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Efficacy of Platlet Rich Plasma in Androgenic Alopecia: Systematic Review & Meta-Analysis

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ABSTRACT

Introduction: Platelet-rich plasma (PRP) helps in hair growth by the release of growth factors and cytokines. Also it has multifactorial capabilities can also be used to treat aging skin, facial scarring, and acne. Hence in our current review we critically examine the success of PRP in the field of dermatology, specifically to the role of PRP in hair restoration. Where possible, meta-analyses were used to evaluate the efficacy of PRP.

Materials and methods: This review directed an electronic systematic literature search in MEDLINE (PubMed) and EmBase. Methodological quality was evaluated by using the Newcastle-Ottawa Scale tool. Odds ratio (OR) with 95% confidence interval (CI) was pooled to estimate the relative outcome of bruxism on dental implant failures. Statistical analyses done by using Review Manager 5.1.

Results: In androgenetic alopecia (AGA) patients, 3 monthly PRP injections showed exhibited greater efficacy over placebo as measured by change in total hair density (hair/cm^2) over the treatment period (mean difference: 25.61, 95% CI: 4.45 to 46.77; P=.02). The studies included in the meta-analysis used a half-head design, that may have influenced the results because of the effects PRP can induce. Organized studies recommend that 2 to 4 sessions of PRP collective with traditional therapies and techniques can help minimize acne scarring and facial burns, improve

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aesthetic results, and decrease recovery time. Nonetheless, data for these indications are lacking and are less robust in design.

Conclusion: It can be suggested that to achieve an improvement in hair restoration in patients with mild AGA, 3 initial monthly PRP injections should be given. Only upon completion of rigorous, randomized, controlled studies can standardized and effective PRP protocols for treating dermatology conditions such as acne scarring, facial burns, and aging skin be determined.

Keywords: PRP, Alopecia Areata, Facial Aesthetics, Meta-Analysis, Platelet-Rich Plasma

Introduction

Platelet-rich plasma (PRP) therapy includes concentration and administration of an autologous solution containing platelets found in whole blood. By the action of the growth factors and cytokines released from α granules found within platelets, PRP can promote cell survival, proliferation, and angiogenesis.[1-3] PRP can be used widely in the dermatology-based applications because of its multifactorial capabilities and anti-inflammatory effects.[4] The anti-inflammatory effect of PRP can combat localized micro-inflammation associated with hair loss conditions such as androgenetic alopecia (AGA).[4,6,7] PRP also improves the density of collagen fibers by activating fibroblasts, that can smooth scarring and revitalize skin's appearance.[8,9,10] There are many questions surrounding the use of PRP such as its effectiveness in a dermatology setting, what protocols dermatologists should be using, and whether these protocols should change based on the condition being treated. Addressing these questions can be difficult as many protocol parameters could influence the efficacy of PRP including the frequency and number of PRP sessions, presence of an activator, and the exact specifications of the collection system. Our study will specifically observe the role of PRP in hair restoration by evaluating its efficacy in AGA, alopecia areata (AA), cicatricial alopecia (CA), along with other potential facial aesthetic applications.

Materials and methods

A literature search in MEDLINE (PubMed) and EMBASE was conducted. The ensuing search terms were used: PRP, platelet-rich plasma, hair, alopecia, facial scarring, skin revitalization, facial burns, and facial surgery. In vitro studies and case studies were excluded. Clinical trials that evaluated the direct injection of PRP as a monotherapy treatment for patients with AGA, CA, or AA (diagnosed prior to treatment) were included.

To generate a meta-analysis, we required a minimum of 3 studies reporting the mean change from baseline for the same outcome metric. A GRADEpro assessment, based on Cochrane methodology, was used to grade the quality of evidence for studies included in the meta-analysis.[11] For hair restoration studies, outcome measures such as hair density (total hairs/cm2), hair count (total hairs/0.65 cm2), hair diameter (mm), hair shedding, and epidermal changes were examined. The meta-analysis was conducted using RevMan 5.3 (Copenhagen, Denmark). Efficacy was calculated using the mean difference (MD) between outcome measures, and heterogeneity was evaluated using the percentage of variation across studies that is due to heterogeneity rather than chance (I^2 statistic).[12,13] The reported efficacy was compared with a control group and $P < .05$ was considered significant.

