Platelet-Rich Plasma as a Treatment for Androgenetic Alopecia

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BACKGROUND Platelet-rich plasma (PRP) treatment may encourage hair growth by promoting cellular maturation, differentiation, and proliferation.

OBJECTIVE The objective of this study was to evaluate the effectiveness of PRP as a treatment for androgenetic alopecia (AGA).

MATERIALS AND METHODS A literature search combined with meta-analysis was used to calculate the overall standardized mean difference (SMD) in hair density in patients treated with PRP injections in comparison with baseline and placebo treatment. Chi squared analysis and Fisher exact test were used to investigate variation in protocols.

RESULTS The overall SMD in hair density was 0.58 (95% confidence interval [CI]: 0.35–0.80) and 0.51 (95% CI: 0.23–0.80, $p < .0004$) in favor of PRP treatment when compared with baseline and placebo treatment, respectively.

CONCLUSION Platelet-rich plasma is beneficial in the treatment of AGA. It is recommended that 3 monthly sessions of PRP (once monthly ×3 treatments) be used followed by a 3- to 6-month maintenance period.

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Platelet-rich plasma (PRP) is created through concentrating platelets found in whole blood.[1] It can aid in tissue regeneration, bone regeneration, and wound repair.[2–7] Platelet-rich plasma treatment has also been suggested to promote hair growth, encourage cell survival and proliferation, and prolong the anagen phase of the hair cycle.[8–13] Platelet-rich plasma is thought to exert its effects in androgenetic alopecia (AGA) via delivery of concentrated growth factors to the hair follicle and surrounding area (Figure 1). Emerging evidence has begun to characterize the dermal and follicular response to several growth factors (e.g., platelet-derived growth factor, transforming growth factor beta).[14–17] The main objective of this article was to assess the effectiveness of PRP as a monotherapy and adjunct treatment for male AGA.

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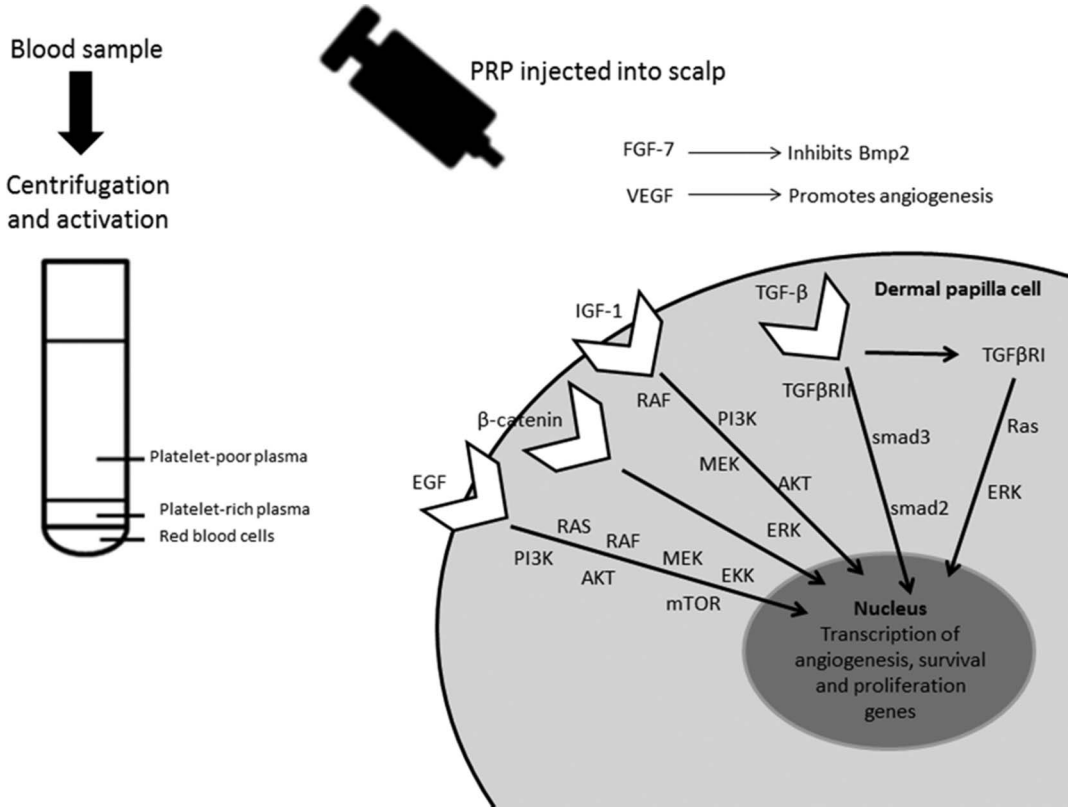

