

EFFICACY OF PLATELET RICH PLASMA IN THE TREATMENT OF ANDROGENIC ALOPECIA: A SYSTEMATIC REVIEW

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ABSTRACT

Background-Platelet Rich Plasma (PRP) has gained a lot of popularity in the last decade for its application in various surgical fields. It has been used in the treatment of Androgenic Alopecia (ADA) in the recent past. This treatment protocol is being used by the surgeons worldwide but a better understanding of the subject is implicated.

Objective-To perform a systematic literature review of the studies conducted to assess the efficacy of platelet-rich plasma injections in the treatment of Androgenic Alopecia.

Methods- A systemic review was performed from 2013-2017. Sixteen articles were selected for the review, which investigated the use of PRP injections in the treatment of AGA. **Results-** A total of 750 subjects were identified with ADA and given PRP injections or were the control in these studies. These patients were then thoroughly examined for hair quality and density, keratinocyte proliferation, anagen/telogen hair ratio, surrounding blood vessels, etc. after the completion of the treatment. Majority of the studies reviewed concluded that PRP is an effective, non-invasive and safe treatment protocol for the treatment of ADA. **Conclusion** -A standardized preparation and treatment protocol should be established with the help of a long term double blinded randomized controlled trials. Based on the current review we suggest that PRP can be used as a viable treatment option in the treatment of Alopecia.

KEYWORDS: PRP, ADA, male pattern baldness, female pattern baldness, Alopecia.

1. INTRODUCTION

Platelet- rich plasma (PRP) can be defined as a high concentration of autologous platelets in a small amount of autologous plasma. PRP acts as a fibrin tissue adhesive with hemostatic and tissue sealing properties. PRP accelerates endothelial, epithelial, and epidermal regeneration, stimulates angiogenesis, enhances collagen synthesis, promotes soft tissue healing, decreases dermal scarring, enhances the hemostatic response to injury, and reverses the inhibition of wound healing caused by glucocorticoids. The high leukocyte concentration of PRP has an added antimicrobial effect.^[1]

Androgenic Alopecia (AGA) is a non-scarring alopecia associated with the miniaturization and eventual loss of terminal scalp hairs under the influence of peripheral androgens in people with a genetic predisposition. AGA, the most common cause of hair loss in both sexes, accounts for 95% of all cases of hair loss.^[1]

Drugs, like minoxidil and finasteride (5-alpha reductase inhibitor), have been used conventionally to treat AGA. Other therapies including dutasteride, ketoconazole,

prostaglandin analogues, and hormonal therapy, have also been used in treating AGA.^[2] The disadvantages are that medication is required for an indefinite period of time, and effectiveness is limited by patient adherence. Also, they may cause side effects such as hypertrichosis close to the area of minoxidil application, and possible birth defects, decreased libido, and prolonged impotence with finasteride use in males. Therefore, medical therapy may not be suitable to all patients.^[2]

In case of inadequacy in clinical improvement, surgical treatment is also used popularly. Most commonly used surgical alternative is Hair Transplantation and Scalp Reduction. But due to their invasive nature and high price, surgeries such as hair transplantation and scalp reduction are generally reserved for patients who do not achieve success with medical therapy.^[1]

Over the years a growing interest has developed in the use of Platelet Rich Plasma injections in the treatment of Androgenic Alopecia and related pattern baldness in men and women. Numerous studies have been done over the years to determine the efficacy of PRP injections in

patients with pattern baldness, mostly in the fields of dermatology and plastic surgery.

Platelet derivatives have a wide variety of roles in the field of oral and maxillofacial surgery. The use of PRP as a treatment modality for ADA is a very new concept and has not been explored much. There have been several studies but there is no substantial evidence on the overall efficacy of the role of PRP in ADA. Therefore, the aim of this review was to determine the efficacy of Platelet Rich Plasma injections in the use of Androgenic Alopecia by performing a systematic review.

2. MATERIALS AND METHODS

2.1 Search Strategy

We searched the databases MEDLINE (through PubMed), EBSCO, SCOPUS and Google scholar articles of the last 10 years, for the terms 'Androgenic Alopecia', 'Platelet Rich Plasma', 'Treatments for AGA', 'Use of

PRP in the treatment of AGA', 'Therapeutic uses of PRP'. Only those articles in the English language were considered. All records, electronically identified, were scanned by title, abstract and/or keywords and full text of all the reports considered potentially relevant, was obtained.

2.2 Study selection

We searched for and assessed studies comparing local injections of PRP with 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 independently reviewed the abstracts and articles.