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Results

In our review 23 met inclusion criteria and used PRP as a monotherapy for treatment of AGA (Table 1). Seven randomized, controlled trials (RCTs) were included[14-20]; all but one used a half-head design.[11] Four studies evaluated the efficacy of PRP in female pattern hair loss (4/23 = 17%),[14,15,21,22] 10 studies evaluated the efficacy of PRP in male pattern hair loss (10/23 = 43%),[17-19,23-27] and 8 studies evaluated PRP both in male and female pattern hair loss (9/23 = 39%).[16,28-35] PRP was most commonly delivered once a month for 3 months (6/23 = 26% of studies)[17-19,22,29,32,33,35] with 47% of studies (11/23) using some form of activation prior to injection (eg, calcium gluconate).[15-19,22,25,28,31-33] Platelet concentrations within PRP solutions varied from 2 to 6 times baseline platelet count, with 3 times baseline platelet count the most common concentration reported (Table 1).

Eight studies reported the leukocyte status of their PRP solutions: Two studies used a PRP solution rich in leukocytes,[21,34] 3 studies used a leukocyte-poor PRP solution,[16,32,35] Two studies used PRP solutions that might include leukocytes,[17,18] and one study used a leukocyte-free PRP solution.[14] Inter-follicular PRP injections (0.05 to 0.2 mL/cm^2) were the most common method used.[17,18,22,29,30] Approximately 50% of studies (6/12 = 50%) that reported needle gauge (G) used a 30-G needle when injecting PRP,[17-19,29,32] Averaging across studies, each patient had a total of 3.9 sessions of PRP at 3.5-week intervals and were age 37.6 years.

Efficacy was measured among AGA studies using a wide array of outcomes including but not limited to hair count(total hairs/0.65 cm2),[17,18] total hair density (total hair/cm2),[16- 18] terminal hair density (terminal hairs/cm2),[17,18] hair diameter (mm),[15,22,30,32] hair shedding,[14,26] and epidermal changes.[17,18,32] Four included studies compared the impact of PRP (3 sessions at 1-month intervals) on mean change in hair count, as defined as total hairs/0.65 cm2 from baseline, with placebo-treated patients.[14-18] Three of these studies found that PRP exhibited greater efficacy over placebo (all 3 studies $P < .05$),[17,18] whereas 1 study did not find a significant difference amongst these 2 treatments ($P > .05$).[16] Terminal hair density (terminal hairs/cm2) was evaluated in 3 placebo- controlled studies.[17,18] In 2 of these studies, 3 PRP sessions administered at 1-month intervals exhibited greater efficacy over placebo with response to mean change in terminal hair density by end of treatment ($P = .0003$ for both studies).[17,18] PRP also exhibited a greater efficacy over baseline measurements in hair diameter (mm) in 4[15],[22,30,32] of the 5 studies that evaluated this endpoint (all studies $P < .05$).[15,22,24,30,32] It was found both that interfollicular[22,30] and intradermal injections[15,24] made a significant impact in hair diameter. Across all included studies that evaluated epidermal change (4 studies), PRP-treated patients had a statistically significant increase in epidermal thickness compared with baseline measurements ($P<0.05$ for all 4 studies).[17,18,22,32] Half these studies reported the use of interfollicular injections, suggesting this depth may be required to create an epidermal change.[17,18] Two included studies evaluated hair shedding by a self-assessment questionnaire.[14,26] One study reported very little improvement in hair shedding 26 weeks post-treatment with 60% (9/15) of PRP-treated patients reporting no improvement, 13.3% (2/15) reporting some improvement, and 13.3% (2/15) reporting substantial improvement.[14] Conversely, in a study by Borhan and colleagues,[26] 71% (12/17) of patients reported a slight to moderate change in hair shedding 4 weeks posttreatment. The major differences between these studies, such as time of evaluation and number of sessions, may have contributed to the differences in shedding improvement. PRP was found to exhibit a greater efficacy over placebo across all controlled studies that evaluated hair density (all studies $P < .05$).[15- 18,27,29] Three of these studies used an interfollicular injection, 2 studies used an

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intradermal injection, and 2 studies did not report injection depth.[15,17,18,27,29] According to the meta-analysis conducted, 3 PRP sessions administered at 1-month intervals exhibited greater efficacy over placebo with response to mean change in total hair density (hairs/cm2) by end of treatment (MD: 25.61, 95% CI: 4.45 to 46.77;I^2 = 23%, P = .02) (3 studies, pooled n = 58) (Figure 1).[16-18]