Figure 1. Mechanism of action. Platelet-rich plasma is prepared from an autologous blood sample that is subsequently centrifuged to concentrate platelets. Platelet-rich plasma is then activated, often with the addition of calcium chloride to stimulate the release of growth factors. Platelet-rich plasma is subsequently injected into the patient's scalp, where various growth factors are thought to stimulate gene upregulation associated with angiogenesis, cell survival, and proliferation. AKT, protein kinase B; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; FGF-7, fibroblast growth factor 7; IGF-1, insulin-like growth factor 1; mTOR, mechanistic target of rapamycin; PI3K, phosphoinositide 3-kinase; TGF-β, transforming growth factor beta; TGFβRI, abrogated transforming growth factor beta receptor I; TGFβRII, abrogated transforming growth factor beta receptor II; VEGF, vascular endothelial growth factor; smad2, mothers against decapentaplegic homolog 2; smad3, mothers against decapentaplegic homolog 3.

Platelet-Rich Plasma as a Monotherapy for Male Androgenetic Alopecia

To analyze the effectiveness of PRP for the treatment of AGA, a meta-analysis was undertaken. A literature search was conducted using PubMed on September 7, 2017 and updated on May 18, 2018. The following terms were used; "PRP," "hair," "platelet-rich plasma," "hair transplant," "hair loss," "androgenetic alopecia," and "alopecia." Studies were included if they evaluated the success of PRP for treatment of AGA using hair density (hairs/cm^2).[18–27] Studies were excluded if they did not use direct injection, contained less than 5 participants per treatment, included only female participants, patients used alternative treatments (5α-reductase inhibitors, minoxidil) within 6 months of study start or if insufficient data were provided. Study parameters are listed in Table 1 with characteristics such as a larger patient population and use of controls, comparators, randomization, and blinding generally considered more scientifically rigorous. The meta-analysis was conducted using RevMan 5.3 (Copenhagen, Denmark). Effect size was measured through use of the standardized mean difference (SMD), where treatment versus comparator results close to 0 suggest no difference and increasingly higher scores are associated with improvement. Heterogeneity was evaluated using the I^2 statistic.[28,29] The reported efficacy was compared to baseline measures, and a p-value < .05 was considered significant. The SMD in hair density was 0.58 (95% confidence interval [CI]: 0.35–0.80) in favor of PRP treatment (10

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TABLE 1. Characteristics of Trials Used in Meta-analysis

Study	*No. of Participants*	*Placebo or Untreated Control*	*Use of Comparator*	*Randomized*	*Blinded*	*Length of Study*	*Study Description*
Alves and Gimalt[18]	25	Placebo	No	Yes	Double	6 mo	Half-head study
Anitua and colleagues[19]	19	No	No	No	No	1 yr	Pilot study
Ayatollahi and colleagues[20]	15	No	No	No	No	22 wk	
Borhan and colleagues[21]	17	No	No	No	No	16 wk	Open monocentric and prospective study
Cervelli and colleagues[22]	10	Placebo	No	No	No	12 mo	Half-head study
Gentile and colleagues[23]	18	Placebo	No	Yes	Double	5 mo	Half-head study
Gentile and colleagues[24]	23	Placebo	No	No	No	5 mo	Half-head study
Gkini and colleagues[25]	20	No	No	No	No	1 yr	Prospective cohort study
Stevens and colleagues[26]	10	Untreated	No	No	No	12 wk	
Takikawa and colleagues[27]	26	Placebo	PRP containing dalteparin and protamine particles	No	No	12 wk	

PRP, platelet-rich plasma.

