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PLATELET RICH PLASMA, 5% MINOXIDIL LOTION AND ORAL DUTASTERIDE VERSUS 5% MINOXIDIL LOTION AND ORAL DUTASTERIDE IN MALE ANDROGENETIC ALOPECIA: A PILOT STUDY IN ROUTINE CLINICAL SETTING

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Abstract

Group B respectively. At the end of six months VAS score was 7.25±1.46 in Group A and 5.75±2.02 in Group B respectively. The differences in results among both the Groups were statistically significant (P<0.05). There were no serious adverse effects observed in either groups.

Conclusions: PRP therapy along with dutasteride 0.5mg twice weekly and minoxidil 5% lotion once daily is an effective and safe modality in management of AGA when compared with minoxidil and dutasteride alone.

Key words: minoxidil 5%, dutasteride, platelet rich plasma, PRP, androgenetic alopecia, AGA.

Key messages: Management of AGA is a long term and challenging exercise with limited pharmacological options such as topical minoxidil with or without oral finasteride and dutasteride. Adjunctive use of autologous PRP with its naturally growth factors holds promise of enhancing efficacy outcome with these drugs with better patient compliance and satisfaction from the treatment.

Introduction

Androgenetic alopecia (AGA) or patterned baldness is a genetically determined hair disorder characterized by the gradual miniaturisation of terminal hairs into vellus hairs and finally leading to bald areas on the scalp[1]. It affects about 50% of men over the age of 50, and about 50% of women over the age of 65 years[2]. Patterned baldness adversely impacts psychosocial state and self-esteem of patients[3].

AGA is determined by genetics and influenced by hormones. Dihydrotestosterone (DHT), a metabolite of testosterone is a key hormone, which activates androgen receptors present on the hair follicles more densely distributed on vertex and fronto-temporal areas. In men, testosterone is converted to DHT by 5α-reductase (5-AR), which exists as 3 isoenzymes namely types I, II and III. Type I isoenzyme is universally present on the skin including the hair follicle and sebaceous glands, whereas type II is predominantly found in the male genitalia, including the prostate, and inner root sheath of hair follicles. Finasteride inhibits type II 5-AR while dutasteride inhibits both type I and type II 5-AR. Minoxidil and finasteride 1 mg are the only drug specifically approved by Food and Drug Administration (FDA) for treating AGA either alone or in combination[4,5]. Dutasteride, which is approved for symptomatic benign prostatic hyperplasia (BPH) at the daily dose of 0.5 mg is approximately three times more potent than finasteride in inhibiting type I 5-AR, and 100 times more potent in inhibiting type II 5-AR. Therefore, dutasteride is theoretically more appropriate choice in AGA[6-9]. Although literature is replete with multiple studies to suggest this, larger trials are needed to establish same.

Platelet rich plasma (PRP), is emerging therapy for AGA. It is essentially an increased concentration of autologous platelets suspended in a small amount of plasma after centrifugation[10]. The adjunctive role of PRP was initially reported in periodontal therapy, maxillofacial surgery, orthopaedics, and sports medicine and has now captured wide attention in the field of dermatology and aesthetic surgery particularly for its role in treating acne scars, fat grafting, wound healing, and hair regrowth[11,12]. Alpha granules of platelets contain seven fundamental growth factors(GF), the more relevant ones to dermatology being Platelet derived growth factors (PDGF), Transforming growth factor beta (TGF β1 and 2), Epithelial growth factor (EGF), and Vascular endothelial growth factor (VEGF). These growth factors modulate cell proliferation, differentiation, angiogenesis, and chemotaxis. GFs appear to act

in the bulge area of the follicle, where they bind to their respective receptors located in stem cells. Therefore, PRP could serve as a potential treatment of AGA[13-15]. This study was conducted with an aim to evaluate real world efficacy and safety of PRP in AGA when combined with minoxidil 5% locally once and tab dutasteride 0.5 mg twice weekly.

