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REVIEW ARTICLE

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Platelet-rich plasma for androgenetic alopecia: Does it work? Evidence from meta analysis

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Summary

Introduction: The use of platelet-rich plasma (PRP) has increased among different surgical specialities for the treatment of various conditions. Androgenetic alopecia is a common condition, with severe attendant psychosocial implications. PRP injections for hair restoration have become a popular practice among plastic surgeons. We performed a meta-analysis comparing local injection of platelet-rich plasma versus control to evaluate this issue in order to investigate the effectiveness of PRP local injections for androgenetic alopecia.

Methods: A systematic literature search was performed. Primary outcome was the increase in number of hairs. Secondary outcomes were the increase in hair thickness and the percentage increase in hair number and thickness. We performed random-effect analysis.

Results: Six studies involving 177 patients were retrieved and included in the present analysis. A significantly locally increased hair number per cm^2 was observed after PRP injections versus control (mean difference (MD) 17.90, 95%CI 5.84-29.95, P=.004). Similarly, a significantly increased hair thickness cross section per 10^{-4} mm^2 (MD 0.22, 95%CI 0.07-0.38, P=.005) favoring PRP group. The pooled results did not show statistically significant differences in percentage increase in hair number (MD 24.12%, 95%CI −12.76-60.99, P=.20) and hair thickness (MD 32.63%, 95%CI −16.23-81.48, P=0.19) among patients treated with PRP.

Conclusions: Local injection of PRP for androgenic alopecia might be associated with an increased number of hairs and some hair thickness improvement in the treated areas with minimal morbidity. The results of this meta-analysis should be interpreted with caution as it consists of pooling many small studies. Larger randomized studies can verify this perception.

KEYWORDS
androgenetic alopecia, hair growth, hair restoration, platelet-rich plasma(PRP)

1 | INTRODUCTION

Androgenetic alopecia also known as male pattern baldness is the most common hair loss disorder affecting up to 80% of men and up to 40% of women with Caucasian heritage. For patients, alopecia causes major discomfort due to altered appearance with significant implications in daily living and possible leading to depression and anxiety symptoms.[1]

Platelet-rich plasma (PRP) injections for hair restoration has emerged to a popular practice, because both highly demanding patients and surgeons are seeking for minimally invasive and

[Corrections added on March 25, 2017, after first online publication: "plated-rich plasma" has been changed to "platelet-rich plasma" throughout the article.]

cost-efficient treatment modalities for androgenic alopecia.[2] The scientific interest for PRP was raised in 2006 when Mishra and Pavelko managed to demonstrate the PRP efficacy in improving elbow epicondylitis, reducing the time for healing.[3]

Platelet-rich plasma is an autologous product that is manufactured by centrifugation from patients own venous blood limiting the potential risk of disease transmission. Components of PRP consist of several growth factors (GF), chemokines and cytokines, suggesting that its benefits include promotion of tissue healing in hard and soft tissues.[4-6]

Although there are several recent reports and small randomized controlled trials (RCT) examining the use of PRP for hair loss treatment, there are no sustained results on their overall efficacy,[7-9] and none of these studies has been sufficiently powered to assess the risk benefit of this modality.[10] We performed a whole comprehensive analysis hypothesizing that PRP might prove significant benefits in improving androgenetic alopecia.

2 | METHODS

The objective of this review was to assess the literature on Platelet-rich plasma outcomes for androgenetic alopecia, with a focus on specific clinical outcomes in a comparative view, in accordance with PRISMA statement for reporting this meta-analysis.[11] The present meta-analysis is registered in PROSPERO, an international prospective register of systematic reviews, with the reference code CRD42016041811.

2.1 | Search strategy

All authors individually carried out a full systematic literature search of all records through Medline, Cochrane Library, Embase, Scopus, Google Scholar, and Research Gate for any study on PRP use for hair growth therapy in androgenic alopecia from inception until September 30, 2016.

