. The

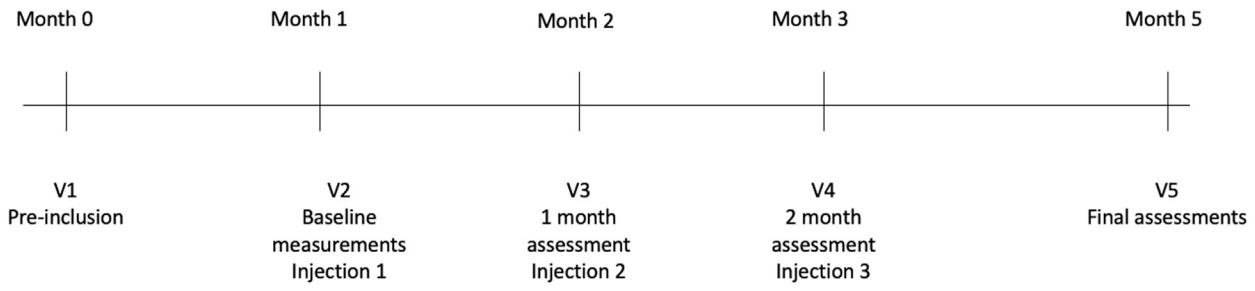

Fig 1. Treatment and assessment timeline. *V*, visit.

Wilcoxon signed rank test was used to analyze tolerance and acceptability for each participant. Results are summarized with descriptive statistics, including percentages and frequencies. Quality of life questionnaire scores were analyzed with a repeated analysis of variance (mixed model for repeated measures).

RESULTS

Demographics

Thirty-five patients with a mean age of 36.5 years participated in the study (Table I). Twenty-one participants previously underwent hair loss treatment.

Changes in hair density

Hair density in the PRP-treated area increased from 151 ± 39.82 hairs/cm^2 to 170.96 ± 37.14 hairs/cm^2, a statistically significant increase of approximately 20 hairs/cm^2. Hair density was significantly increased at each visit compared with baseline; however, the increase in hair density was not significantly greater than the increase in hair density in the placebo group. Hair density in placebo-treated areas was significantly increased over baseline after visit 4 (Fig 1; Table II), with an ultimate increase of approximately 16 hairs/cm^2, from 151.04 ± 41.99 hairs/cm^2 to 166.72 ± 37.13 hairs/cm^2 (Table II).

Hair diameter

The mean hair diameter increased from 56.75 ± 11.62 μm to 61.23 ± 13.12 μm in the PRP-treated area and from 56.43 ± 10.63 μm at baseline to 62.63 ± 13.41 μm in the placebo-treated area. Both of these increases were statistically significant compared with baseline, although no significant differences in hair diameter were observed between the PRP and the placebo-treated areas at any visit.

Table I. Demographic data of patients at baseline

Variable	No. (%) or mean ± SD (range)
Age, y	36 ± 11.01 (18-56)
Sex	
Male	18 (51.43)
Female	17 (48.57)
Androgenetic alopecia type	
Norwood classification (male pattern hair loss)	
Class 3	13 (72.22)
Class 4	1 (5.56)
Class 5	4 (22.22)
Ludwig classification (female pattern hair loss)	
Grade I	11 (64.71)
Grade II	5 (29.41)
Unknown	1 (5.88)
Duration of hair loss, y	11 ± 9.05 (1-34)

No., number.

Investigator Global Assessment

In 23 patients there was slight or moderate improvement in the PRP-treated area, and 16 showed such an improvement in the placebo-treated area. No change in the PRP-treated area was seen in 12 patients, and no change in the placebo-treated area was seen in 16 patients. In 3 patients, the placebo-treated area demonstrated worsening.