These results suggest that PRP is an effective treatment for AGA; however, the quality of evidence from these trials is low. Risk of bias and imprecision were judged as serious with inconsistency and indirectness considered not serious. Only one included study directly compared PRP with a comparator.[30] In this study, PRP (2 sessions at 12-week intervals) was compared with placental extract in a nonrandomized fashion.[30] A statistically greater level of improvement in hair thickness and overall clinical improvement was found with PRP-treated patients compared with placental extract–treated patients (P = .027 and P = .023, respectively).[30]

For Alopecia Areata: Three patchy AA studies met inclusion criteria; however, not enough quantitative data were included to conduct a meta-analysis.[36-38] Only 2 studies (2/3 = 67%) were randomized and controlled, comparing PRP with a placebo and an active comparator (minoxidil or triamcinolone ace- tonide).[36,37] One study used a half-head design,37 and PRP sessions were delivered monthly across all included studies (Table 1).[36-38] Two studies evaluated the efficacy of PRP both in men and women,[36,37] and one study did not report gender.[38] Two studies also reported the use of activation (calcium gluconate)[36,37] and only one study reported platelet concentration (3.5× whole blood).[37] None of the studies included information on leukocyte status, needle gauge, or the collection system used. The depth of injection varied across studies reporting both intralesional injections [37] and subfollicular injections.[38] Most studies used a single-spin technique (2/3 = 67%),[36,37] with each patient on average receiving 4 PRP sessions. The average age of the patient included in these studies was 24.6 years. Efficacy was measured across AA studies using hair regrowth and relapse rates.[36-38]

Across all studies that measured hair growth (2/3 = 67% of studies), patchy AA patients treated with PRP had a significantly greater improvement in hair growth compared with placebo-treated patients (both studies P < .05).36,37 Relapse rates reported in PRP-treated patients were low and ranged from 5% to 31%, 6 to 9 months post-PRP treat Minoxidil (P < .05).[36] The lack of quantitative data limits the ability to understand how significant these data are and what factors could contribute to PRP's success as an AA treatment. Further research in the use of PRP in AA is needed.

For Cicatricial Alopecia: No studies that met the inclusion criteria.

Discussion

We can propose from that from our findings in this meta-analysis, that 3 monthly PRP injections (1 PRP session every 4 weeks, 3 sessions in total) significantly enhanced hair density in AGA patients. In addition to total hair density, several AGA studies report a PRP-induced improvement in hair count, terminal hair density, hair shedding, and hair diameter.[14,15,17,18,22,26,30,32] Various studies also suggested that PRP is an effective hair restoration treatment. PRP could also be a beneficial adjunct to hair transplantation. In a small, controlled study, incorporating PRP treatment into a follicular unit extraction procedure resulted in greater hair density compared with control (saline). This study also found that PRP treatment increased

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skin recovery and reduced catagen loss of transplanted hair. An increase in hair density was also found with follicular units treated with PRP in a half-head study.

The conducted meta-analysis using monthly PRP studies included patients with Norwood Hamilton scores between II and V.[16-18]Maparet al[19] suggest the failure to observe a positive effect of treatment may be due to hair loss severity. Thus, the development in hair restoration found with monthly PRP injections may not range to patients with more severe forms of AGA. In addition, the studies captured by the meta-analysis included men and women alike using a half-head design. This trial design may influence the results found as PRP can cause angiogenesis and cross-signaling between growth factors, which can affect placebo sites.[1,5] All 3 studies included in the meta-analysis used a total of 3 PRP sessions. The use of 3 sessions is recommended as a progressive effect of PRP from the first injection, which peaks after 3 to 5 injections and is attenuated with cessation of treatment. Thus, monthly PRP injections occurring for a minimum of 3 months may be necessary to ensure patients receive the optimal number of injections at an appropriate frequency.

There was a significant variability in the method of preparation and administration of PRP used across included hair loss studies such as activation, frequency, number of sessions, injection technique, and patient characteristics. Despite its frequent use, the role of activation remains unclear as a significant alteration in growth factor concentrations, which may influence outcomes, may not always occur.[20]Unfortunately, because of the limited number of studies, a meta-analysis comparing the results from monthly PRP injection with other injection frequencies (eg, PRP session every week) was not possible. However, a recently published study[35] found monthly injections achieve better hair counts compared with quarterly injections ($p < .001$). Based on the evidence, originally prescribing monthly PRP sessions may be necessary to attain an improvement in hair restoration parameters (eg, hair count, hair density).