The terms employed in the search were as follows: "androgenic alopecia," "hair growth," "hair restoration," "baldness," "hair loss" combined with "platelet-rich plasma," "PRP"; and they were combined using Boolean operators. Each author's search results were merged, and duplicate citations were discarded. The search was performed aiming at those studies comparing outcomes of PRP treatment versus control for hair restoration. No language restrictions were applied.

2.2 | Study selection

We searched for and assessed studies comparing local injections of PRP compared to any control for androgenetic alopecia. Studies to be included in this review had to match predetermined criteria according to the PICOS (patients, intervention, comparator, outcomes, and study design) approach. Criteria for inclusion and exclusion are specified in Table 1. No limitations were applied on ethnicity, age of patients, or method of PRP processing. Two authors (SG and PL) independently reviewed the abstracts and articles. In addition, the reference lists of all relevant articles were scrutinized as well.

For the purpose of this analysis, the eligible studies were those reporting on quantitative outcomes on PRP compared with control treatment for androgenetic alopecia. Each study was independently evaluated by all three coauthors (SG, MR, PL) for inclusion or exclusion from this analysis (Table 1). In order to be included, studies had to provide details on baseline characteristics, type of procedure, method of PRP processing, and outcomes on hair regrowth compared with control patients or areas in the same patient (internal control).

2.3 | Data extraction

Data were independently collected by two investigators (SG and PL) and checked by a third investigator (MR) only from the retrieved articles. Disagreement on collected data was settled by consensus between these investigators. No any attempt was made to obtain specific or missing data from the authors. The following data were extracted: first author, year of publication, study design, number of patients, type of procedure, and primary and secondary measures.

TABLE 1 PICOS criteria for inclusion and exclusion of studies

Parameter	Inclusion criteria	Exclusion criteria
Patients	Patients of any age and stage of androgenetic alopecia	Other types of alopecia (ie alopecia areata or cicatricial alopecia)
Intervention	Local injections of any autologous platelet-rich plasma (PRP) preparation	
Comparator	Any type of control, internal, external, and different product.	
Outcomes	*Primary outcome measure*: increase hair number per cm^2. *Secondary outcome measures*: increase of hair thickness, percentage increase in hair number and thickness.	
Study design	Randomized controlled trials, nonrandomized observational trials, retrospective, prospective, or concurrent cohort studies. At least 10 patients. At least 3-month follow-up.	Reviews, expert opinion, comments, letter to editor, case reports, studies on animals, conference reports. Less than 10 patients. Shorter follow-up than 3 months. Studies with no outcomes reported.

The quality of the included studies was independently assessed by three investigators (SG, MR, and PL) using the Cochrane Collaboration's Risk of Bias Assessment tool for Randomized Controlled Trials (RCT),[12] while using the Newcastle–Ottawa Scale to evaluate the individual nonrandomized studies.[13] The research team convened to resolve any disagreement on the assessment and to reach consensus.

2.4 | Outcome measures

The primary outcome was the difference in number of hairs per square centimeter. Secondary outcomes were hair cross section increase, hair regrowth, and thickness percentage increase.

All outcomes obtained from the studies were reported with the same measurements retrieved from the articles. From one article, percentages were calculated from the patients' individual data showed in the study.[14] The patient's contralateral side was used as control in some of the included studies; while patients were allocated into groups where PRP was either used or not in the other studies. In both cases were accounted as one. Missing data were dealt according to previously validated estimations.[15,16]

2.5 | Statistical analysis

Statistical analysis was performed using Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Differences in continuous variables were expressed as mean difference (MD) with 95% CI. Heterogeneity was assessed by using I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[17] In all cases, we performed random-effect analysis, which consider the variation both within and between studies,[18,19] because of the observational nature of some studies included in this analysis. A $P<.05$ was considered statistically significant.

Finally, we conducted sensitivity analyses omitting each study in turn, using the "leave one out" methodology to determine whether the results were influenced excessively by a single study. Publication bias was assessed using the funnel plot for the primary outcome.