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studies, pooled $N = 165$, $p < .00001$) (Figure 2A). This result is consistent with a previously published meta-analysis that also favored PRP over baseline (SMD: 0.51, 95% CI: 0.14–0.88, $p = .006$).[30] Likewise, PRP exhibited a greater efficacy over placebo treatments (SMD: 0.51, 95% CI: 0.23–0.80, $p < .0004$) with the inclusion of 6 trials (pooled $N = 99$)[18,22–24,26,27] (Figure 2B).

In this study, interestingly, and similar to some of the observations from previous research,[31] evidence for investigating male and female patients separately was found. Inclusion of an all-female study[32] in the current meta-analysis (otherwise composed of all male and mostly male studies) was not possible due to an introduction of high heterogeneity (measured $I^2 = 89\%$), leading to the suggestion that female patients should be investigated distinctly. This idea has practical implications for clinicians as there are few AGA treatment options for female patients and encourages new research directions to test this hypothesis with the possibility of creating a unique PRP protocol targeted directly to female patients.

Investigating methods across AGA studies, with the exception of a few minor modifications, only 2 PRP protocols were duplicated.[33,34] Both studies reported that subjects treated with PRP had a greater change in hair density compared to placebo-treated subjects. Khatu and colleagues and Singhal and colleagues both used an activated (calcium chloride) PRP treatment (2-week interval between sessions, 4 sessions total) created using a double spin technique (1,500 rpm for 6 minutes and 2,500 rpm for 15 minutes).[33,34] These 2 studies did differ in how much PRP was injected; 2 to 3 mL per injection versus 8 to 12 mL per injection.[33,34] Cervelli and colleagues and Gentile and colleagues also used a similar protocol, administering PRP (0.1 mL/cm^2 per injection) every 4 weeks for a total of 3 sessions.[22,35] Both studies used the Cascade-Selphyl-Esforax system, centrifuging the PRP solution at 1,100g for 10 minutes.[22,35] Cervelli and colleagues and Gentile and colleagues reported that PRP-treated patients had a significantly greater mean change in hair density as compared to placebo-treated patients (both studies $p < .0001$).[22,35] Overall, the results suggest that PRP therapy resulted in a significantly greater increase

