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ARTICLE

Platelet-rich plasma as a therapy for androgenic alopecia: a systematic review and meta-analysis

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ABSTRACT

Objective: The past decade has seen platelet-rich plasma (PRP) become a popular therapy around the world as a treatment for androgenetic alopecia (AGA). These systematic review and meta-analyses assess the effectiveness and adverse effects of PRP to determine the role of PRP as a treatment for AGA among the other non-surgical treatment modalities.

Methods: This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and is registered under the PROSPERO ID CRD42019136329. Seven databases were searched from inception through May 2019. Meta-analyses of randomized controlled trials (RCTs) were performed to evaluate the effect of PRP treatments on hair density and hair thickness.

Results: Thirty studies, including 687 patients, met our inclusion criteria. Twenty-nine studies reported beneficial results, and 24 studies reached statistical significance on a measured outcome. Ten RCTs were included. Our meta-analyses show that PRP treatment increases hair density and hair thickness.

Conclusions: PRP is an autologous treatment that lacks serious adverse effects and effectively improves hair density and hair thickness in men and women with AGA. Future research should include low risk-of-bias RCTs to optimize treatment protocols, investigate variability among studies, and to obtain more data on hair thickness changes.

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KEYWORDS
Platelet-rich plasma; androgenic alopecia; hair loss; injection therapy

Introduction

Androgenic alopecia (AGA) is the most common type of hair loss and affects up to 80% of men and 50% of women in their lifetime (1,2). The typical pattern for men is a loss of hair at the temporal, frontal, and vertex areas of the scalp, graded by the Hamilton–Norwood Scale, while affected women typically experience a diffuse thinning of hair at the crown, graded by the Ludwig System (3). Affected patients may experience decreases in quality of life, loss of confidence, poor self-image, and depression with societal withdrawal (4,5).

AGA is a non-scarring, chronic, and progressive disease characterized by terminal hair miniaturization to become vellus-like hairs (6). The process of miniaturization includes inflammation and shortening of the anagen hair cycle phase which may lead to permanent hair loss (7,8). Dihydrotestosterone (DHT) is the primary implicated hormone. This hormone is produced by irreversible conversion of testosterone by 5-alpha reductase occurring in cells of hair follicles and leads to hair loss via binding of anagen receptors of the hair follicles (9).

Established therapies for AGA include oral finasteride, low-level laser light therapy (LLLLT), and topical minoxidil. These modalities are ineffective for many patients, and include serious side effects including decreased libido, erectile dysfunction, impaired hepatic function, testicular pain, or contact dermatitis (10,11). Hair transplantation is an effective, but cost-prohibitive surgical approach for which not all patients are surgical candidates (12). Low-level laser therapy has been utilized in recent years to some success that is theorized to be attributed to increased circulation to the hair follicular unit (13). Platelet-rich plasma (PRP) is a novel treatment that has shown promise in treating AGA since research began only one decade ago. This study will explore the current state of research on PRP as a treatment for AGA.

Platelet-rich plasma preparation

PRP is an autologous product that has emerged as a promising treatment for AGA that is also low risk, low down-time, and low cost. Protocols for preparing PRP are non-standardized, and the concentration of its component parts are often highly variable between patients (14). However, the past decade has seen the development of systems to standardize the reporting of PRP preparation protocols. Details that may be pertinent include the centrifugation force, centrifugation time, number of centrifugations, platelet concentration, anticoagulant or activator additives, and the presence of white blood cells (15–18).

To prepare PRP, a venous blood draw is performed with a vacuum tube containing an anticoagulant such as acid citrate dextrose (ACD) solution A, sodium citrate, or

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Supplemental data for this article can be accessed here.

ethylenediaminetetraacetic acid (EDTA) (19). Centrifugation is performed to separate the sample into component parts of red blood cells, the leukocyte containing buffy coat, and the supernatant. The supernatant is further divided either by a second centrifugation step, a filter, or by pipetting to create two solutions. The less dense platelet-poor plasma (PPP) is often delineated as the top two-thirds of the supernatant while the more dense PRP is the bottom one-third.

Whether or not leukocytes from the buffy coat are included determines whether the PRP is leukocyte-rich (LR-PRP) or leukocyte-poor (LP-PRP). Another variant of PRP may be created if platelet activators such as calcium chloride, calcium gluconate, or thrombin are added to the solution in order to create a supraphysiologic concentration of fibrin. The viscous platelet gel formed is sometimes referred to as platelet-rich fibrin (PRF), platelet-rich fibrin matrix (PRFM), and 2nd generation platelet gels (20–22).

PRP mechanism of action

The activation of platelets, whether physiologic or following the addition of a platelet activator, results in the release of over 30 growth factors and cytokines from primarily alpha granules (23,24). Standard blood contains 16–50% of the platelet concentration of PRP (14), and the growth factors and cytokines released from platelets modulate cellular functions including angiogenesis and inflammatory cascades (23,24). The resultant effects are being investigated as a treatment option in numerous fields including orthopedic surgery for the treatment of osteoarthritis, dermatology for scar reduction, and plastic surgery for facial rejuvenation (25).

The major factors released which are believed to contribute to hair regeneration include platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF) (26). The receptors to which these factors bind are primarily located on undifferentiated stem cells in the bulge region of the follicle (27,28). Although the exact mechanism of PRP-induced hair restoration remains unclear, PDGF is well established as in prolonging the anagen phase of the hair cycle, and activated PRP has been shown to provide extracellular signal-regulated kinase (ERK) pathway activation and cell growth similar to sildenafil, while also providing Akt-pathway increased cell survival to hair follicle cells (29–31). Hair growth is also resultant from the follicular keratinocyte proliferating growth factor IGF-I, as well as other PRP growth factors including FGF and PDGF (26,29). The process of hair growth is thought to be supported by perifollicular neovascularization stimulated by VEGF, FGF, EGF, and PDGF (26). Additional effects include the upregulation of the Wnt pathway, which encourages cycle stability and growth after the administration of activated PRP (26).

Therefore, this study aims to summarize all published literature investigating PRP as a treatment for AGA, and includes meta-analyses of hair density and hair thickness.

Materials and methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (32). A detailed protocol was developed prior to initiating the systematic review and is registered under the PROSPERO ID: CRD42019136329.

Search strategy

Two reviewers (J.M. and M.I.) performed independent literature searches of all published articles up to June 2019 using the databases Cochrane Library, Ovid Medline, Ovid Embase, Web of Science, EBSCO, and the clinical trials registries ClinicalTrials.gov (http://clinicaltrials.gov/), and the World Health Organization Clinical Trials Registry Platform (WHOCTRP) (http://apps.who.int/trialsearch/). The search was conducted in June 2019 using the Boolean operators 'OR' and 'AND' in conjunction with search terms including and related to 'alopecia' and 'platelet-rich plasma,' with word variations and MeSH terms. The search strategy was adapted as necessary and appropriate to each database (Supplementary Appendix). Bibliographies of included studies and relevant reviews were also searched. Disagreement in article selection was resolved through discussion involving a third author (A.E.). To capture all published clinical trials, both randomized controlled trials (RCTs) and non-randomized studies of interventions (NSRI) were included. The largest cohort was included in the study if multiple publications described the same cohort. Data extraction was performed by one reviewer (J.M.) using a piloted form excel spreadsheet, and a second reviewer (A.E.) checked over 90% of the extracted data. Experts in the field of plastic and reconstructive surgery and in the application of PRP were consulted and included in the study.