3 | RESULTS

Literature search yielded 16 articles, six[14,20-24] of which were pertinent to this issue and sources of information on outcomes using PRP injections on scalp for androgenetic alopecia (Table 2). The literature search flowchart is shown in Figure 1.

Four studies were RCT,[14, 22-24] while the other two were retrospective studies. [20,21]

In the RCT, the risk of bias was either low or unclear using the Cochrane Collaboration's tool for assessing risk of bias (see Table S1).[12] The non-RCTs were assessed with the Newcastle–Ottawa Scale for risk of bias resulting in 0-4 stars per category, indicating a high to low bias (see Table S1).[13] The difficulty blinding participants and researchers as well as the presence of internal control increased the overall risk of bias.

The age of the patients ranged from 19 years to 63 years, with a follow-up from 3 to 24 months. All the studies showed different centrifugation methods (Table 2).

Five studies,[14,20,21,23,24] involving a total of 117 patients, reported results on mean difference of number of hairs per cm^2 vs control and pooled analysis showed a significant difference between the two treatment groups (MD 17.90, 95%CI 5.84-29.95, $P=.004$; Figure 2). Similarly, this outcome persisted when only the 3 RCT were pooled together (MD 22.92, 95%CI 5.51-40.33, $P=.010$; Figure 3).

Among secondary outcomes, we also observed a significant difference between the two treatment groups concerning the hair cross section measured per 10^{-4} mm^2 (MD 0.22, 95%CI 0.07-0.38, $P=.005$; Figure 4) favoring PRP group, but these data were reported by only two studies.[14,21] We did not found a significant difference between the two treatment groups concerning the percentage increase in hair number (MD 29.19%, 95% −22.04, 80.41, $P=.26$ nor hair thickness (MD 32.63%, 95% −16.23, 81.48, $P=.19$). Although not statistically significant, these pooled results showed a trend toward an increase in hair number and hair thickness percentage.

Four of the included studies[20,22-24] did not report any adverse effects or complications associated with PRP injections. In the other two publications, information about possible adverse effects was not reported.

Finally, the exclusion of most studies from the analysis did not materially change the summary estimates, with sensitivity analysis using the "leave one out" methodology; however, significant asymmetry in the funnel plot was observed for primary outcome (Figure 5).

4 | DISCUSSION

The present meta-analysis, including six studies and encompassing a total of 177 patients, provides compelling evidence about PRP treatment for hair restoration in androgenetic alopecia. A significantly increased number of hairs per cm^2 was observed after treatment with PRP (Figures 2 and 3). We found interesting results also in hair cross section thickness and other secondary outcomes which showed a trend toward benefit (Figures 4). This is the first pooled analysis on this emerging topic, showing overall quantitative outcomes.

Platelet-rich plasma (PRP) therapy is an appealing emerging minimally invasive therapeutic modality to enhance tissue healing. PRP is an autologous product that is manufactured from patients own venous blood limiting the potential risk of disease transmission. By definition, PRP contains concentrated amount of platelet concentration, 1.000.000 per uL platelet count, threefold to eightfold superior amount as compared to the normal peripheral blood (range 150.000-350.000 uL).[24-26] Upon activation, platelets undergo degranulation, and rapidly an array of growth factors is released from platelet