Subjects and methods

Patients

This was a prospective, open label, controlled study, conducted at a tertiary care hospital in India over a period of one year from June 2015 to June 2016 following prospective clearance from institutional ethics committee. 300 consecutive male patients of AGA between ages of 20 years to 50 years were enrolled in the study following individual informed consent and assigned equal groups A(study group) and B(control group). Group A received topical minoxidil 5% lotion once in the night, dutasteride 0.5mg twice a week (sat and sun) and PRP 0.1ml/cm^2 intradermally and in interfollicular pattern every month. Group B received minoxidil and dutasteride as in Group A but instead of PRP received normal saline 0.1ml/cm2 every month.

AGA was graded according to the Hamilton-Norwood scale. Stage II to stage VI was included in the study. Patients who had received any topical or systematic treatment for their hair loss during the last 6 months or any anticoagulant therapy, those with immunosuppression (malignancy, HIV, diabetes), or on any immunosuppressant (chemotherapy, steroid) therapy, dermatological diseases affecting the scalp, keloidal tendency, autoimmune disorders, hematologic disorders, platelet dysfunction syndrome were excluded from the study. Patients taking aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) was discontinued 7 days before treatment. Patients who had known allergy to tab dutasteride or minoxidil or having liver disease were also excluded from the study. Laboratory tests conducted at baseline included: CBC; random blood sugar, Liver function test (LFT) with liver enzymes SGOT & SGPT , serological tests for HIV, HBS Ag, and Anti HCV antibodies. Serum iron, serum ferritin, TIBC (Total Iron-Binding capacity); T3, T4, TSH, anti-TPO Ab were planned for those who shown clinical suspicion of anaemia, poor nutrition, thyroid dysfunction, or any immunosuppressive or systemic illness. CBC, LFT with SGOT and SGPT were repeated at the end of six months.

PRP preparation and administration

PRP was prepared with double spin method. Total 18 ml of venous blood was collected from the antecubital vein of the patient in 20 ml of syringe with 18-gauge needle. The blood was then introduced into three tubes of sodium citrate vacutainer having capacity of 6 ml. for the first spin, these tubes were centrifugated for 5 min at 1500 rpm (soft spin), using centrifuge machine (Remi). This separated blood into three layers, lowermost RBC, intermediate buffy coat and top clear to yellowish plasma layer. The buffy coat with plasma was collected with the help of a Finn pipette in a separate sterile test tube. This tube was subjected to a second 'hard spin' at 3000 rpm for 10 minutes. At the end of the second spin, a small platelet pellet at the bottom and overlying platelet poor plasma was yielded.

Table1. General profile of the patients of both the study groups. (p- value of difference in mean age is 0.788) HN- Hamilton Norwood scale

	Age(years)	HN-II	HN-III	HN-IV	HN-V	HN-VI
Gp A (n=148)	33.75±8.37 (21-50)	11 (7.4%)	86 (58.1%)	38 (25.6%	8 (5.4%)	5 (3.3%)
Gp B (n=147)	34.5±7.50 (22-48)	15 (10.2%)	82 (55.7%)	35 (23.8%)	9 (6.1%)	6 (4%)

The upper two third layer containing PPP was discarded, and the lower third layer of PRP prepared by agitation of the platelet pellet in remainder of plasma was aspirated into an insulin syringe. Four such insulin syringes having total 4 ml of PRP were collected for each patient. The activation process included the addition of calcium gluconate in a 1:9 ratio (0.1 ml calcium gluconate per 0.9 ml of PRP). The platelets in whole blood and PRP were randomly submitted for microscopic examination to the hospital laboratory, which reported a consistent figure of 4-5 times average platelet concentration when compared to whole blood of patient. Local anaesthetic cream (lidocaine 2.5% & prilocaine 2.5%) was applied over the area of the scalp to be treated and was cleaned with spirit and betadine before infiltration. PRP was injected intradermally in interfollicular areas with an average density of 0.1 ml/cm^2. Patients from Group B received normal saline instead of PRP in similar way.

Table 2. Age wise distribution of both the study groups.