Inclusion and exclusion criteria

Included studies were: (1) peer reviewed, (2) using PRP to treat AGA, (3) published in English, (4) and had a minimum follow-up of 1 month.

Excluded studies were: (1) studies with less than 10 total patients, (2) studies with absence of significant demographic information, baseline data, or results, (3) studies applying PRP without injection or microneedling, (4) animal studies, case reports, retrospective studies, review articles, meta-analyses, duplicates of cohorts, (5) studies on non-AGA forms of alopecia, and (6) non peer-reviewed 'grey' literature.

Risk of bias

Risk of bias assessment was performed for RCTs at a study and outcome level using the Cochrane risk-of-bias tool RevMan 5.3.5 software package (Cochrane Collaboration, London, UK).

Outcomes

The primary outcomes assessed were hair count, hair density, and hair diameter. Secondary outcomes tracked included patient satisfaction scores, global physician assessment (GPA) scale evaluations, percentage of anagen and telogen hairs, percentage of vellus and terminal hairs, capillary density, epidermal thickness, follicle number, hair pull test, and reports of adverse effects.

Statistical analysis

RevMan 5.3.5 software package (Cochrane Collaboration, London, UK) was utilized for all statistical analyses. Only RCTs were included in the meta-analysis. Dichotomous variables were

presented as odds ratios with a 95% CI. To incorporate heterogeneity between studies, I^2 values were calculated. I^2 values over 50% were considered highly heterogeneous and warranted investigation of study details that may contribute to heterogeneity. Meta-analysis was performed for data of hair density and hair thickness using a random-effects model. Continuous data were presented as mean differences (MDs) and standard deviations comparing PRP versus the control. Mean difference with a confidence interval of 95% was analyzed for hair density and hair thickness. A p value $<.05$ was considered significant.

Results

Article selection

Applying our search strategy resulted in 808 records being identified. A full text review performed of 38 articles led to the exclusion of eight articles for the reasons of significant absence of baseline information (33,34), not published in English (35), PRP applied without injection or microneedling (36), retrospective (37), pending trial (38), basic science study (39), and duplicate cohort (40). One additional article was comprised of two studies and had one study excluded due to having fewer than 10 patients (41). Therefore, 30 articles were included (41–70), five of which were utilized in quantitative synthesis. The article selection process is depicted in Figure 1.

Study characteristics and treatment protocols

Table 1 summarizes characteristics of the 687 men and women included in the 30 studies. As demonstrated by Table 2, PRP preparation and delivery methods varied greatly among the studies. The amount of blood collected from patients for preparation ranged from 8 mL to 60 mL, and two studies did not report the amount of blood collected. Twenty-seven studies reported on centrifugation details, of which eight (30%) were double-spin methods and 19 (70%) were single-spin methods. For double-spin protocols, the mean first centrifugation time was 10.5 min (range: 6–15 min) and the mean second centrifugation time was 10 min (range: 5–15 min). For single-spin methods, centrifugation times averaged 7.8 min (range: 5–15 min). Reported centrifugation speeds ranged from 160 to 2000 g and 1000 to 3500 rpm. Sixteen studies (53%) activated PRP using calcium (e.g. calcium chloride or calcium gluconate), and 16 studies (53%) reported use an anesthetic prior to injection. In the 22 studies reporting on the quantity of PRP injected, the mean total quantity injected was 5.4 mL (range: 1.5–14 mL), made up of individual injections averaging 0.18 mL (range:

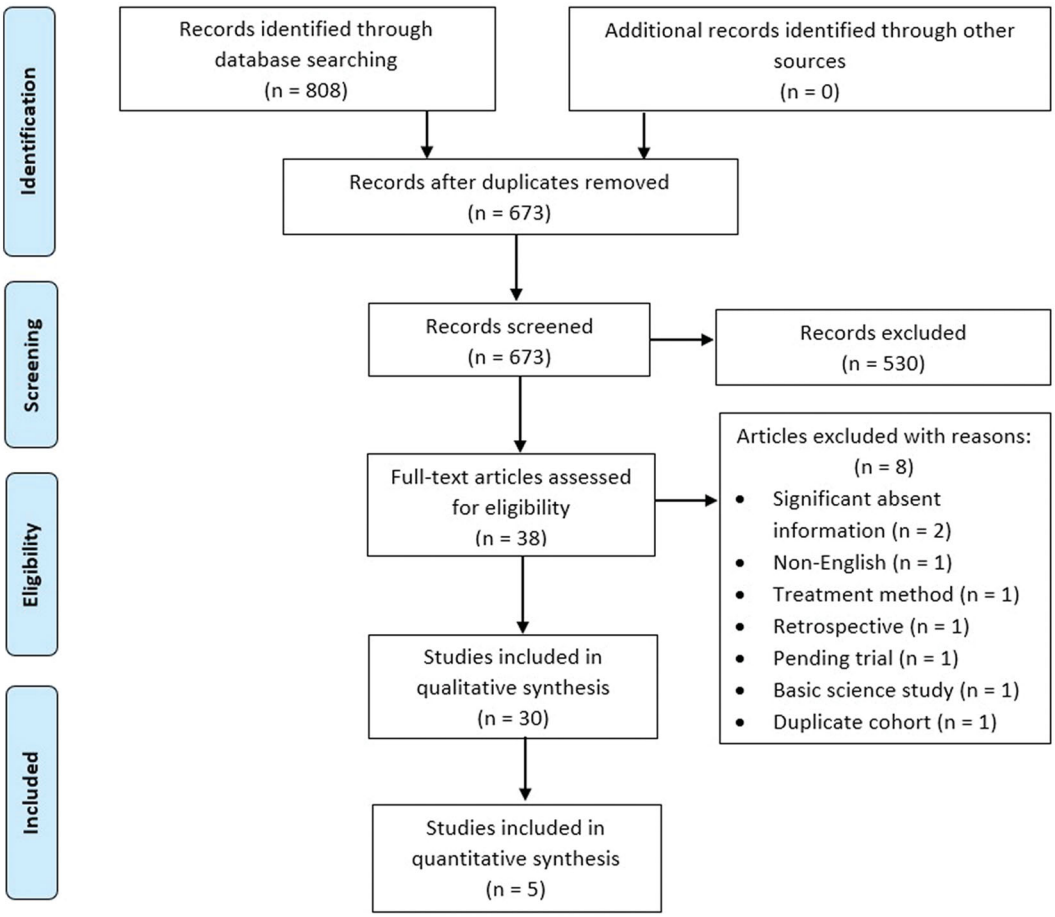

Figure 1. Eight hundred and eight records were identified from database searches, and 0 additional articles were identified by other methods. After 135 duplicates were removed, a screen of 673 articles by title and abstract resulted in 38 articles eligible for full text review. A full text review of these 38 articles led to the exclusion of eight articles for reasons. One included article was comprised of two studies, one of which had fewer than 10 patients and was excluded. In total, 30 articles were included in the systematic review and five were utilized in quantitative synthesis.

Table 1. Study type and patient demographics.