TABLE 2 Characteristics of the included studies

Authors	Study type/ level of evidence	Number of patients	Control	Mean age (years)	Mean follow-up	Injection protocol	PRP preparation	Assessment method	Injected areas	Complications
Takikawa (2011)[14]	RCT/II	26	13	28-59	3 months	Injection 5 times (3 mL) of Dalteparin and protamine microparticles (D/P MPs) with PRP or PRP alone	15 mL of blood centrifuged for 15 minutes at 1700 rpm. The upper 1 cm collected and centrifuged for other 5 minutes at 3000 rpm	Dermoscopy	Frontal or parietal sites with lanugo-like hair	N/A
Cervelli (2014)[20]	Retrospective nonrandomized/ IV	10	Internal control	20-60	12 months	N/A	18 mL centrifugated at 1100 rpm for 10 minutes according to the method of Cascade–Selphyl–Esforax system	Dermoscopy	Frontal, parietal, vertex, and occipital areas at the amount of 0.1 mL/cm^2	none
Kang (2014)[21]	Retrospective nonrandomized/ IV	13	13	22-62	6 months	CD34+ cell-containing PRP preparation (4 mL) at 0.05-0.1 mL/cm^2 performedtwice at 3-month interval. Control received interfollicular placental extract.	60 mL of blood transferred to tubes containing 8 mL of 4% sodium citrate solution (Baxter Healthcare Corp., Deerfield, IL, USA). Then, the blood was centrifuged with SmartPReP2 platelet concentrate system (Harvest Technologies Corp., Plymouth, MA,USA)	USB camera magnification	(Follioscope®)	N/A
N/A										
Lee (2015)[22]	RCT/II	40	20	33.9 20-60	3 months	One PRP injection + 12 sessions polydeoxyribonucleotide (PDRN) injections weekly	60 mL of blood transferred to tubes containing 8 mL of 4% sodium citrate solution (Baxter Healthcare Corp., Deerfield, IL, USA). CD34+ cell-containing, leukocyte-rich PRP was prepared using SmartPReP2 platelet concentrate system (Harvest Technologies Corp., Plymouth, MA)	Digital camera at 40-fold magnification	0.05-0.1 mL/ cm^2 of the CD34+ cell-containing PRP preparation (4 mL in total) was injected along the scalp	none
Gentile (2015)[23]	RCT/II	20	Internal control	19-63	24 months	PRP injection 3 times at 1-month interval	60 mL of blood centrifugated at 1100 rpm for 10 minutes according to the Cascade–Selphyl–Esforax procedure, or at 1200 rpm for 10 minutes according to the P.R.L. (Platelet Rich Lipotransfert system).	Trichoscan digital image analysis	Injected frontal, parietal and vortex at the amountof 0.1 mL/cm^2	none

(Continues)

TABLE 2 (Continued)

Authors	Study type/ level of evidence	Number of patients	Control	Mean age (years)	Mean follow-up	Injection protocol	PRP preparation	Assessment method	Injected areas	Complications
Alves (2016)[24]	RCT/II	22	Internal control	21-62	6 months	PRP injection 3 times at 1-month interval	18 mL of blood transferred to tubes with 2 mL of 3.8% sodium citrate solution. Then, the citrated blood was centrifugated at 460 rpm for 8 minutes.	Trichoscan digital image analysis	PRP was injected into 4 areas (0.15 mL/cm^2)	none

PRP, Platelet-rich plasma; RCT, Randomized Controlled Trial; N/A, Not Available; rpm, revolutions per minute.

Alpha-granuli,[25] and growth factor release is continued in lesser extend up to several days.[27] PRP also contains plasma and over 20 growth factors, which include platelet-derived endothelial growth factor (PDGF), transforming growth factor-β (TGF-β), fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), epidermal growth factor, insulin-like growth factor-1 (IGF-1), and, in addition, thrombin, which has biological and adhesive properties.[28] PRP induces also overexpression endogenous expression of growth factors.[29,30] Through the complex interaction of growth and differentiation factors and along with adhesive protein factors, PRP is believed to stimulate healing by promoting regenerative chemotaxis, cell proliferation, angiogenesis, extra-cellular matrix formation, and collagen synthesis.[31,32]

Platelet-rich plasma is not a homogenous standardized product and differences in composition may lead to altered function, in part offering an explanation to the controversy in the literature. In part, differences in PRP composition result from differences in the samples retrieved from person to person. Differences in manufacturing of the inoculate result especially from the routine of centrifugation and whether either bovine thrombin or calcium chloride are used in activation.[10,26] The used end product may vary by the used volume and the number of injections administered, as well as the color, platelet count, the number or absence of leukocytes, and its protein content.[26]