Patient satisfaction and self-assessment

Overall patient satisfaction was 5.24 ± 2.28 on the quality of life questionnaire. Most patients did not have the impression that hair growth, quality, or strength had changed. However, 45.8% of patients noted a discrete or noticeable change in scalp appearance (increased scalp coverage with hair). Almost 86% of the patients would maybe or definitely recommend the treatment, and the same percentage would consider or definitely repeat the treatment.

The treatment was rated moderately comfortable or tolerable by 54.3% of patients, whereas 42.9% considered the treatment clearly unpleasant. The main complaint was pain (91.4% of patients). The mean score of approximately 6 on a 10-point visual analog scale did not differ between visits.

Adverse effects and events

The main reported adverse effects were pain during the procedure and sensitive scalp or head after the procedure. Few reported whole-scalp sensitivity, but most indicated sensitivity to the injection area, forehead/front/temple, or side of the scalp (Table III). Itchiness resolved in all patients except 1 within 3 days. No serious adverse events were reported.

DISCUSSION

There is interest in PRP treatment of AGA due to its low adverse effect risk and decreased treatment frequency compared with current treatments. However, despite increasing evidence that PRP can stimulate hair growth, a standardized protocol still does not exist.

This study was initiated to compare the efficacy of PRP treatment against placebo, because such studies are currently lacking.[17] Adequately controlled studies with sufficient numbers of participants are essential to

Table II. Changes in hair density and hair diameter after treatment with platelet-rich plasma (*PRP*) and placebo

	PRP		Placebo		PRP vs placebo
Variable	**Mean ± SD**	***P* (compared to V2)***	**Mean ± SD**	***P* (compared to V2)***	***P***
Hair density, per cm^2					
V2	151.00 ± 39.82		151.04 ± 41.99		>.05
V3	160.28 ± 37.25	**<.05**	154.27 ± 39.15	>.05	>.05
V4	167.35 ± 37.92	**<.05**	165.06 ± 39.06	**<.05**	>.05
V5	170.96 ± 37.14	**<.05**	166.72 ± 37.13	**<.05**	>.05
Mean increase (V2-V5)	20.00		16.00		>.05
Hair diameter, μm					
V2	56.75 ± 11.62		56.43 ± 10.63		>.05
V3	58.27 ± 9.99	>.05	58.14 ± 10.37	>.05	>.05
V4	58.88 ± 11.50	>.05	57.99 ± 12.7	>.05	>.05
V5	61.23 ± 13.12	**<.05**	62.63 ± 13.41	**<.05**	>.05

V, Visit.
*Bold *P* values are statistically significant ($P < .05$).

Table III. All reported adverse effects after injection

Variable	**Patients, No.**	**%**
Pain	32	91.4
Sensitive areas		
Whole scalp	3	8.7
Injection area	7	20.3
Crown/top	5	14.5
Forehead/front/temple	10	29.0
Side of scalp	8	23.2
Headache	7	20.0
Itching	4	11.4
Erythema	1	2.9
Dry scalp	1	2.9
Sensitive scalp	1	2.9
Swelling	1	2.9
Acne	1	2.9
Bleeding	1	2.9

No., Number.

exclude confounding factors such as interpatient and procedural variations. Interindividual differences exist in PRP growth factor concentrations, and although factors such as glial cell line-derived neurotrophic factor have been positively correlated with hair density, key growth factors and their optimal therapeutic concentrations remain to be determined.[7,18]

We found that PRP treatment significantly improved hair density between baseline and the final visits with a mean increase of approximately 20 hairs/cm^2 in the PRP-treated area compared with 16 hairs/cm^2 in the placebo-treated area. These findings are in line with the study by Ayatollahi et al[19] that reported a hair density increase of 18.84 hairs/cm^2.