Study author, year	Country	Study type, blinding	Control type	# Treated, # controls	# Males (AGA stage)[a], # females (AGA stage)	Age (year range)
Rodrigues et al., 2019	Brazil	RCT, double	Saline	15, 11	26 (III), 0	18–50
Tawfik and Osman, 2018	Egypt	RCT, single	Saline (half-head)	30, 30	0, 30 (I–III)	20–45
Hausauer and Jones, 2018	USA	RCT, single	2nd PRP method	20, 20	30 (II–V), 10 (I2–II1)	18–60
Schiavone et al., 2018	Italy	RCT, single	Not treated	139, 29	102 (II–V), 66 (I–II)	Median (28M, 36F)
Starace et al., 2018	Italy	UCT		10, 0	0, 10 (I–III)	33–64
Shetty and Goel, 2018	India	UCT		20, 0	20, (II–VI), 0	18–45
Butt et al., 2018	Pakistan	UCT		30, 0	20 (III–VI), 10 (I–III)	19–47
Al-aajem, 2018	Iraq	UCT		64, 0	32 (II–V), 32 (NR)	18–48
Ahmad et al., 2018	Pakistan	UCT		10, 0	7 (NR), 3 (NR)	19–34
Gentile et al., 2018	Italy	CCT	Saline (half-head)	23, 23	18 (I–V), 5 (I–II)	21–70
Pakhomova et al., 2018	Russia	UCT		25, 0	25 (II–IV), 0	20–43
Lakshmi et al., 2018	India	UCT		30, 0	16 (II–V), 14 (NR)	25–50
Ayatollahi et al., 2017	Iran	UCT		13, 0	13 (III–VI), 0	24–60
Gentile et al., 2017 Group A-PRP	Italy	RCT, double	Placebo (half-head)	18, 18	18 (II–IV), 0	19–63
Jha et al., 2017	India	CCT	Minoxidil with Finasteride	20, 20	20 (II–V), 0	22–40
Anitua et al., 2017	Spain	UCT		19, 0	13 (III–VI), 6 (II)	27–60
Kachhawa et al., 2017	India	CCT	Saline (half-head)	44, 0	44 (III–VI), 0	18–55
Ince et al., 2017	Turkey	RCT, not blinded	2nd PRP method, Donor matched platelets	15, 16, 15	46 (II–IV), 0	25–35
Puig et al., 2016	USA	RCT, double	Saline	15, 11	0, 26 (II)	>18
Alves et al., 2016	Spain	RCT, double	Saline (half-head)	25, 25[b]	12 (II–V), 13 (I–III)	18–65
Gentile et al., 2015	Italy	RCT, single	Saline (half-head)	23, 23	23 (IIa–IV), 0	19–63
Mapar et al., 2015	Iran	RCT, single	Saline (half-head)	17, 17	17 (IV–VI), 0	25–45
Singhal et al., 2015	India	CCT	Unspecified medical treatment	10,10	16 (I–IV), 4 (I–II)	25–35
Gkini et al., 2014	Greece	UCT		20, 0	18 (II–V), 2 (I3)	24–72
Kang et al., 2014	Korea	CCT	Placenta extract	13, 13	15 (NR), 11 (NR)	22–62
Khatu et al., 2014	India	UCT		11, 0	11 (II–IV), 0	20–40
Schiavone et al., 2014	Italy	UCT		64, 0	42 (II–V), 22 (I–II)	Median (28M, 32F)
Sclafani et al., 2014	USA	UCT		15, 0	9 (III–V), 6 (I–II)	43.2
Betsi et al., 2013	Switzerland	UCT		42, 0	34 (I–VII), 8 (I–II)	32–67
Takikawa et al., 2011	Japan	CCT	Saline (half-head)	26, 26	16 (NR), 10 (NR)	28–59

RCT: randomized controlled trial; CCT: controlled clinical trial; UCT: uncontrolled clinical trial.
[a]Alopecia staging for males is by the Hamilton–Norwood Scale and for females is by Ludwig Scale.
[b]Patient dropout of one male and two female patients were not reported as being treatment or control groups, so table numbers for this study are those of initial enrollment.

0.04–1 mL cm^{-2}). PRP treatment methods included injection (e.g. subcutaneous or intradermal) or by topical application combined with microneedling, and one study used a mechanical gun to deliver interfollicular injections (63). The number of treatment sessions was a mean of 3.3 (range: 1–6), with most investigators spacing out the treatments by 1 month (range: 1 week to 3 months).

Risk of bias assessment

Cochrane risk of bias analysis of the 10 RCTs is described in Figure 2 (41,44–46,50,54–57,64).

Outcomes

Table 3 outlines the outcome measurements of patients treated with PRP. Twenty-nine studies (97%) reported positive outcomes for hair growth with 24 (77%) reaching statistical significance ($p<.05$) in at least one measured outcome. Of the RCTs, eight out of 10 reported a statistically significant improvement to hair growth following PRP treatment.

Meta-analysis

Among the studies selected for qualitative analysis that measured hair density, five RCTs had comparable data on hair density (41,45,56,57,64), and two RCTs had comparable data on hair thickness (56,57). Treatment protocols included in the meta-

Table 2. PRP preparation and treatment protocols.

Study author, year	Blood drawn	Centrifugation protocol: setting, time	Activators	Anti-coagulant	PRP injected (total, each injection) platelet concentration	Depth of injection	Treatment times	Anesthesia
Rodrigues et al., 2019	60 mL	Single spin: 1258 g for 15 minutes	Autologous serum[a]	EDTA or ACD	2 mL, 0.1 mL 5× more than normal	Subcutaneous	Day 0, 15, 30, and 45	Topical 10% lidocaine
Tawfik and Osman, 2018	10 mL	Double spin: (1) 1200 g for 15 minutes (2) 2000 g for 10 minutes	Calcium gluconate	Sodium citrate	NR, 0.9 mL NR	Intradermal	Week 0, 1, 2, and 3	NR
Hausauer and Jones, 2018	22 mL	Single spin: 3500 rpm for 10 minutes	NR	NR	~4–6 mL, 0.2–0.5 mL 4–6× more than normal	Subdermal	Group 1: month 0, 1, 2, and 5 Group 2: month 0 and 3	Optional topical lidocaine 23%, tetracaine 7% ointment
Schiavone et al., 2018	60–120 mL	Single spin: 1500 rpm for 5 minutes	[b]	ACD	6–14 mL, NR 4.5× more than normal	Very superficial scalp after 1–2 mm microneedling	Month 0 and 3	NR
Starace et al., 2018	10 mL	Single spin: 2500 rpm for 10 min	NR	ACD	5 mL, 1 mL NR	Interfollicular	Week 0, 2, 4, and 6	Topical cream
Shetty and Goel, 2018	20 mL	Double spin: (1) 1500 rpm for 6 minutes (2) 1062 g for 15 minutes	None	Sodium citrate	2–3 mL, NR 6× more than normal	Nappage technique	Week 0, 3, and 6	Topical cream
Butt et al., 2018	9 mL	Single spin: 1000 rpm for 10 minutes	None	Yes	NR, 0.005–0.1 mL/cm^2 NR	Depth of 1.5–2.5 mm (Nappage technique)	Month 0 and 1	Topical gel
Al-aajem, 2018	9 mL	Single spin: 3500 rpm for 10 minutes	None	Sodium chloride	4–5 mL, NR NR	NR	3–6 sessions; 2–4 weeks apart	Topical lidocaine
Ahmad et al., 2018	NR	NR	NR	NR	NR	NR	Month 0, 1, and 3	NR
Gentile et al., 2018	55 mL	Single spin: 260 g for 10 minutes	None	ACD	~9 mL, 0.2 mL/cm^2 NR	Intrafollicular via needle or at 5 mm depth by mechanical gun	Month 0, 1, and 2	None
Pakhomova et al., 2018	18 mL	Double spin: (1) 1800 rpm for 5 minutes (2) 2500 rpm for 10 minutes	Calcium chloride	Sodium citrate	NR, 0.15 mL NR	Intradermal	Month 0, 1, 2, and 3	None
Lakshmi et al., 2018	20 mL	Double spin: (1) 1500–2000 rpm (2) 2500 rpm for 15 minutes	Calcium chloride	Sodium citrate	2–3 mL, NR NR	Nappage technique	4 sessions; 14–21 days apart	PRP anesthetic cream
Ayatollahi et al., 2017	8 mL	Single spin: 1500 g for 5 minutes	None	NR	2–4 mL, 0.05 mL/1–2 cm NR	Intradermal	Week 0, 2, 4, 6, and 8	NR
Gentile et al., 2017 Group A-PRP	55 mL	Single spin: 1200 rpm for 10 minutes	None	Sodium citrate	9 mL, 0.2 mL/cm^2 NR	Interfollicular at depth of 5 mm using mechanical gun	Month 0, 1, and 2	None
Jha et al., 2017	15 mL	Double spin: (1) 160 g for 10 minutes (2) 400 g for 10 minutes	[b]	Yes	NR, NR NR	Injection depth of 1.5 mm after microneedling	Week 0, 3, 6, and 9	Supratrochlear and supraorbital nerve block (lidocaine)
Anitua et al., 2017	18 mL	Double spin: (1) 580 g for 8 minutes (2) 1000 g for 10 minutes	PRGF activator	Sodium citrate	3–4 mL, NR 2× more than normal	NR	Month 0, 1, 2, 4, and 7	NR
Kachhawa et al., 2017	16 mL	Double spin: (1) 1200 rpm for 8 minutes (2) 2400 rpm for 4 minutes	NR	ACD	1–2 mL, NR NR	Intradermal; 1 mm apart	Week 0, 3, 6, 9, 12, and 15	Topical cream