Recently, a number of reports have been published showing promising results for the treatment of androgenetic alopecia. Unfortunately, these studies were generally poorly controlled, without outcomes' objective and measured quantification, and therefore, they were not included in this meta-analysis. Besti et al.[8] treated 42 alopecia patients with PRP, five times during over 2 months showing an improvement in hair pulling test and a high overall patient satisfaction. Indeed, they found in 31% of cases some drowsiness and sensible scalp. Schiavone et al.[9] performed so far the largest study on this topic, including 64 male patients with androgenetic alopecia and they were treated with a regimen of PRP enriched with leukocytes in addition to concentrated plasma proteins. Two sequential injections were performed at initiation of the study and subsequently at 3 months. Evaluation was performed on the basis of global assessment of before and after photographs by unblinded assessors showing an improvement in appearance for 62 of the 64 patients.[9] Another noncontrolled, nonblinded study of 22 patients found an increase in total hair density from a mean of 143.1 at baseline to a maximum of 170.7 hairs/cm^2 at 3 months follow-up.[33] Another noncontrolled, nonblinded study of 11 patients[34] detected a significant reduction in hair loss between first and fourth injection. Particularly, hair count increased from average number of 71 hair follicular units to 93 hair follicular units, with a negative pull test was in nine patients.[34]

Singhal et al.[35] performed a similar study on 10 patients also showing clinical improvement in the hair counts, thickness, and root strength. They indeed had three patients complaining a mild headache after the initial procedure. More recently, Navarro et al.[9] reported an overall increase in hair density and an increase of 6.2%