Unfortunately, the included studies did not compare PRP with approved nonsurgical treatments. Minoxidil was compared with PRP in AA patients; however, minoxidil is not an approved treatment for AA.[36] PRP as a treatment for AGA has recently been compared with other approved nonsurgical AGA treatments in a network meta-analysis.In this analysis, low-level laser therapy was considered the superior treatment based on relative effects when compared with PRP, Finasteride, Minoxidil and Dutasteride. Further research using direct head-to-head studies are necessary to confirm this finding.

Conclusion

Based ontheevidence,monthlyPRPtreatments (3 sessions initiallyfollowed by a maintenanceregimen) can significantly improve hair density, hair count,hairshedding,andhairdiameter.Theseresultsmayberestricted to patients with mild AGA(Norwood Hamilton 11to V). Evidence has suggestedthat combining*PRP* (2 to 3sessions) with traditional aesthetic therapies and procedurescanimproveoutcomes.Owingto inconsistentmeasurements and protocols, however, comparisons between studiesare limited.Withfurtherinvestigationusingrandomized,controlled studies, standardized and effective PRP protocolsfor dermatological conditionscouldbe determinedin thenearfuture.

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Table 1. Trial Characteristics of Studies Investigating the Efficacy of Platelet-Rich Plasma (PRP) as a Treatment for Hair Loss.

Study	TrialCharacteristics Treatment GroupsAndrogenetic		Centrifugation and Collection SystemDetails	Characteristics of PRP Solution Used Characteristics	Injection Details	Patient
1 PRP Session						
Gentile etal,2017[17] (Study2)	Not randomized 2 PRP techniquesNot blinded	Regen PRP Arthrex PRP	Regen Blood Cell Therapy Arthrex Angel System	Activated(CG) 5-fold increaseOWB	25-Gneedle 1 mL per treatment section1 session	N=6 men Age: 40.8±11.3 HN IIIa to IIIv
Puig etal,2016[14]	Randomized (TA) Placebo-controlledDouble-blinded(EandS)	PRP Saline	Angel PRP system	Leukocyte-free Not activated 2.75 to3.4×PC	Subcutaneous injection 10 mL per session1 session	N=26 women Age:≥18yearsLudv II
PRPSessionEveryvve k						
Leeetal,2015[21]	Randomized (TA) 2 PRP techniquesSingle-blinded(E)	CD34++PDRN PRPPDRNP RP	SmartPReP2 platelet concentrate system	Leukocyte-rich Not activated	Intraperifollicularinjection 0.05to0.1mL/cm212 or 13 sessions	N=40 women Age:33.2
Marwah et al,2014[23]	Not randomizedNot controlledNot blinded	PRP	Not reported	Not reported	6 sessions	N=10menII to III
Tawfik and Osman, 2018[15]	Randomized (TA) Placebo-controlled (1/2)Double-blinded	PRP Saline	1200 *g* 15 mins 2000 *g* 10 mins	Activated(CG)	Intradermal injection 4 sessions	N=30 women Age: 29.3±6.56 Ludwig I tolII
PRP Session Every 2 weeks						
Ayatollahi etal,	Not randomized2017[24] Not controlled Not blinded	PRP	RegenLab PRP Kit-Regen ACR 1500 *g* 5 mins	Not activated	Intradermal injection 0.05 ml per area5 sessions	N = 15 menAge:39±9.7HI III to VI Hair loss: 36 months(median)
Khatu etal,2014[25]	Not randomized Not controlledNot blinded	PRP	1500 rpm 6 mins 2500 rpm 15 mins	Activated(CC)	2 to 3 cc 4 sessions	N=11 men Age: 20 to 40H II to IV
Singhaletal,2015[28b]	Not randomized ControlledNotblinded	PRP No PRP	1500 rpm 6 mins 2500 rpm 15 mins	Activated(CC)	8 to 12 cc 4 sessions	N=16 men, 4 wom Age: 25 to 35
Staraceetal,2018[22]	Not randomized Not controlledNot blinded	PRP	My Cells system 2500 rpm 10 mins	Not activated	25-Gneedle Interfollicular injection1cc per	N=10 women Age:47.1 Ludwig I tolII

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Table1.(continued)