Age group	GpA	Gp B
20-30	44 (29.7%)	46 (31.2%)
31-40	76 (51.3%)	68 (46.2%)
41-50	28 (18.9)	33 (22.4%)

Assessment of patients

Evaluation of hair loss as well as objective improvement was conducted by hair pull test, dermoscopic photomicrographs, macroscopic photographs and a satisfaction scale. Any adverse effects were also noted. All patients were evaluated over six visits i.e. V0(Baseline), V1(04 weeks), V2(08 weeks), V3(12 weeks), V4(16 weeks), V5(20 weeks), V6(06 months) and V7(01 year).

Table 3. Comparison of hair pull test in both the study groups at different time interval.

Hair pull test (no of hair)	Gp A	Gp B	P value
Base	9.5 ±2.29	09.75±2.58	0.150
After 12 weeks	04.25±2.03	7.75±1.42	<0.0001
After 24 weeks	1.75±2.04	4.75±1.45	<0.0001
After one year	1.25±.90	3.25±2.03	<0.0001

Hair pull test was performed by grasping a bundle of approximately 50-60 hair between the thumb, index and middle

Table 4. Comparison of hair density in both the study groups at different time interval.

Hair density (per cm^2)	Gp A	Gp B	P value
Base	34.75 ±4.90	35.25±5.49	0.169
After 12 weeks	39.5±4.59	36.5±4.61	<0.0001
After 24 weeks	46.5±5.75	42.75±4.90	<0.0001
After one year	50.5±8.6	43.5±4.6	<0.0001

finger from the base close to the scalp. The hair was firmly tugged away from the scalp, and the extracted hair was counted in every session. To evaluate overall hair growth, hair volume, hair quality and fullness, global pictures were taken in every session from front, vertex, lateral and back view. Standardized high-resolution digital macrophotographs were taken at every visit using identical camera settings (Canon DSLR, EOS 1100D, Tokyo, Japan). We used 'V' (Kang's point), as proposed by Lee *et al* [16] as assessment point for objective assessment of hair growth. 'V' is the point of intersection between the midsagittal line and the coronal line connecting the tips of the tragus which can be done by using a plastic tape.

Table 5. Comparison of Visual analogue scale (VAS) in both the study groups at different time interval.

Visual analogue scale	Gp A	Gp B	P value
At four weeks of therapy	3.25 ±1.46	2.75 ±1.25	0.0017
After 12 weeks	3.75±1.42	2.75±0.82	<0.0001
After 24 weeks	7.25±1.46	5.75±2.02	<0.0001
After one year	7.5±1.70	6.25±2.03	0.032

Table 6. Adverse effects in both the studied groups

Adverse effects	Gp A	Gp B	X^2	P value
Mild Pain at the site of injection	142 (96%)	138 (93.8%)	0.14	0.93
Post procedure mild Headache	11 (7.4%)	9 (6.1%)		
Sexual dysfunction	Nil	Nil		

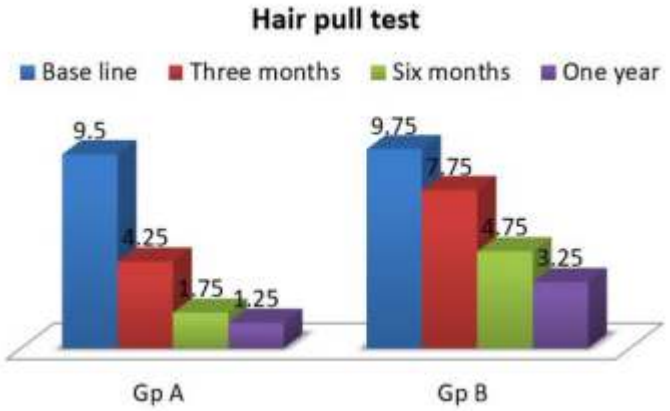
The evaluation of results was performed by an independent blinded observer. For each patient, six PRP/normal saline sessions were performed. At each visit, hair count was checked over the prefixed "V" area. Subjective satisfaction to treatment was noted on a Visual Analogue scale(VAS) of 01(no satisfaction) to 10(maximum satisfaction).