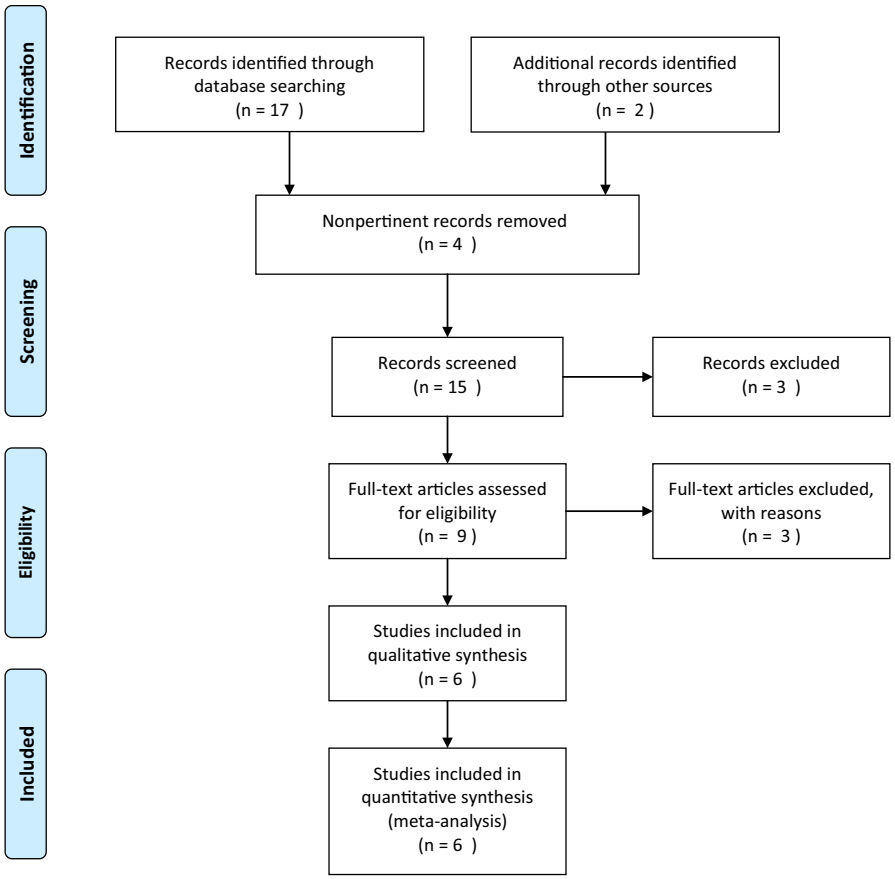

FIGURE 1 Flowchart summarizing the literature search results

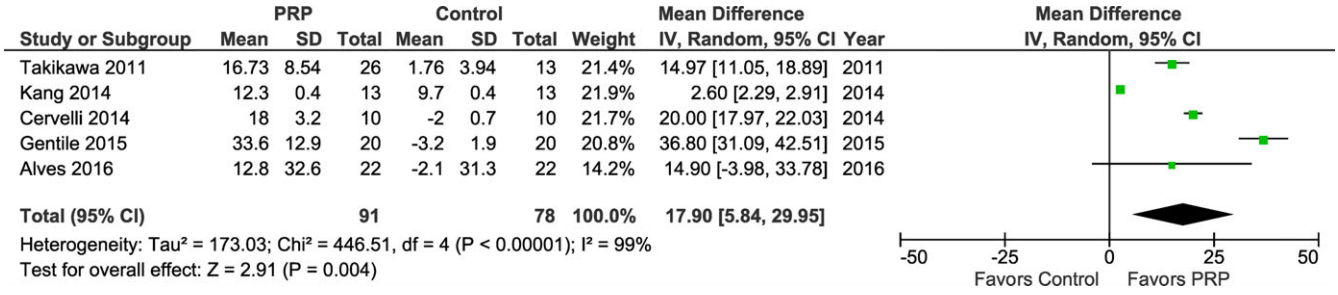

FIGURE 2 Forest plot showing the significantly increased number of hairs per cm^2 compared with control

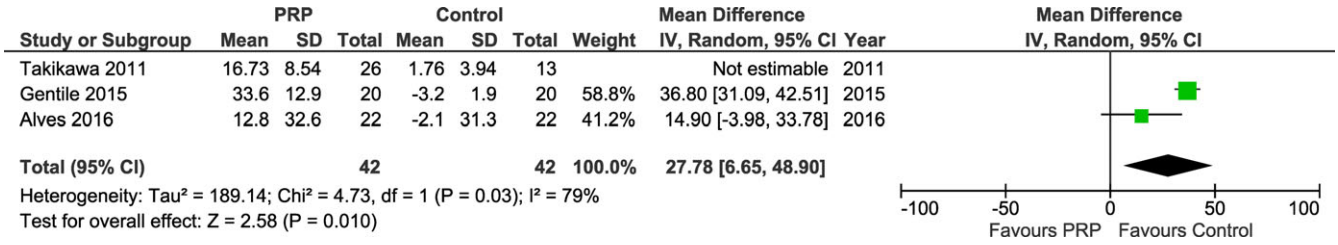

FIGURE 3 Forest plot showing the significantly increased number of hairs per cm^2 compared with control among RCT studies

anagen hair follicles, while a decrease of 5.1% among telogen ones on 100 patients treated with PRP, similarly to Alves et al.[24] We did not attempt to pool the data existing on hair follicle cycles, as they were not consistent among the included studies. Nonetheless, PRP showed promising results also combined with hair follicular transplant to enhance the postoperative outcomes.[36,37] Particularly, Uebel

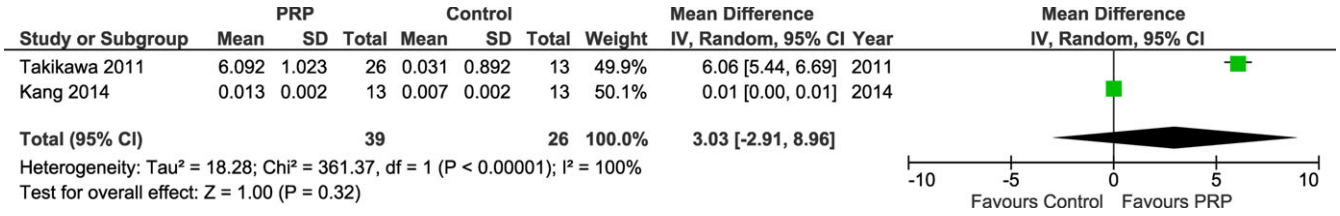

FIGURE 4 Forest plot showing the significantly increased thickness of hairs section expressed as 10^{-4} per mm^2 compared with control