(*continued*)

Table 2. Continued.

Study author, year	Blood drawn	Centrifugation protocol: setting, time	Activators	Anti-coagulant	PRP injected (total, each injection) platelet concentration	Depth of injection	Treatment times	Anesthesia
Ince, 2017	n-PRP: 40 mL a-PRP: 10 mL h-PRP: NS	n-PRP: single spin 3000 rpm for 15 minutes a-PRP: double spin (1) 3000 rpm for 15 minutes (2) 2000 rpm for 5 minutes h-PRP: N/A; blood bank	n-PRP: none a-PRP: calcium chloride	NR	n-PRP: 4–5mL, 0.05–0.1 mL (803,000 platelets/μL) a-PRP: 4–5 mL, 0.05–0.1 mL (1,120,000 platelets/μL) h-PRP: NR, 0.05–0.1 mL (1,420,000 platelets/μL)	Intradermal (depth of 1.5–2.5 mm)	Month 0, 1, 2, and 6	Local anesthetics
Puig et al., 2016	60 mL	NR	None	NR	10 mL, NR 2.75–3.4× more than normal	Subcutaneous	1 session	Ring block of 50:50 lidocaine 2%, bupivacaine 0.5%
Alves et al., 2016	18 mL	Single spin: 460 g for 8 minutes	Calcium chloride	Sodium citrate	3 mL, 0.15 mL/cm^2 3× more than normal	NR	Month 0, 1, and 2	None
Mapar et al., 2016	9 mL	Double spin: (1) 3300 rpm for 6 minutes (2) 3330 rpm for 3 minutes	Calcium gluconate	ACD	1.5 mL, NR 3× more than normal	Deep dermal	Month 0 and 1	NR
Gentile et al., 2015	18 mL and 60 mL	(18 mL) single spin: 1100 g for 10 min or (60 mL) single spin: 1200 rpm for 10 min	18 mL: calcium concentrate 60 mL: none	Sodium citrate	9 mL, 0.1 mL/cm^2 1,484,555 platelets/μL	Interfollicular	Month 0, 1, and 2	None
Singhal et al., 2015	20 mL	Double spin: (1) 1500 rpm for 6 min (2) 2500 rpm for 15 min	Calcium chloride	ACD	8–12 mL, NR NR	Nappage technique	Week 0, 2, 4, and 6	NR
Gkini et al., 2014	16 mL	Single spin: 1500 g for 5 min	Calcium gluconate	Sodium citrate	6 mL, 0.05–0.1 mL/cm^2 5.8× whole blood	Nappage technique (depth of 1.5–2.5 mm)	Week 0, 3, 6, and 26	Local anesthetic
Kang et al., 2014	60 mL	NR	NR	Sodium citrate	4 mL, 0.05–0.1 mL/cm^2 5.9×	Interfollicular	Month 0 and 3	Local lidocaine 2%
Khatu et al., 2014	20 mL	Double spin: (1) 1500 rpm for 6 min (2) 2500 rpm for 15 min	Calcium chloride	Sodium citrate	2–3 mL, NR NR	Nappage technique	Week 0, 2, 4, and 6	Anesthetic cream
Schiavone et al., 2014	T1: 60 mL T2: 40 mL	T1: single spin T2: double spin	Filtered PPP protein concentrate	NR	9–12 mL, 0.2–0.3 mL 1,000,000 platelets/μL	Intradermal/ subdermal after microneedling at depth of 1 mm	Month 0 and 3	Local xylocaine 1%
Sclafani et al., 2014	18 mL	Single spin: 1100 g for 6 minutes	Calcium chloride	NR	6.68 mL ± 1.6 (8–9 produced), 0.1 mL NR	Intradermal	Month 0, 1, and 2	NR
Betsi et al., 2013	16 mL	Single spin: 1500 g for 5 minutes	NR	NR	8–12 mL, NR NR	NR	Month 0, 2, 4, 6, and 8	Anesthetic cream and cold roller
Takikawa et al., 2011	15 mL	Double spin: (1) 1700 rpm for 15 minutes (2) 3000 rpm for 15 minutes	Group 1: D/P MPs[a] Group 2: None	Sodium citrate	3 mL, NR 882,000 platelets/μL	Subcutaneous	5 sessions; 14–21 days apart	NR

D/P MPs: dalteparin and protamine microparticles; NR: not reported; RPM: rotations per minute; G: gravitational acceleration or relative centrifugal force; EDTA: ethylenediaminetetraacetic acid; ACD: anticoagulant citrate dextrose; PPP: platelet poor plasma; ∼: approximately.

[a]Extra non-activator additive.

[b]Microneedling performed is considered to be a physiological activator.