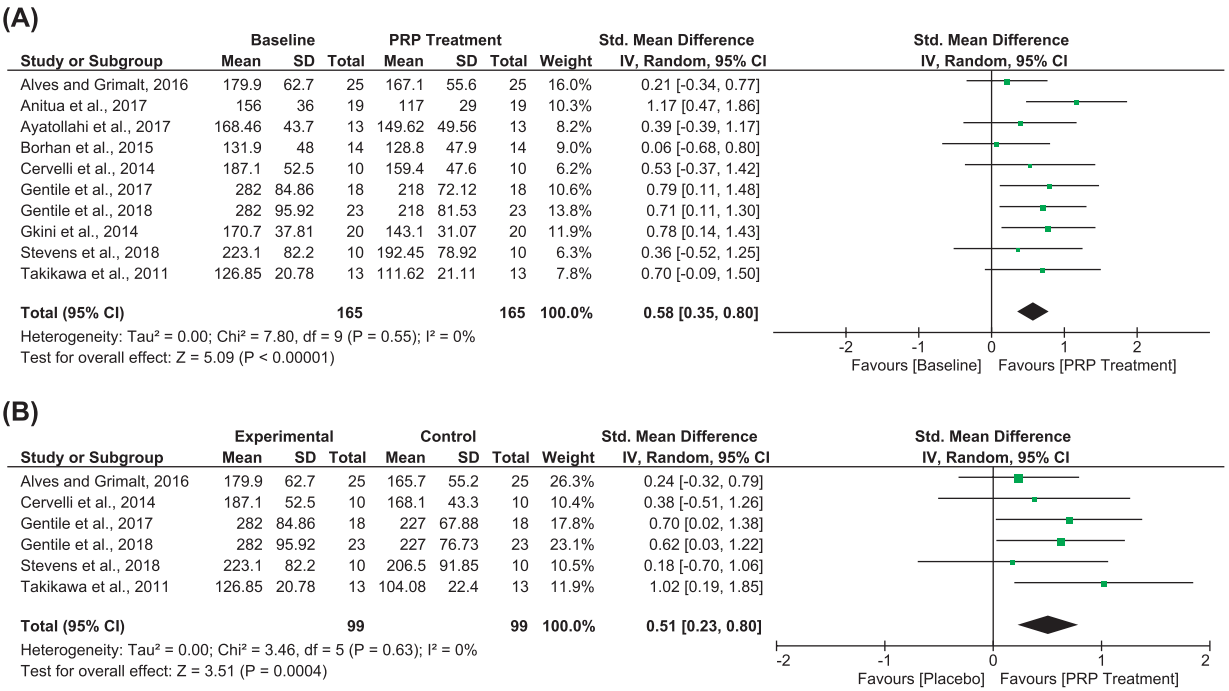

Figure 2. Forest plot illustrating the results of a meta-analysis of PRP as a treatment for hair loss in AGA patients. (A) Ten studies (pooled $N = 165$ participants) that used hair density as a measure of efficacy were compared to baseline. (B) Six studies (pooled $N = 99$ participants) that used hair density as a measure of efficacy were compared to placebo. AGA, androgenetic alopecia; PRP, platelet-rich plasma.

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TABLE 2. Analysis of Platelet-Rich Plasma Protocols and Techniques

Collection systems	Use of a closed system is recommended for patient safety and reproducibility[24]
	Examples of collection systems that are FDA approved (510k clearance) include the Arthex Angel System,[41] Biomet GPS III,[42] Eclipse PRP system,[43] Emcyte PurePRP Genesis CS concentrating device,[44] Harvest SmartPrep,[45] Magellan TruPRP™,[46] RegenKit Blood Cell Therapy,[47] and the Selphyl system[48]
	Each system incorporates its own feature such as an agar plug that may facilitate a high-volume PRP yield in the Eclipse PRP system,[49] the compartmentalized reservoir bag that enables different mediums (whole blood or mixture of blood and bone marrow) to be separated through centrifugation in the Arthex Angel System,[50] and the use of calcium chloride in the Selphyl System to enhance delivery of growth factors through fibrin matrices created by the conversion of fibrinogen to fibrin[51]
	Each collection system also varies in growth factor and cytokine concentrations, platelet capture efficiencies, and resulting monocyte populations[23,38,39]
	A high platelet recovery rate, elevated growth factor and cytokine concentrations, and a low red blood cell count is desired
	The optimum platelet concentration has been shown to be 1.5 million per microliter (about 5-fold more concentrated than the normal range of 150,000–400,000),[52] although currently there are no in vivo studies that compare results for hair growth directly
Centrifugation and sonication	During centrifugation, high speeds and long durations can inadvertently precipitate platelets or discharge growth factors (e.g., platelet-derived growth factor), influencing the efficacy of PRP[53,54]
	As a potential alternative to centrifugation, acoustic-based particle manipulation methods could be used to separate blood cells[55]
	Sonication can lyse platelet cell membranes, allowing the release of growth factors and be more effective in separation of red and white blood cells[56]
	Ultrasound-generated PRP demonstrated a greater platelet recovery rate as compared to PRP obtained through centrifugation (79 $\pm$ 9% vs 54 $\pm$ 10% over baseline, respectively)[56]
	Sonication may increase the survival rate of transplanted follicular units[57]
Activation	Activation using calcium chloride or calcium gluconate is frequently used in hair loss studies to induce α granule release of growth factors from platelets[18,23,25,32–34,58–61]
	Extracellular matrix materials such as ACell (FDA approved to repair and remodel damaged tissue) could also be used to activate PRP solutions, although current evidence for this technique remains anecdotal
	Alternatively, microparticles could be a functional and cheaper substitute[62,63]
	The combination of microparticles, adipose derived stem cells, and follicular stem cells could also be advantageous and are currently under investigation
	Scalp needling to induce inflammation leading to platelet activation has been suggested to be as effective as use of an exogenous activator[64]
	Similarly, it has been suggested that exogenous activation may not make a significant impact on specific growth factors and cytokines, such as platelet-derived growth factor BB and transforming growth factor β1,[23] although a direct comparison (n = 40) of nonactivated versus calcium chloride–activated PRP resulted in significantly more effective treatment in the former[40]
	Thus, although it is clear that activation is necessary for growth factor release, further research is necessary to determine the impact of various methods of activation on the efficacy of PRP
Needle size	It is unknown if needle size can influence the efficacy of PRP
	In AGA studies, needles used to administer PRP have ranged from 20 to 32 G, with 30-G needle as the most commonly used[18,19,21,23–26,35,59,64]
Injection depth	Follicles vary in length below the skin surface, averaging 4.2 mm in length[65]
	Subdermal injections have been shown to be efficacious and tolerable in a blinded randomized clinical trial (n = 40)[66]; success has been found with intradermal injections, injections into recipient slits during transplantation, and injections into microneedling channels[54,67]
	Use of a mechanical and thus reproducible device has also been recommended for controlled delivery of PRP[24]