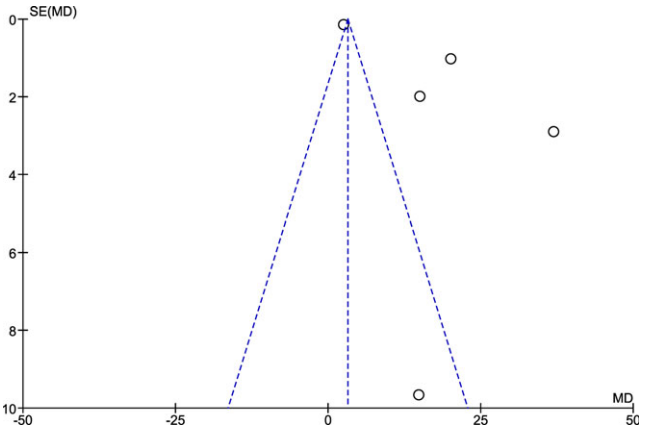

FIGURE 5 Funnel plot for bias assessment in hair number increase

studied a short series of patients comparing two areas of hair transplant with and without PRP in the root of the grafts. Two areas (2.5 cm^2) were marked on the scalp and each planted with 20 grafts/cm^2. After 1 year, the area implanted with the PRP-enriched grafts demonstrated a higher follicle units survival rate and density. In a murine model, Miao et al.[38] demonstrated some influence of PRP on hair regrowth when simultaneously injected with transplanted hair follicles, further encouraging clinical applications. Again, the data about PRP and hair growth, together with surgical hair transplant, are sparse and heterogeneous although promising. Nevertheless, these outcomes can be explained by the physiological role of platelets degranulation during inflammation, which is stimulated by surgical hair transplantation, a traumatic event causing inflammatory response and chemotaxis.[3]

The results of this meta-analysis must be viewed in light of a number of limitations and potential bias influencing these findings. Only six studies were used for this pooled analysis, only four of them were randomized controlled trial[14,22-24] and two were observational[20,21] with clear heterogeneity in methods and settings (Table 2). We wanted to include only comparative studies in order to better assess the efficacy of PRP, missing the outcomes of one-arm studies.

The number of patients considered was very small, and there were differences in patients' age and areas of treatment, particularly, the indications, the devices used, centrifugation methods, which all might be a confounding factors for the results presented in this meta-analysis.

Important statistical heterogeneity (I^2>75%) was found in all analysis (Figures 2-6), showing important differences in methods and study settings.

Other major limitations of this pooled analyses include the fact that most of the included studies used internal controls, where the patient's contralateral side or other areas served as its own control; while in others, patients were randomized into groups where PRP was either used or not used (Table 2). There were differences in the treated scalp areas, and in some cases, the control group was treated with placental extract[21] or dalteparin and protamine containing microparticles[14] with no placebo control.

Platelet-rich plasma injection for local hair restoration in patients with androgenetic alopecia seems to increase hairs number and thickness with minimal or no collateral effects. However, the current evidence does not support this treatments modality over hair transplantation due to the lack of established protocols (ie number of sessions, centrifugation, and zones to be injected), and long-term follow-up outcomes. Thus, the results of this meta-analysis should be interpreted with caution because it consists of pooling many small studies and larger randomized studies should be performed to verify this perception. The addition of PRP might be useful in improving the outcomes of hair transplantation procedures. Both paths of investigation must be traded to clarify these points.

The studies conducted so far on the effects of PRP on androgenic alopecia overall have shown quantitatively beneficial outcomes. Because of the low level of invasiveness, minimal side effects reported, and biological reasonableness, the research of PRP in future as possible therapeutic agent will benefit men and women with androgenic alopecia and allow to adopt more standardized treatment protocols.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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