Unlike Gkini et al,[12] who found hair density peaked at 3 months, at our study's 3-month follow-up (5 months after the first injection), hair density was still increasing, albeit at a slower rate than after the first injections. This may be due to nonactivated PRP allowing a sustained long-term response compared with activated PRP. The latter results in a high concentration of growth factors being delivered to the injection site, which may saturate available receptors. Most studies used activated PRP and few extended follow-up beyond 3 months after the last treatment. A 12-month study evaluating 3 treatments with plasma rich in growth factors at 1-month intervals, followed by boosters at 4 and 7 months, reported an increase of almost 40 hair follicles/cm^2 at 12 months.[9] Three PRP treatment sessions have been considered the minimum number of sessions required for treating hair loss,[20] but these 2 studies suggest that additional booster sessions are beneficial.

We also observed a statistically significant increase in hair diameter, although no significant differences were observed between the PRP and placebo groups. Takikawa et al[10] reported a statistically significant increase in hair shaft diameter compared with control at 12 weeks after 5 sessions of treatment. The number of hairs also increased in their study, but the rate of increase was less than that for hair diameter.

We did not perform scalp biopsies; however, biopsy specimens may provide additional insight into PRP's mechanisms of action in AGA. Histologic evaluation of biopsy specimens from patients with AGA before and after PRP treatment have shown increased epidermal thickness, cell proliferation, and improved vascularization.[8,9]

Although the quantitative measures did not differ significantly between PRP- and placebo-treated scalp, the blinded Investigator Global Assessment noted improvement in a greater number of PRP-

treated areas. The lack of significant differences in quantitative measures between the PRP- and placebo-treated areas may be due to vascular flow from the central scalp regions. Vascular diffusion of PRP or biomolecules released from platelets from the PRP-treated area may have enhanced results in the placebo area.[21]

Another contributing factor may be that treatment was applied to approximately 60 cm^2 areas. Other studies have used a limited area (<10 cm^2). In our study, the larger treatment zone together with PRP diffusion may have contributed to the reduced impact of PRP compared with placebo. Additional treatment sessions and a longer follow-up might have resulted in a more marked difference between the PRP- and placebo-treated areas. Wounding from the injections may have also stimulated hair growth in placebo-treated areas, similar to microneedling. Microneedling is theorized to cause hair growth through stimulation of growth factors and hair bulge stem cells along with activation of the Wnt/β-catenin pathway.[22,23]

No serious adverse events occurred. The main adverse effects reported were injection pain and postprocedure scalp sensitivity. These effects all resolved quickly.

CONCLUSION

This study used a standardized PRP preparation that was safe and tolerated. Hair density and hair diameter increased in PRP-treated scalp areas, suggesting it is a promising treatment approach for AGA, although we did not find significant differences in the quantitative measures between PRP-and placebo-treated scalp. Previous studies show PRP has a moderate effect on hair growth in patients with AGA, but comparing studies is difficult due to different PRP preparations and treatment protocols. A standardized PRP preparation is essential for result comparison and continued protocol development to improve clinical outcomes. The standardized PRP preparation used in this study may provide a basis for future developments to optimize dosage, timing, and administration of PRP for AGA treatment.