Statistical analysis

Statistical analysis was performed using SPSS software (version 22.0). Description of quantitative variables was as mean and standard deviation. Paired t test was used for analysing metric variables satisfying the normality assumption. Wilcoxon signed rank test was used for ordinal variables (patient satisfaction) and metric variables not satisfying the normality assumption. Statistical significance was considered using Pearson Chi-square test (x^2 test) and p value. P value less than or equal to 0.05 was considered statistically significant.

Results

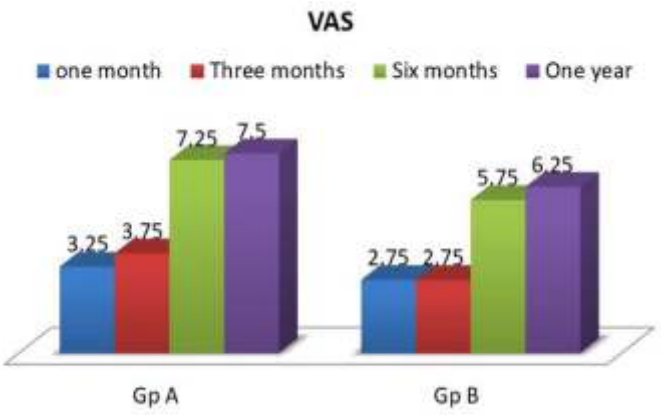
A total of 300 consecutive patients of AGA were enrolled in to the study. Two patients from the Group A and three patients from the Group B, who did not complete the therapy protocol and were not included in the statistical analysis. Hence, 148 patients in Group A and 147 patients in Group B were finally included in the study. The mean age of Group A was 33.75±8.37 yrs and Group B was 34.5±7.50yrs. Maximum number of patients belonged to age group 30 to 40 years and Hamilton-Norwood Grade III in both the groups. The general profile of patients is depicted in the Table 1 & 2. There was marked reduction in hair pull test value in Group A after three months of therapy which further reduced to almost negligible hair pull test value. However, at the end of six months Group B also shown reduction in hair pull test value (Table 3 & Graph 1). Like hair pull test, hair density measured by dermoscope also shown similar trend in both the groups (Table 4 & Graph 2).Group A patients shown early satisfaction to therapy in comparison to the Group B which was statistically significant (Table 5 & Graph 3).



Graph 1. Comparison of hair pull test result at different time interval in the Gp A and Gp B

Graph 2. Comparison of hair density test result at different time interval in the Gp A and Gp B

There were significant differences in images of global photography at the end of six months of therapy in Group A in comparison to Group B. The images of dermoscopy as well as global photography are illustrated in Figures 1a & 1b and 2a & 2b showing visible changes after six months.



Graph 3. Comparison of visual analogue scales at different time interval in the Gp A and Gp B

Even though both the groups were subjected to systemic as well as injectable therapy in routine clinical setting, there were no major adverse effects noticed during as well as follow-up period of the therapies. Almost all patients described minimal transient pain or discomfort at the site of local infiltration even after application of local anaesthesia. Post procedure, mild self-limiting headache was noticed in 11 patients (7.4%) of Group A while 9 patients (6.1%) of Group B patients. No patients developed any sexual side effects like loss of libido, premature ejaculation, increased in breast size. Adverse effects profile is further detailed in Table 6.

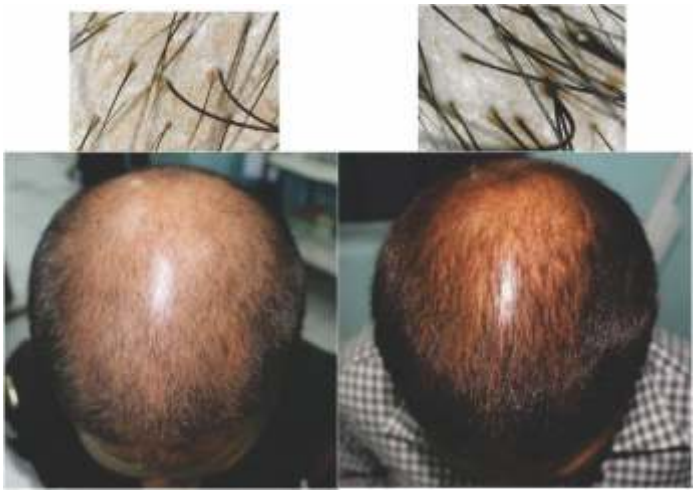


Figure 1a, 1b: Pre and post treatment photographs with the dermoscopic images in Gp A patient.