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TABLE 2. (Continued)

Treatment frequency and no. of sessions	Monthly PRP injections had a significantly greater increase in hair count as compared to injections every 3 mo (mean percent change of 29.6 vs 7.2%, $p < .001$)[68]
	Substantial improvements in hair restoration parameters (e.g., hair density, hair count) have frequently been reported in PRP studies that administer 3 monthly sessions, suggesting that 3 sessions may be necessary to achieve desired results[18,22–24,35,60,61]
	A 3- to 6-mo maintenance interval after a monthly PRP treatment regimen could be beneficial[69]
	Follow-up periods should extend to 12 mo post-treatment, as an early decrease in hair density coinciding with the PRP-driven stimulation of hairs into the anagen stage is expected

AGA, androgenetic alopecia; FDA, Food and Drug Administration; PRP, platelet-rich plasma.

in hair density compared to baseline counts and placebo.

There are a number of factors that could explain the variation seen in PRP results (Table 2). Differences in preparations and delivery have been suggested as a possible explanation.[36,37] In addition to platelet concentration, white blood cell, neutrophil, and red blood cell concentration varies with separation systems as well.[38,39] The resulting effect on efficacy is unknown; however, individual advantages are expected with the various systems.[38] For example, in direct comparison ($n = 6$), the Arthex Angel System resulted in significantly improved hair density versus the Regen Cell Therapy collection system.[23]

Patient characteristics may also influence the results of PRP treatment (Table 3). Variables from each study (Table 4) were examined using a chi squared analysis and Fisher exact test to identify any protocol trends that led to significant results more often than expected. Specifically, each variable (population demographics, centrifuge process, concentration of platelets, injection process, needle gauge, method of platelet activation, quantity and intervals of treatment, and time of analysis) was examined in search

TABLE 3. Factors That Could Influence the Efficacy of Platelet-Rich Plasma

Patient Characteristics	*Evidence*
Gender	Male patients experienced new growth 2 wk earlier and had a higher increase in hair counts in comparison to the female population ($n = 115$)[31]
	Statistically significant increase in the mean total hair density for male patients in comparison to female patients ($n = 25$)[18]
Severity of alopecia	Significantly better response from patients with a lower grade of alopecia (Grade III–IV alopecia, Hamilton–Norwood)[21,25,53,59,70]
Disease duration	Most studies observed a significantly better response from patients with a shorter disease duration[21,53,59]
	Alves and Grimalt[18] observed a statistically significant increase in the mean total hair density in patients with greater than 10 years of disease duration
Age	Alves and Grimalt[18] observed a statistically significant increase in the mean total hair density for patients younger than 40 years
	Borhan and colleagues[21] observed the best response in patients in their early 30s
Onset of alopecia	Alves and Grimalt[18] observed a statistically significant increase in the mean total hair density for patients with hair loss beginning after 25 years
Presence of vellus hair	Presence of vellus hair led to better results compared to those who had few but normal hair[25,70]