REFERENCES

1. Kelly Y, Blanco A, Tosti A. Androgenetic alopecia: an update of treatment options. *Drugs*. 2016;76:1349-1364.
2. Lolli F, Pallotti F, Rossi A, et al. Androgenetic alopecia: a review. *Endocrine*. 2017;57:9-17.
3. Kaliyadan F, Nambiar A, Vijayaraghavan S. Androgenetic alopecia: an update. *Indian J Dermatol Venereol Leprol*. 2013;79:613-625.
4. Singh B, Goldberg LJ. Autologous platelet-rich plasma for the treatment of pattern hair loss. *Am J Clin Dermatol*. 2016;17:359-367.
5. Trueb RM. Molecular mechanisms of androgenetic alopecia. *Exp Gerontol*. 2002;37:981-990.
6. Vasserot AP, Geyfman M, Poloso NJ. Androgenetic alopecia: combing the hair follicle signaling pathways for new therapeutic targets and more effective treatment options. *Expert Opin Ther Targets*. 2019;23:755-771.
7. Rodrigues BL, Montalvao SAL, Cancela RBB, et al. Treatment of male pattern alopecia with platelet-rich plasma: a double-blind controlled study with analysis of platelet number and growth factor levels. *J Am Acad Dermatol*. 2019;80:694-700.
8. Gentile P, Garcovich S, Bielli A, Scioli MG, Orlandi A, Cervelli V. The effect of platelet-rich plasma in hair regrowth: a randomized placebo-controlled trial. *Stem Cells Transl Med*. 2015;4:1317-1323.
9. Anitua E, Pino A, Martinez N, Orive G, Berridi D. The effect of plasma rich in growth factors on pattern hair loss: a pilot study. *Dermatol Surg*. 2017;43:658-670.
10. Takikawa M, Nakamura S, Nakamura S, et al. Enhanced effect of platelet-rich plasma containing a new carrier on hair growth. *Dermatol Surg*. 2011;37:1721-1729.
11. Qu Q, Shi P, Yi Y, et al. Efficacy of platelet-rich plasma for treating androgenic alopecia of varying grades. *Clin Drug Investig*. 2019;39:865-872.
12. Gkini MA, Kouskoukis AE, Tripsianis G, Rigopoulos D, Kouskoukis K. Study of platelet-rich plasma injections in the treatment of androgenetic alopecia through an one-year period. *J Cutan Aesthet Surg*. 2014;7:213-219.
13. Navarro RM, Pino A, Martinez-Andres A, et al. The effect of plasma rich in growth factors combined with follicular unit extraction surgery for the treatment of hair loss: a pilot study. *J Cosmet Dermatol*. 2018;17:862-873.
14. Uebel CO, da Silva JB, Cantarelli D, Martins P. The role of platelet plasma growth factors in male pattern baldness surgery. *Plast Reconstr Surg*. 2006;118:1458-1466. discussion 67.
15. Gupta AK, Versteeg SG, Rapaport J, Hausauer AK, Shear NH, Piguet V. The efficacy of platelet-rich plasma in the field of hair restoration and facial aesthetics-a systematic review and meta-analysis. *J Cutan Med Surg*. 2019;23:185-203.
16. Martinez-Jacobo L, Ancer-Arellano CI, Ortiz-Lopez R, et al. Evaluation of the expression of genes associated with inflammation and apoptosis in androgenetic alopecia by targeted RNA-Seq. *Skin Appendage Disord*. 2018;4:268-273.
17. Giordano S, Romeo M, Lankinen P. Platelet-rich plasma for androgenetic alopecia: does it work? Evidence from meta analysis. *J Cosmet Dermatol*. 2017;16:374-381.
18. Siah TW, Guo H, Chu T, et al. Growth factor concentrations in platelet-rich plasma for androgenetic alopecia: an intra-subject, randomized, blinded, placebo-controlled, pilot study. *Exp Dermatol*. 2020;29:334-340.
19. Ayatollahi A, Hosseini H, Shahdi M, et al. Platelet-rich plasma by single spin process in male pattern androgenetic alopecia: is it an effective treatment? *Indian Dermatol Online J*. 2017;8:460-464.
20. Badran KW, Sand JP. Platelet-rich plasma for hair loss: review of methods and results. *Facial Plast Surg Clin North Am*. 2018;26:469-485.
21. Cole JP, Cole MA, Insalaco C, Cervelli V, Gentile P. Alopecia and platelet-derived therapies. *Stem Cell Investig*. 2017;4:88.
22. Kim YS, Jeong KH, Kim JE, Woo YJ, Kim BJ, Kang H. Repeated microneedle stimulation induces enhanced hair growth in a murine model. *Ann Dermatol*. 2016;28:586-592.
23. Dhurat R, Sukesh M, Avhad G, Dandale A, Pal A, Pund P. A randomized evaluator blinded study of effect of microneedling in androgenetic alopecia: a pilot study. *Int J Trichology*. 2013;5:6-11.