Discussion

Notwithstanding our current concepts and knowledge of hair follicle and hair growth, treatment of AGA remains challenging for Dermatologists. Conventionally, minoxidil lotion and tab finasteride are ubiquitously employed. Even systemic reviews and metanalysis of treatment of AGA revealed that only low-level laser light therapy in men, 5% minoxidil in men, 2% minoxidil in men, 1 mg finasteride in men, and 2% minoxidil in women were superior to placebo[17]. Recent studies on dutasteride 0.5 mg and its comparison to finasteride 1 mg revealed superior results in AGA[6-9]. In a study by Jung et al. dutasteride is suggested to be an alternative treatment option to patients with AGA who do not clinically respond to finasteride in six months[18]. Although, routinely used as an off label indication, dermatologists routinely prescribe dutasteride 0.5 mg and minoxidil 5% lotion in AGA. However, studies demonstrating adjunctive benefit of PRP when combined with minoxidil and tab dutasteride are lacking. PRP with advantage of hair related growth factors have been proposed to aid in the long term management of AGA[13-15].

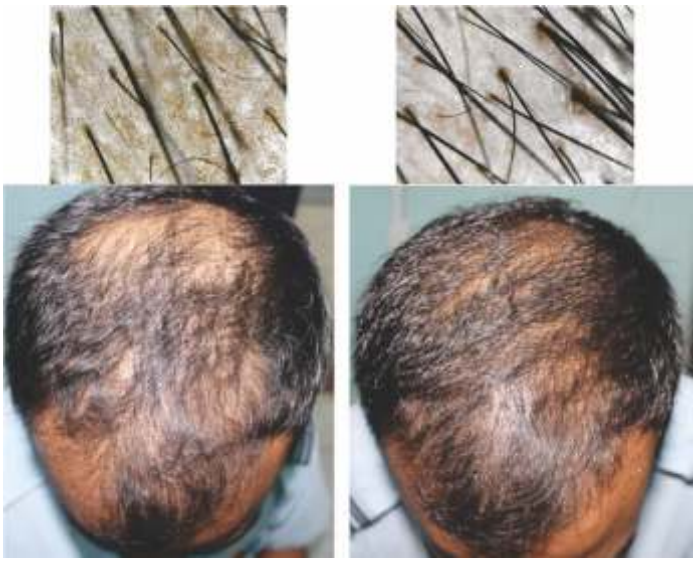


Figure 2a, 1b: Pre and post treatment photographs with the dermoscopic images in Gp B patient.

In our study, PRP group showed a decrease in mean hair pull test score from 9.25 (SD 2.29) at base line to 1.75 (SD 2.04) after six month of therapy while in normal saline group it decreased from 9.75 (SD 2.58) to 4.75(SD 1.45). Hair density in PRP group increased from a mean of 34.75 (SD 4.9 cm2) at baseline to 46.5 (SD 5.75 cm^2) after six months of therapy while it increased from 35.25 (SD 5.49) to 42.75 (SD 4.9) in normal saline group. When comparing the VAS score, PRP group showed increase in satisfaction to therapy from mean of 3.23(SD1.46) at baseline to 7.25 (SD 1.46) after six months while it was 2.75 (SD 0.82) to 5.75 (SD 2.02) in normal saline group. These findings were comparable to that of Toama MA et al19 which was conducted in forty males and females with AGA. Mean numbers of hairs were 37.35 ± 7.49, 44.2 ± 5.87 at the experimental site (1 cm2) before administration of PRP and saline in groups A and B respectively. After 3 months when patients had received all five treatments, mean numbers of hairs were 45.4 ± 9.25, 44.95 ± 10.42 /cm^2 respectively. After 6 months mean numbers of hairs were 56.65 ± 10.99, 46.55 ± 10.27.