Study	TrialCharacteristics	Treatment Groups	Centrifugation and Collection System Details	Characteristics of PRP Solution Used	InjectionDetails	Patient Characteristics
Gkinietal,2014[29d]	Not randomized	PRP	RegenKit BCT-3	Activated(CG)	27G needle	N=20 men, 2 women
	Not controlled		1500 *g* 5 mins	5.8×OWB	0.05 to0.1 mL/cm^2	Age: 34±11.8
	Single-blinded(E)				3 sessions	HN II to V, Ludwig I to 3
					5.5×10^7to1.1×10^8 platelets/cm^2	
Kachhawa et al, 2017[27]	Not randomized	PRP	1200 rpm 4 mins	Not reported	1 to2 cc per injection	N=50 men
	Placebo-controlled (1/2)	Saline	2400 rpm 4 mins		Intradermal injection	Age: 34
	Not blinded				6 sessions	NH III to VI
PRP Session Every 4 Weeks						
Alvesand Grimalt,	Randomized (LR)	PRP	Omnigrafter-Proteal	Leukocyte-poor	30-Gneedle	N=12 men, 13 women
2016[16]	Placebo-controlled (1/2)	Saline	460 *g* 8 mins	Activated(CC)	0.15 mL/cm^2per area	Age: 39
	Double-blinded(E and S)			3×OWB	3 sessions	HN II to V, Ludwig I to III
Anituaetal,2017[30e]	Not randomized	PRP	BTI System IV	Leukocyte-poor	30-Gneedle	N=13 men, 6 women
	Not controlled		580 *g* 8 mins	Activated	3 to 4cm^3 per injection	Age: 45±11
	Single-blinded(E)			2×OPB	5 sessions	N III to VI,

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 2, 2021, Pages. 3650 - 3663
Received 20 January 2021; Accepted 08 February 2021.

						Ludwig II
					1.4×10^3to1.8×10^3 platelets/cm^2	
Cervelliet al,	Randomized	PRP	Cascade-Selphyl-Esforax	May include	0.1mL/cm^2	N=10 men
2014[20]	Placebo-controlled (1/2)	Saline	1100 *g* 10 mins	leukocytes	3 sessions	Age: 32.7±10.6
	Single-blind(E)			Activated(Ca+)		HN IIa to IV
Ferrando et al,	Not randomized	PRP	Omnigrafter	Activated(CC)	Intradermal injection	N=19 men, 59 women
2017[31a,f]	Not controlled		460 *g* 1800 rpm 8 mins		0.1cc/cm^2	Age: 18 to 72
	Not blinded				6 sessions	Ebling scale II to IV
Gentile etal,2018[32]	Not randomized	PRP	260 *g* 10 mins	Not activated	30-Gneedle	N=18 men, 5 women
	Placebo-controlled (1/2)	Saline			Interfollicularinjection	Age: 21 to 70
	Not blinded				0.2ml/cm^2	HN I to V, Ludwig I to II
					3 sessions	
Gentile etal,2017[17] (Study1)	Randomized (TA)	PRP	CPunT Preparation System	Not activated	30-Gneedle	N=18 men
	Placebo-controlled (1/2)	Saline			Interfollicularinjection	Age: 37.4±9.4
	Double-blind(E and S)		1200 rpm 10 mins		0.2mL/cm^2	HN II to IVa
					3 sessions	
Gentile etal,2015[17]	Randomized (TA)	PRP	Cascade-Selphyl-Esforax	May include	30-Gneedle	N=23 men
	Placebo-controlled (1/2)	Saline	system	leukocytes	Interfollicularinjection	Age: 34.7±11.7
	Double-blind(E and S)		1100 g 10 mins	Activated(Ca+)	0.1mL/cm^2	HN IIa to IV

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 2, 2021, Pages. 3650 - 3663
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			Platelet-richlipotransfer 1200 rpm 10 mins		3 sessions	
Mapar etal,2016[19]	Randomized (SQ) Placebo-controlled (1/2) Single-blinded	PRP Saline	PRP tube Tubex 3000 rpm 6 mins 3300 rpm 3 mins	Activated(CG) 3-foldincrease in BPC	30-Gneedle Deepdermis injection 2 sessions	N=19 men Age: 25 to 45 N IV to VI

(continued)

Table1.(continued)