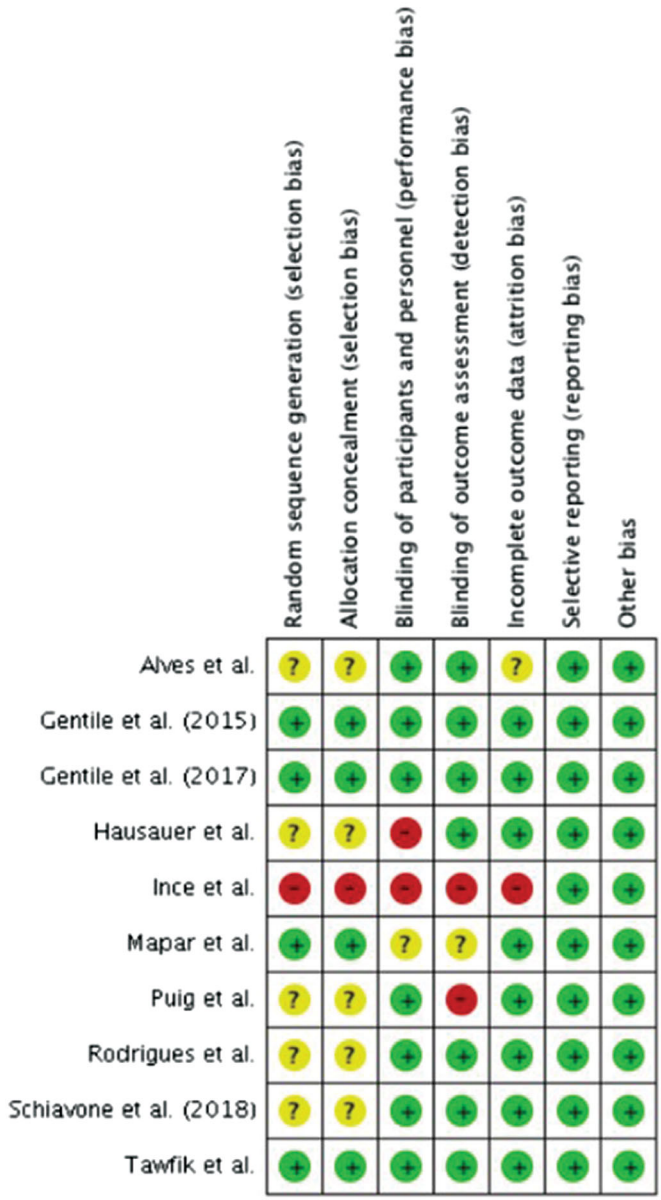

Figure 2. Cochrane risk-of-bias assessment was performed for 10 randomized controlled trials. Three studies had low risk-of-bias, four had unclear risk-of-bias, and three had high risk-of-bias.

analysis were four weekly treatments (56), three monthly treatments (41,45,64), or three monthly treatments followed by a treatment 3 months later (57). Controls included in the meta-analysis were placebo, physiologic solution, and saline (41,45,56,64).

Analysis of hair density

Five RCTs provided data on hair density (hairs cm^{-2}). Figure 3 illustrates the significant ($p<.0001$, $I^2=21\%$) increase in hair density between baseline measurements and measurements taken 3–7 months after PRP treatment initiation. Comparing hair density following treatment with PRP or control, Figure 4 illustrates that the hair density obtained following treatment with PRP was superior to control ($p=.002$, $I^2=0\%$). The change in hair density of the PRP and control groups from their baseline was compared as illustrated in Figure 5, demonstrating that PRP treatment resulted in a larger increase in hair density from baseline than the control group ($p=.003$, $I^2=0\%$).

To calculate a percentage increase of hair density following treatment with PRP, we used the nine measurements included in Figure 3. The mean increase in hairs cm^{-2} following treatment with PRP was 33 (range: 4–77), which is a 20% increase from the mean 163 hairs cm^{-2} present at baseline.

Analysis of hair thickness

Two RCTs provided comparable data on hair thickness (μm) for three groups of patients treated with PRP. Comparison of hair thickness following PRP treatment and the baseline measurements were performed as described in Figure 6. The meta-analysis contains significant heterogeneity between the two studies and shows that PRP significantly increases hair thickness from baseline ($p<.00001$, $I^2=97\%$). The study of Tawfik and Osman reported a doubling of hair thickness following PRP treatment, an improvement that may be attributed to their more frequent treatment protocol or to a difference of hair type inherent to the different patient populations presenting to the Egyptian clinic of Tawfik and Osman as compared to the United States clinic of Hausauer and Jones (56,57).

Hair thickness changes demonstrated in Figure 6 represent an increase from baseline of 49%; the mean increase in hair thickness was 32 μm (range: 8–110), and the baseline mean thickness was 65 μm (range: 55–100).

Adverse effects

Fifteen studies (50%) collected information on adverse effects, described in Table 3. No serious adverse events were reported. Study reporting on adverse effect incidence ranged from 0% to 100%, reflecting whether immediate post injection effects were included such as pain, erythema, edema, pinpoint bleeding, headaches resolving within 24 h, hematomas arising 48–72 h after treatment and resolving on days 4–5, and scalp sensitivity when washing their hair for the first time after treatment.

Discussion

Meta-analysis of increases to hair density and hair thickness

Our meta-analyses of RCTs demonstrate that PRP treatments significantly increase both hair density and hair thickness. The mean increase in hair density across our studies of 33 hairs cm^{-2} is highly clinically significant and represents a 20% increase in hair coverage before accounting for hair thickness. Although the hair thickness meta-analysis contained a limited number of studies containing high heterogeneity, it demonstrates that PRP increases hair thickness by 49%. The combined effect of a 20% increase in hair density and a 49% increase in hair thickness result in a 79% increase of hair coverage following treatment with PRP.

Comparison to other non-surgical treatments

In a 2017 meta-analysis of FDA approved treatment modalities, minoxidil, finasteride, and low-level laser light treatment were all shown to be effective treatments for specific demographics

Table 3. Study measurements of outcomes.