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TABLE 4. Characteristics of Platelet-Rich Plasma Studies Conducted in Androgenetic Alopecia Patients Using Hair Density as a Measure of Efficacy

Study	*Study Type*	*PRP Method*	*Concentration Increase*	*Injection Depth*	*Needle Gauge*	*Activation*	*Treatment Duration*	*Assessment Date*	*Results*
Kachhawa and colleagues[70]	Split head study of placebo versus PRP, 50 male patients, HN III–VI	Double spin		Intradermal			6 treatments at 21-d intervals	4 mo	Density increased significantly compared to baseline and placebo
Starace and colleagues[71]	Pilot study, open-label, single-group, single-centre study; 10 female patients not responding to treatments; Ludwig I–III	My Cells system			25		Every 2 wks for 4 sessions	12 and 24 wks	Mostly all positive and increasing over time, corresponding to a clinical improvement
Ayatollahi and colleagues[20]	13 male patients, HN III–VI uncontrolled	Regen Lab PRP Kit—RegenACR	Estimate 1.6-fold from Regen Lab data				5 treatments every 2 wks	22 wks	Not significant, $p = .37$
Stevens and colleagues[26]	10 male patients, HN II–III	PRP and adipose-derived stromal vascular fraction, Arthrex Angel System			20		1	6 and 12 wks	Hair density was significantly increased after 6 and 12 wks, $p = .013$, $p < .013$
Gupta and colleagues[53]	Open-label pilot study, 30 male patients, HN III–VII	Double spin		Massage into scalp		Microneedling	6 treatments at 15-d intervals	6 mo	Increase in hair density is observed but significance is not reported
Gentile and colleagues[23] (study 1)	Half-head comparison with placebo, 18 male patients, HN II–IV	CPunT preparation system	5-fold	5 mm	30		3 treatments at 30-d intervals	12 wks	Significant improvement compared to baseline and placebo as well as to a previous study $p = .0029$
Gentile and colleagues[23] (study 2)	Half-head comparison with comparator, 6 male patients, HN IIIA–IIIV	Regen Blood Cell Therapy or Arthrex Angel System	5-fold		25	Calcium	1 treatment	6 mo	Significant improvement in Arthrex Angel versus Regen Blood Cell Therapy

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TABLE 4. (Continued)

Study	*Study Type*	*PRP Method*	*Concentration Increase*	*Injection Depth*	*Needle Gauge*	*Activation*	*Treatment Duration*	*Assessment Date*	*Results*
Alves and Grimalt[18]	Randomized, placebo-controlled, double-blind, half-head parallel-group study; 12 male patients, HN II–V; 13 female patients, Ludwig I–III	Single spin, leukocyte poor	3-fold		30	Calcium	3 treatments at 1-mo intervals	3 and 6 mo	Significant improvement from baseline and placebo $p < .05$
Anitua and colleagues[19]	Uncontrolled study; 13 male patients, HN III–VI; 6 female patients, Lugwig II/frontal	Single spin BTI system, leukocyte layer not collected	2-fold		30		4 treatments at 1-mo intervals with a final treatment at 7 mo	12 mo	Significant improvement $p < .05$
Tawfik and Osman[32]	Double-blinded, randomized, placebo-controlled, half-head study; 30 female patients; Ludwig I–III	Double spin				Calcium	4 treatments at 1-wk intervals	7 mo	Significant improvement $p < .05$ compared to placebo and baseline
Cervelli and colleagues[22]	Randomized, placebo, half-head study; 10 male patients	Cascade-Selphyl-Esforax, 0.1 mL/cm^2 per injection, leukocytes not excluded			30	Calcium	3 treatments at 1-mo intervals	12 mo	Significant improvement, control versus treatment, $p < .0001$
Gkini and colleagues[25]	Prospective cohort study; 18 male patients, HN II–V; 2 female patients; Ludwig I–III	RegenKit BCT-3	5.8-fold	1.5–2.5 mm	27	Calcium	3 treatments at 21-d intervals, booster at 6 mo	12 mo	Significant improvement at 6 wks and 12 mo compared to baseline
Borhan and colleagues[21]	Open, monocentric prospective study, 3 female and 11 male patients, HN III–IV	Regen Lab, 4–5 mL used per session, 0.05–0.1 mL per injection		Superficial dermis	32		4 treatments total at 3-wk intervals, last treatment at 6-wk interval	16 wk	Not significant, $p = .8638$