Results of PRP in our study were also similar to that by Gentile et al[20] which was a randomized, placebo-controlled, half-head group study to compare the hair regrowth with PRP versus placebo. At the end of the three treatment cycles, the patients presented clinical improvement in the mean number of hairs, with a mean increase of 33.6 hairs in the target area and a mean increase in total hair density of 45.9 hairs per cm2 compared with baseline values. In another study by Gkini et al[21]; PRP was injected in 20 patients, males and females, with AGA. Three months after the first treatment, a significant increase in hair density was noted (170.70±37.81,

P<.001). At 6 months and at 1 year, hair density was also significantly increased, 156.25±37.75 (P<.001) and 153.70±39.92 (P<.001) respectively comparing to that of baseline. Patients were satisfied with a mean result rating of 7.1 on a scale of 1-10.

The difference in response to therapy in both the groups was statistically significant at three months, six months and even at the end of one year. Group A, which was receiving PRP along with tab dutasteride 0.5 mg twice weekly and minoxidil 5% lotion once daily, showed early response to the therapy. The response was well maintained till the end of one year of follow-up. A similar study by Tawfik AA et al[22] in which 30 cases of female androgenetic alopecia who received weekly PRP, revealed that there was a statistical significant difference between PRP and placebo areas (P<.005) with respect to both hair density and hair thickness as measured by a folliculoscope. The hair pull test became negative in PRP-injected areas in 25 patients (83%) with average number of three hairs. Global pictures showed a significant improvement in hair volume and quality together with a high overall patient satisfaction in PRP-injected sites, and these results were maintained during the 6-month follow up. However, these patients were not subjected to any oral treatment. Patients with grade II-III alopecia according to the Norwood-Hamilton scale had better results compared to patients with more advanced alopecia. Mild pain and self limiting headache at the site of infiltration was common and universal to both the groups. However, there was no major adverse effects noted in either groups.

An extensive review by Cervantes J et al[23] on effectiveness of PRP in androgenetic alopecia revealed therapeutic effectiveness in 10 of the 12 reviewed studies. However, there were several study design limitations which need to be addressed before PRP is widely introduced as a treatment option in the clinical setting. Our study was unique, in that we tried to study the role of PRP when combined with the real world usage of drugs like minoxidil 5% lotion once daily and dutasteride 0,5 mg twice in the management AGA. With a fairly large sample size of 147 patients with similar number of control group we are confident in sufficiently addressing confounding factors, such as any microtrauma which may have been the cause of additional hair growth.

The results of present study while comparable to similar studies elsewhere, differs from any similar existing study in true sense as it has been conducted in routine clinical setting exclusively in males with combinations of multiple modalities. The study had certain limitations. It was performed without randomisation and double-blinding. Although hair pull test was performed in prescribed manner in standard protocol, it remains a subjective evaluation method with potential bias. Dermoscopic photomicrographs were objective measures to show an increase in hair density as number of hairs were counted manually by the investigator during follow-up visits. Phototrichogram, which is a more objective evaluation method was not performed as it needs to be performed on a shaven part of the patient's scalp which was not accepted by most patients. Macroscopic photographs at best revealed global benefit in hair growth and hair density.

Conclusion

PRP is rapidly emerging therapy in different indications of aesthetics as well as dermatology. Combination of PRP therapy monthly with tab dutasteride 0.5mg twice weekly and minoxidil 5% lotion once daily produced statistically significant and better results in comparison to minoxidil 5% lotion with tab dutasteride 0.5 mg twice weekly in the management of AGA. Management of AGA is long term and consequently prescribing drugs for that much duration such as daly local application of minoxidil have inherent challenges of compliance, high costs and adverse effects to therapies. Adjunctive use of autologous PRP has advantage in augmenting faster control of hair loss with these drugs with better patient compliance and satisfaction from the treatment. However, a larger sampled, double blinded, placebo-controlled randomized study with precise objective parameters is required to establish its greater role in AGA.

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