Study author, year	Follow up	Outcomes result and measurement	Adverse events
Rodrigues et al., 2019	3 months	SS findings vs. control: increases to hair count, hair density, anagen hair %; decrease to telogen hair % (TrichoScan) NS findings vs. control: terminal/vellus hair ratio (Trichoscan); Individual PDGF, EGF, VEGF correlation with outcomes	NR
Tawfik and Osman, 2018	6 months	SS findings vs. control: increased hair thickness, hair density (Folliscope) NS findings vs. control: hair pull test; patient satisfaction mean score of 7.0 out of 10	Pain, pinpoint bleeding
Hausauer and Jones, 2018	6 months	SS findings vs. other PRP group: hair count % change (Folliscope) SS findings vs. baseline: both groups increased hair count, hair shaft caliber (Folliscope) NS findings vs. other PRP group: hair caliber (Folliscope) NS findings vs. baseline: hair count of group 2 at 3 months (Folliscope); patient satisfaction mean score of 2.3 (0–3 scale); 82% patients satisfied or highly satisfied at 6 months	Pain, headache, itching
Schiavone et al., 2018	6 months	SS findings vs. control: GPA scale, Jaeschkle's scale	Bruising for 2–3 days
Starace et al., 2018	24 weeks	SS findings vs. baseline: increased hair diameter (Trichoscan) NS findings vs. baseline: hair density, vellus hair % (Trichoscan); measurement of differences between scalp areas	NR
Shetty and Goel, 2018	3 months	SS findings vs. baseline: increased hair count, hair density (Trichoscopy) NS findings vs. baseline: 50% of patients achieved a negative hair pull test; 35% of patients reported a 50–75% improved hair growth, terminal hair counts increased, decreases in perifollicular pigment, hair diameter diversity, yellow dots, white dots, multifollicular hair units, hidden hairs, honeycomb pigment patterns	Pain, erythema, burning sensation
Butt et al., 2018	6 months	SS findings vs. baseline: PRP increased hair density (TrichoScan), global assessment scores, and decreased hairs pulled out (hair pull test)	NR
Al-aajem, 2018	1 year	SS findings vs. baseline: increased hair number, hair growth, hair diameter, and hair thickness (subjective clinical assessment), and reduced hair loss and hairs pulled out (hair pull test) NS findings vs. baseline: treatment efficacy correlated with treatment number. Patients with *Staphylococcus aureus* scalp ulcers had lesion improvement 45% of the time following treatment with PRP	NR
Ahmad et al., 2018	9 months	SS findings vs. baseline: increased hair caliber (hair caliper)	NR
Gentile et al., 2018	3 months	SS findings vs. baseline: increased hair count and hair density (Tricoscope)	NR
Pakhomova et al., 2018	4 months	SS findings vs. baseline: increased hair density, vellus hair %, hair diameter, telogen hair %, telogen/anagen ratio (trichoscopic analysis), and histologically measured hair follicles at the levels of sweat glands and the hair follicle mouth. At the level of the sebaceous glands, PRP increased vellus hair % and telogen hair %. NS findings vs. baseline: histologically measured hair follicles at the levels of the subcutaneous adipose tissue and sebaceous glands, and hair diameter at the level of the sebaceous glands.	NR
Lakshmi et al., 2018	3 months	SS findings vs. baseline: decreased hair loss (hair pull test) NS findings vs. baseline: global photography showed moderate improvement in hair coverage for 23 of 30 patients	Minimal pain, erythema, and pinpoint bleeding
Ayatollahi et al., 2017	3 months	SS findings vs. baseline: increased telogen hairs and decreased anagen hairs and lowered anagen/telogen ratio (Trichogram). NS findings vs. baseline: hair count, hair thickness (Trichogram). Patient satisfaction peaked following 4 injections. Physician global assessment showed no improvement and mild improvement in equal patients, and worsening in 1 patient.	Tolerable pain
Gentile et al., 2017 Group A-PRP	6 months	SS findings vs. control: increased hair count and hair density (TrichoScan). SS findings vs. baseline: histologic increase of epidermal thickness, follicle count, capillary density, Ki67+ containing % of epidermal and follicle cells (histology, growth factor quantification). NS findings: darker coloring of hair was achieved following 3 treatments.	NR
Jha et al., 2017	3 months	NS findings vs. baseline: increase in vellus and total hairs (Dermoscope), decrease in black dots and yellow dots (Global Photographs), 90% of patients had satisfaction over 75%, and hair pull test was negative following treatment in 70% of patients.	Mild pain in 35% of patients
Anitua et al., 2017	1 year	SS findings vs. baseline: PRGF increased hair density, hair diameter, terminal/vellus ratio, thick hair %, and decreased thin hair % (TrichoScan). Histologically, PRP increased epidermal thickness, Ki67+ basal keratinocytes, follicular Ki67+ cells per follicle, blood vessel density, and the terminal:miniature hair follicle ratio NS findings vs. baseline: 79% of patients reported decreased hair loss, 68% reported improved hair quality and appearance, and 58% wanted to continue the treatment. The mean blinded clinician improvement score was 0.75 out of 1.	Transient erythema and local edema.
Kachhawa et al., 2017	18 weeks	SS findings vs. baseline: increased hair density and hair thickness (TrichoScan) NS findings vs. baseline: hairs pulled out decreased (hair pull test). Mean satisfaction was 7.0 on 0–10 scale.	Pain in all patients

(*continued*)

Table 3. Continued.

Study author, year	Follow up	Outcomes result and measurement	Adverse events
Ince et al., 2017	12 months	SS findings for PRP groups: hair density increased most for h-PRP, then n-PRP, then a-PRP. SS findings vs. baseline: increase in hair density (Dermoscope) Other findings: platelet concentration was highest in h-PRP, then n-PRP, then a-PRP. Mean a-PRP platelet count was 57% of the platelet count of h-PRP.	NR
Puig et al., 2016	26 weeks	NS findings vs. control: increased hair mass index and hair density (Cohen hair check system, photography) Other findings: with treatment 13.3% reported substantially decreased hair loss, rate of hair loss, and increases in hair thickness and ease of styling (0% in control).	NR
Alves et al., 2016	6 months	SS findings vs. control: increased hair density (TrichoScan). SS findings vs. baseline: increased anagen hair %, terminal hair density, and anagen/telogen ratio, and decreased telogen hair % (TrichoScan, Global Photographs). Other findings: density was only significant when reported as hairs/cm^2, not when reported as hairs/0.65 cm^2	Pain
Mapar et al., 2016	6 months	NS findings vs. baseline: Increased Terminal hair count, vellus hair count (magnifying glass)	NR
Gentile et al., 2015	2 years	SS findings vs. control: increased hair density, hair count, terminal hair density (Trichogram, Global Photographs), SS findings vs. baseline: histologically increased epidermal thickness, follicle count, capillary density, Ki67+ containing % of epidermal and follicle cells. NS findings vs. control: increased vellus hair density Other findings: 12 months after last treatment, 4 patients relapsed with signs of progressive hair loss, this was most obvious at 16 months after treatment (Global Photography).	NR
Singhal et al., 2015	3 months	NS findings vs. baseline: hair pull test had a 65% mean reduction in hairs pulled out. Hair growth was observed by 7–15 days in all patients (Global Photographs).	Headache (30%) resolved with paracetamol.
Gkini et al., 2014	1 year	SS findings vs. control: increased hair density (Dermoscopy) and decreased hairs pulled out in the hair pull test. Other findings: improvements peaked at 3 months after the study start. Patients reported increased hair quality and hair thickness (85%) and hair density (65%), and an overall satisfaction of 7.1 out of 10.	Pain in all and temporary scalp sensitivity in 60%.
Kang et al., 2014	6 months	SS findings vs. control: increased hair thickness at 6 months (Folliscope). SS findings vs. baseline: PRP increased hair thickness and hair count (Folliscope, Phototrichogram). NS findings vs. control: hair thickness at 3 months, hair count at 3 and 6 months. Other findings: gender, age, and concomitant finasteride in males did not significantly affect outcomes.	Pain, transient erythema, and edema ($n = 3$).
Khatu et al., 2014	3 months	SS findings vs. baseline: decreased hairs pulled out in the hair pull test, and increased hair count (TrichoScan, Global Photographs). Other findings: patient satisfaction was a 7.0 out of 10	Pain, transient erythema, and pinpoint bleeding.
Schiavone et al., 2014	6 months	NS findings vs. baseline: clinical rating change was not determined by patient gender, age, blood platelet count, or baseline GPA (clinical rating change, Global Photographs). Other findings: 2 evaluators noted improvement in 100% and 97% of patients, with chi-square showing a significant trend for higher baseline GPA predicting more improvement.	NR
Sclafani et al., 2014	6 months	SS findings vs. baseline: increased hair density index at 2 and 3 months NS findings vs. baseline: improved hair density index at 6 months Other findings: 25% improvement in hair density index at 2 months predicts the response retained at 6 months. Moderate baseline AGA improved more than severe baseline AGA.	Pain
Betsi et al., 2013	3 months	SS findings vs. baseline: reduced hairs pulled out in the hair pull test. Other findings: patients with more severe baseline AGA had less hair regrowth (Global Photography). Patient satisfaction was 7.0 out of 10.	Drowsiness and scalp sensitivity (31%)
Takikawa et al., 2011	12 weeks	SS findings vs. PRP and saline: the addition of D/P MPs increased hair cross sectional area (Dermoscopy). SS findings vs. baseline: groups had histologic increases in epithelium thickness, fibroblasts, collagen, and perifollicular vascularity. NS: no difference in hair count between PRP groups. Other findings: patients in both PRP groups reported less depilation following shampooing, and increased bounce and resilience of hair.	Pain

SS: statistically significant finding; NS: non-statistically significant finding; GPA: global physician assessment score is 5-point scale assessing severity of AGA as very mild, mild, moderate, severe, or very severe; GAS: growth assessment score is a 4-point scale assessing treatment response as poor, satisfactory, good, or excellent; NR: not reported.