TABLE 4. (Continued)

Study	*Study Type*	*PRP Method*	*Concentration Increase*	*Injection Depth*	*Needle Gauge*	*Activation*	*Treatment Duration*	*Assessment Date*	*Results*
Gentile and colleagues[35]	Randomized, placebo-controlled, half-head study; 2 male patients; HN II–IV	Modified versions of the Cascade-Selphyl-Esforax system and platelet-rich lipotransfert system, may include leukocytes			30	Calcium	3 treatments at 30-d intervals	2 yrs	Significant improvement in control versus treatment, $p = .001$
Gentile and colleagues[24]	18 male patients, HN I–V; and 5 female patients, Lugwig I–II			5 mm with medical injector gun	30		3 treatments at 30-d intervals	5 mo	31 ± 2% increase in hair density for the treatment group versus less than 1% increase in hair density for the placebo group compared to baseline
Takikawa and colleagues,[27]	Controlled, half-head study; 26 participants	Cascade-Selphyl-Esforaxsystem, PRP mixed with 2 mg/mL of D/P MP	6-fold	Subcutaneous injection	25	Calcium	5 treatments at 2-wk intervals; last treatment at 3-wk intervals	12 wks	No significant difference between PRP and PRP & (D/P MP) treatments but significant improvement from control

D/P MP, dalteparin and protamine microparticles; PRP, platelet-rich plasma.

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TABLE 5. Recommended Techniques for Platelet-Rich Plasma Treatment of Androgenetic Alopecia

Treatment frequency and no. of sessions	Three sessions of PRP at 1-mo intervals followed by a 3- to 6-mo maintenance period
Injection depth	Subdermal
Collection systems	Capable of high platelet recovery rate (1.5 million platelets per microliter,[52] which is 5 times basal concentration), although the average reported concentration is 3 times the basal amount and influence of the balance of white blood cells, neutrophils, and red blood cells is still under investigation[38] (Kushida and colleagues, 2014)
Activation	Activation should be considered; however, the best method is up for debate as use of exogenous agents such as calcium chloride have been contrasted with alternate techniques, such as scalp needling,[67] or natural contact with dermal fibroblasts through the PRP preparation and injection process[72]
Centrifugation and sonication	Use of sonication and microparticles is preferred
Needle size	Impact is unclear

PRP, platelet-rich plasma.

of a similar variable appearing more often than by random probability in the protocols of studies which achieved statistically significant results. The use of an exogenous activator appeared the most connected to achieving desirable results ($p = .08$) that was similar to the conclusions of an earlier meta-analysis.[30] Nonetheless, this suggestion contrasts a direct comparison of nonactivated versus calcium chloride–activated treatments ($n = 40$), which concluded the former to be significantly more effective.[40] From this analysis combined with the results of the meta-analysis (above), specific PRP techniques and methods are recommended (Table 5).

Conclusions

Platelet-rich plasma could be used to improve hair restoration parameters (e.g., hair density) in AGA monotherapy or adjunct therapy. For the former, 3 sessions of PRP at 1-month intervals followed by a maintenance regimen is recommended.

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