Study	TrialCharacteristics	Treatment Groups	Centrifugation and Collection System Details	Characteristics of PRP Solution Used	InjectionDetails	Patient Characteristics
Hausauer and Jones,2018[35a,g]	Randomized (TA) 2 PRP techniques Singleblinded	PRP	Eclipse PRP kit 3500 rpm 10 mins	Leukocyte-poor Not activated 4 to6×OWB	32-Gneedle Subdermalinjection 0.2to 0.5 mL per aliquot 2 to 4 sessions	N=30 men, 10 women Age:43.75 NH II to V, Ludwig I2 to II1 Hair loss: 6.45 years
ElTaieb et al, 2017[36]	Randomized (TA) Placebo-controlled Comparator Not blinded	PRP Minoxidil Panthenol	3000 rpm 10 mins	Activated(CG)	3 sessions total	N=39 men, 51 women Age:21.09 Hair loss:28±16.15 months
Trinketal,2013[37]	Randomized (TA)	PRP	70 *g* 8 mins	Activated(CG)	Intralesionalinjection	N=20 men, 25

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 2, 2021, Pages. 3650 - 3663
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	Placebo-controlled (1/3) Comparator Double-blind(ES)	TRA Placebo		3.5×OWB	3 sessions total	women Age:28.03 Hair loss: 4.52 years
Singh,2015[38]	Not randomized Not controlled Not blinded	PRP	Not reported	Not reported	Subfollicularinjection 6 sessions total	N=20 Age: 25 to 35

Abbreviations: 1/2, half-head design; 1/3, 3 lesions treated on each patient, 1 lesion per treatment; BPC, baseline platelet count; CC, calcium chloride; CG, calcium gluconate; E, evaluator; H, Hamiltonclassification;LR,leftorrightsideofscalp;Mins, minutes;N,Norwoodclassification;NH,NorwoodHamiltonclassification; Notblinded,openlabelorthestudydid notspecifythatblindingoccurred;OPB, over peripheral blood; OWB, over whole blood; PC, baseline platelet concentration; PDRN: polydeoxyribonucleotide; SQ, square assignment; S, subject; TA, treatment allocation; TRA,triamcinolone acetonide.

[a]Concomitant hair loss treatment(s) wereallowed (or recommended) during studyprotocol (eg, finasteride).

[b]Fifteen-day intervalbetweensessions.

[c]Treated every 3 weeks forthe first 3 sessions and6 weeks for thelast session, 4 sessions total.

[d]Treated every 3weeks fora total of3 sessions+1 boostersession atmonth 6.

[e]Two additional reminderinjection doses wereadministered at months4 and 7.

[f]Injected in affected areas for 3 monthly sessions,followed by 3 bimonthly sessions and 2 or3 annual follow-up sessions.

[g]Two different PRP regimensused: 3 monthly PRPsessions +1 boostersession 3 monthslater vs PRP sessionsevery 12 weeks (2sessions total).

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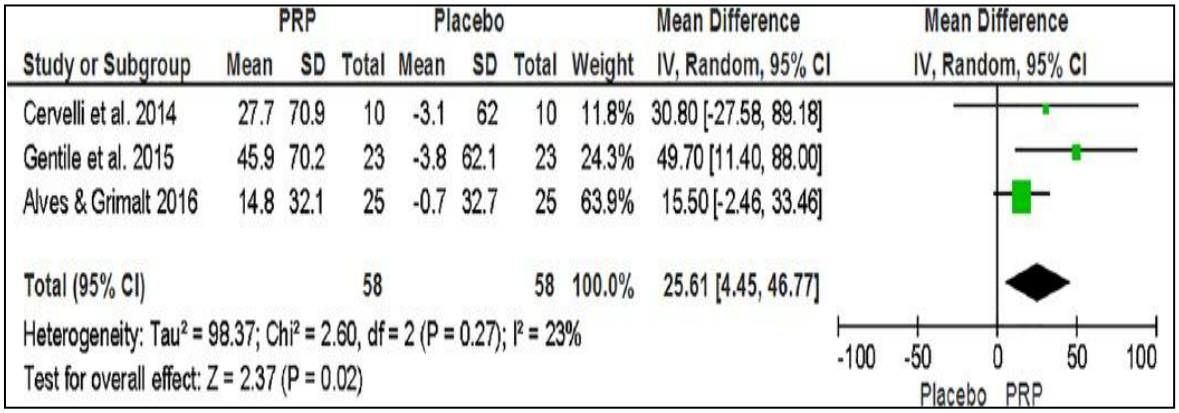

Figure 1: Three studies evaluated the impact of 3 monthly platelet-rich plasma (PRP) sessions (1 session per month) on hair density (total hairs/cm2) in patients with androgenetic alopecia (pooled N = 58 participants). Mean change from baseline to end of treatment was used as the unit of measure. IV indicates inverse variance.