TrichoScan and Folliscope are commercial brands of noninvasive phototrichogram systems. Trichogram is a semi-invasive test that extracts roughly 50–100 hairs allowing for in depth assessment of the hair roots.

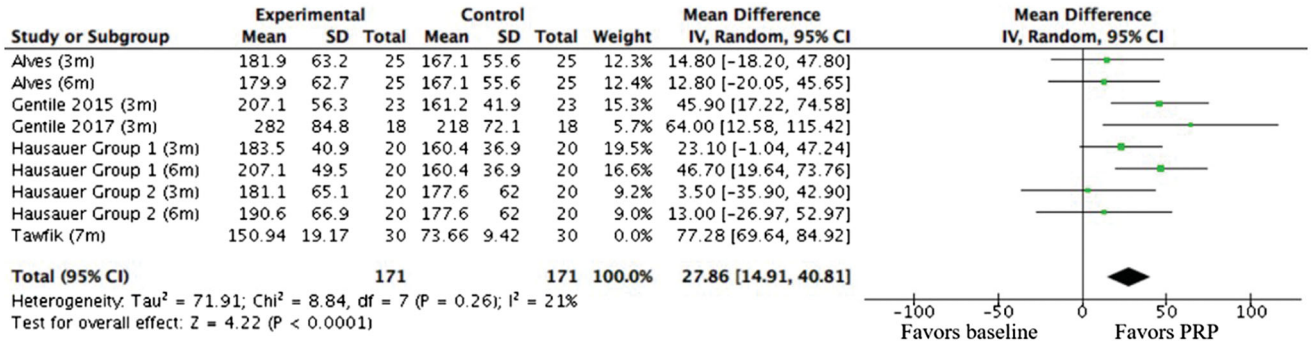

Figure 3. Meta-analysis of hair density data from five randomized controlled trials demonstrates that groups treated with PRP had statistically significant increased hair density as compared to baseline.

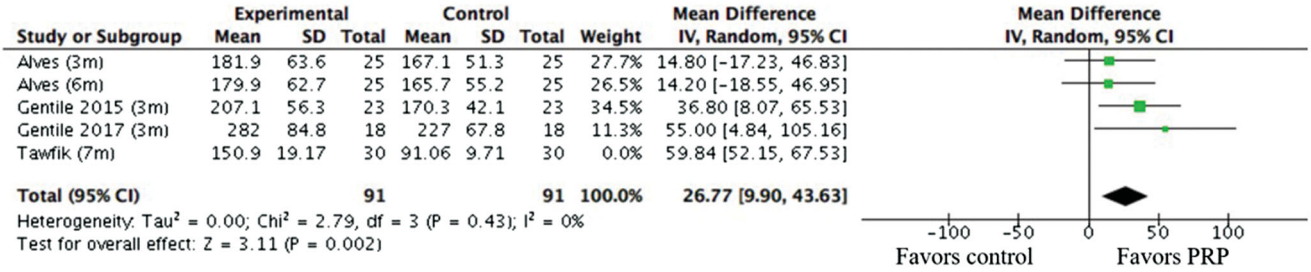

Figure 4. Meta-analysis of hair density data from four randomized controlled trials demonstrates that groups treated with PRP had statistically significant greater hair density than control.

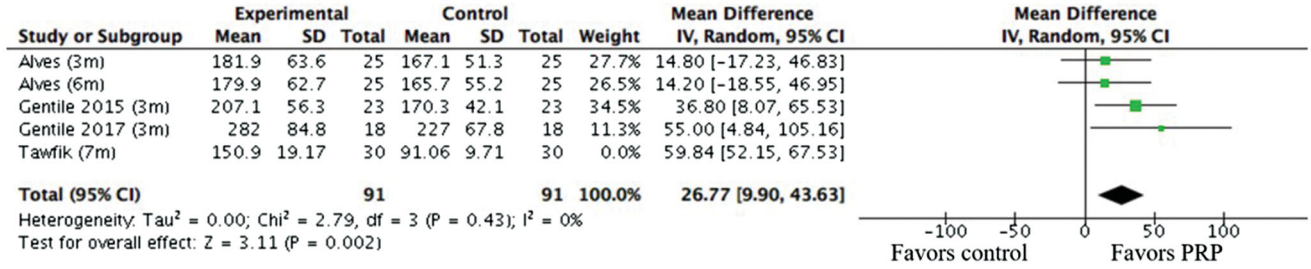

Figure 5. Meta-analysis of hair density data from four randomized controlled trials demonstrates that PRP treatment produces a change in hair density that is statistically significant as compared to control.

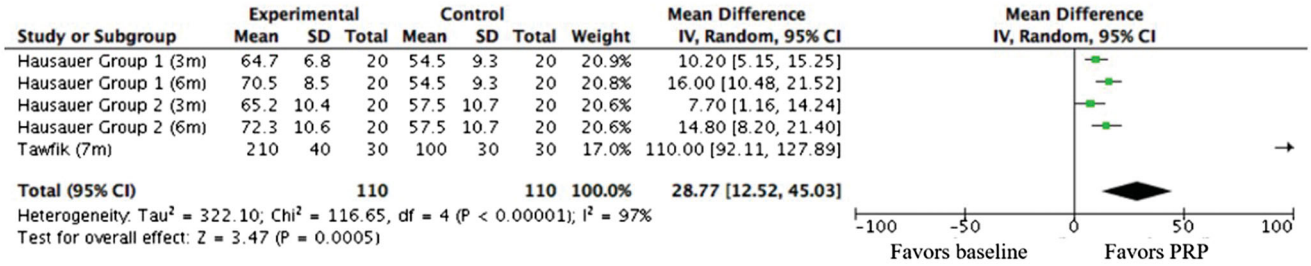

Figure 6. Meta-analysis of hair thickness data from two significantly heterogeneous randomized controlled trials demonstrates that groups treated with PRP had statistically significant increased hair thickness as compared to baseline.

of patients suffering from AGA (11). When comparing the results, our meta-analysis of PRP to the FDA approved treatments, PRP appears to be as effective, if not more effective.

With an average increase in hair density from baseline of 21–111 hairs cm^{-2} in RCTs, PRP appears to outperform finasteride 1 mg daily (18.37 hairs cm^{-2}), LLLLT (17.66 hairs cm^{-2}), 5% minoxidil twice daily (14.94 hairs cm^{-2}), and 2% minoxidil twice daily (8.11 hairs cm^{-2}) (11). The consistent positive trend across all analyses should prompt clinicians to consider PRP as a viable alternative to approved modalities. Additionally, given the recent results of Starace et al. that pointed to some female patients having success with PRP after failing minoxidil, the evidence points to a stronger role for PRP in the treatment of AGA (58). The very minimal and transient side effects of PRP injection like pain or pinpoint bleeding are highly favorable compared to the potential effects of approved treatments which include decreased libido, erectile dysfunction, and impaired hepatic function (10,11).

Recent studies

Rodrigues et al. (55) conducted an RCT on the efficacy of activated PRP in 26 male patients. The participants in this study received four sessions of either subcutaneous PRP injections, or saline injections in the control arm every 15 days. After final injection, patients were evaluated by TrichoScan (*TRICHOLOG GmbH*, Freiburg, Germany) at 15 days, and 3 months where there was a significant increase in hair density ($p=.012$), hair count ($p=.016$), and percent follicles in anagen phase ($p=.007$) in the study group, while in the saline control group there were no significant changes to any of these parameters at follow up. No significant differences in terminal to vellus hair ratios were observed. Additionally, the authors measured concentrations of VEGF, PDGF, and EGF within the PRP preparations; however, they were unable to draw a correlation between hair parameters and growth factor concentrations (55).

In 2018, Tawfik and Osman (56) examined 30 female patients in a half-head, double-blind RCT with activated subcutaneous PRP versus saline. Treatments were administered once-weekly for four weeks and patients were followed up to 6 months. Measured by Folliscope (Model DLite, STR Company, Felton, CA), there was a significant increase in both hair density and hair thickness in the PRP treatment areas with a negative hair pull test, an average of three hairs in 83% of patients. Overall patient satisfaction with the PRP treatment areas was seven out of 10 with results maintained at 6-month follow-up (56).

An RCT examining 30 male and 10 female patients was completed by Hausauer and Jones (57) examining the effects of the number of PRP treatments on AGA in both genders. In this single blind study, patients were either treated with three monthly injections of non-activated PRP with an additional treatment 3 months after that, or were treated with two treatments every 3 months. At 6 months of follow-up, both groups demonstrated a significant increase in hair count and shaft caliber measured by Folliscope (Folliscope 2.8; Anagen Corp., Seoul, Korea) ($p<.001$). The monthly treatment group had a more substantial increase in mean percent change of hair count (29.6, SD 13.6) compared to the less frequent protocol (7.2, SD 10.4, $p<.001$), however, both treatments overall had 82% either 'satisfied' or 'highly satisfied' patients (57).

Schiavone et al. (50) conducted a 2018 RCT on 102 male and 66 female patients who received two treatments with activated injectable leukocyte-rich PRF, injected after microneedling of the scalp over the course of 3 months. These patients were compared to controls who received no intervention, and were assessed at 6 months after treatment by GPA by five blinded experts. There was a significant improvement in the GPA across all ages ($p<.001$) and genders ($p<.001$). It is also worth noting that the clinical and statistical significance appeared to increase in more severe grades of AGA. Even patients with very mild AGA showed significant improvements ($p=.038$). Using a similar administration method, Jha et al. (68) examined the effects of non-activated PRP injection after micro needling, once a month for three months in 20 male patients with mild to moderate AGA in a prospective. Assessment after final treatment demonstrated a 70% reduction in positive hair pull tests in the treatment cohort (68).

A prospective half-head controlled trial was conducted by Gentile et al. (63) in 2018 assessing the effects of non-activated PRP injection on half the scalp of five female and 18 male patients with AGA. Over the course of three monthly treatments with PRP and control with saline, follow-up three months after final treatment showed a 31% increase in hair density in the treatment sections versus a 1% increase in the control sections of the scalp ($p<.05$) (63).

In a 2018 prospective cohort study, Bayat et al. (33) injected activated PRP into the scalps of 19 men with Hamilton–Norwood grade III to V AGA for three monthly sessions. Upon follow-up at 3 months, there was a significant increase in hair thickness and number by dermoscopy in addition to a positive change by Jaeschkle's 15 point scale ($p<.001$); however, they did not note any additional benefit after the second injection (33).

Starace et al. (58) studied 10 female patients who had failed treatment with minoxidil or other oral antiandrogens. Patients were treated with non-activated PRP every 2 weeks for four total rounds. Using global photographs and Trichoscan FotoFinder dermatoscope® (Teachscreen Software, Bad Birnbach, Germany), patients had a significant relative percent increase in hair diameter of 14.6% ($p<.05$) at 24 weeks; however, the results of global assessment and hair pull were not reported (58). In a similar prospective comparative study, Shetty and Goel (60) administered three treatments with non-activated PRP over the course of 3 months to 20 males and found a 27.4% increase in hair number and 15.7% increase in hair density ($p<.05$) at 3 months from baseline measurements. They also found improvement in hair pull test in 70% of patients. An important limitation in this case is that this was a shorter follow up period than is needed to assess longevity of results (60).

Butt et al. (61) conducted a prospective study of 20 male and 10 female patients who received two total injection treatments with non-activated PRP, a month apart and were assessed at 6 months after final treatment. Using TrichoScan (*TRICHOLOG GmbH*, Freiburg, Germany) and hair pull test, they observed a 29.2% reduction in hair pull test ($p<.05$), and a 46% increase in hair density of treated areas ($p<.05$) at final assessment (61). This is similar to the results of Jhansi Lakshmi et al. (66) in their uncontrolled clinical trial of 16 male patients with male- and female-pattern AGA, treated with activated PRP injected every 2 weeks for four total sessions. At final assessment 12 weeks after initiation of treatment, hair pull test was negative in nine patients versus 0 patients prior to treatment initiation; however, changes in hair count and hair density were not reported (66). This trend in negative hair pull tests was observed by Al-aajem (62) when in 32 male and 32 female patients with AGA, treated with 3–6 sessions of monthly PRP injection, there was 100% conversion to negative hair pull test as well as a 30% increase in overall hair growth ($p<.05$) (62).

When examining the morphological effects of non-activated PRP administration, Pakhomova et al. (65) found that in 22 males with AGA, once monthly treatment over 4 months resulted in a 10% increase in hair diameter and an 11% increase in hair density ($p<.01$) with this diameter increase seen at the level of the bulb of the follicle and the sweat gland (65).

Limitations and future opportunity

Substantial variability exists in PRP preparation methods between recent studies. There is support for improved results following protocols using activated PRP and double-spin protocols (21,71). Furthermore, the studies that did not report statistically significant results mainly utilized single spin protocols and were less likely to add an activator of PRP. Until future

research elucidates comparable results from optimized protocols, it is prudent for clinicians to utilize double spin protocols with added activators as a standard preparation.

Tawfik and Osman reported astounding results relative to other RCTs; a doubling of both hair thickness and hair density with low standard deviations (56). Their study provided significant heterogeneity to the meta-analysis and therefore was weighted at 0%, but presents opportunity for future studies to investigate whether their protocol or Egyptian population contributed to the success of their treatment. They also utilized a frequent injection protocol of four total injections within 1 month, whereas most other RCTs utilized three total injections spaced out over 2 months. Future studies investigating higher numbers of injections should bear in mind that Ayatollahi et al. reported a telogen effluvium induced by their five injections that were separated by 2 weeks (67).

There remains a need for clinical trials providing an evaluator-blinded, direct comparison between FDA approved therapies and the PRP treatment regimens shown to be superior. Such a direct comparison may help elucidate the role of PRP in managing AGA. Additionally, future trials should ensure a more rigorous matching of cohorts by age, gender, and grade of AGA.

Conclusions

Autologous PRP is an effective treatment for increasing hair density and hair thickness in AGA. Compared to other approved treatments, PRP appears to be more effective and is also a treatment option that lacks serious adverse effects. As a new treatment option, many opportunities exist for future research. More large RCTs with low risk-of-bias are needed to evaluate the effect on hair thickness, to optimize treatment protocols, to investigate variability between different study populations, and to compare PRP with the other approved non-surgical treatment modalities for AGA. Investigation of treatment protocols should proceed with a stepwise modification of the protocols that have been shown to be superior in published studies.

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