2.3 PICOS criteria for inclusion and exclusion of studies

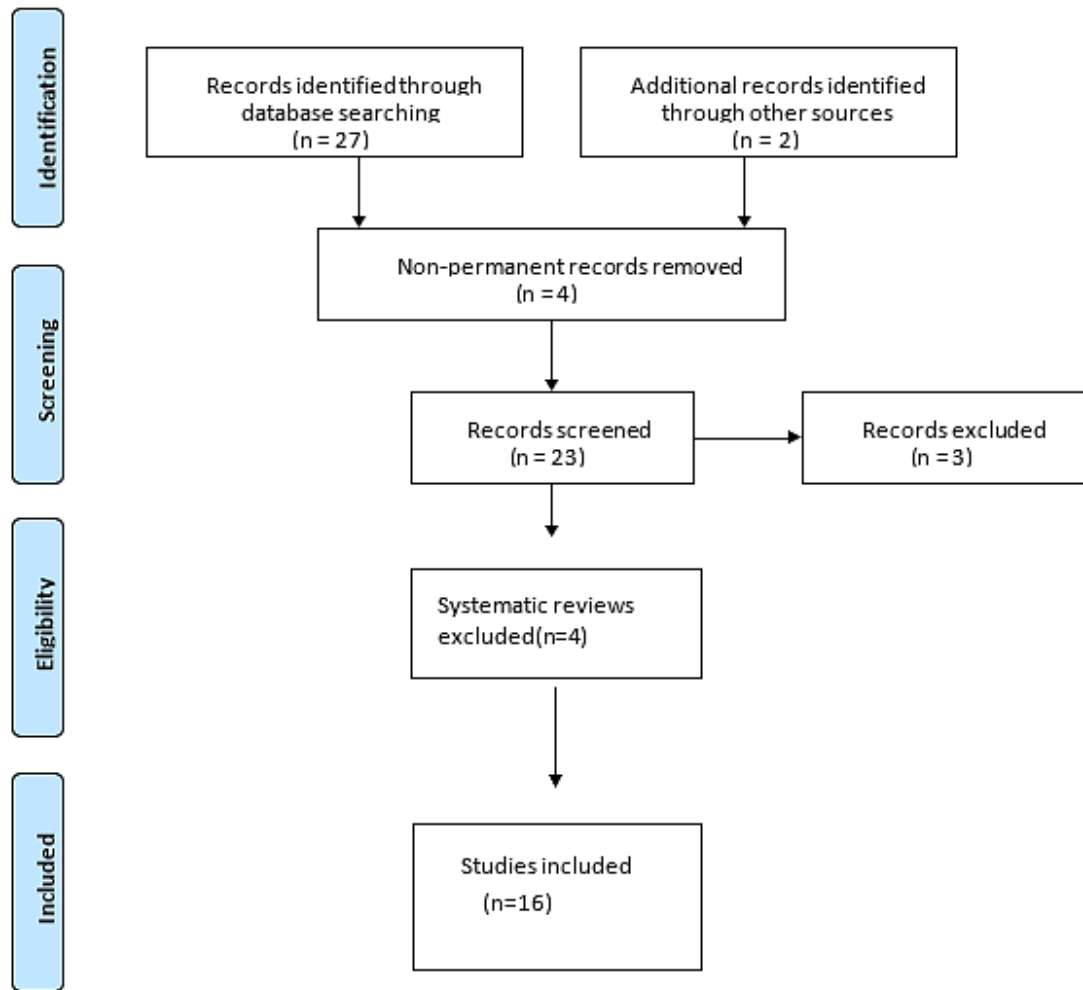
Table 1: Inclusion and Exclusion criteria.

Parameter	Inclusion criteria	Exclusion criteria
Patients	Adults ≥ 18 years with ADA Patients of any age and stage of androgenetic alopecia	Patients under 18 years of age Other types of alopecia (ie alopecia areata or cicatricial alopecia)
Intervention	Local injections of any autologous plated-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.	Studies without defined clinical outcomes
Study Design	Randomized controlled trials Non-randomized controlled trials Retrospective, prospective, or concurrent cohort studies Cross sectional studies	Case reports Editorials & opinion pieces Reviews Animal studies Abstracts

2.4 Data extraction

Data were independently collected by two investigators and checked by a third investigator only from the retrieved articles. Disagreement on collected data was

settled by consensus between these investigators. No attempt was made to obtain specific or missing data from the authors.



Flowchart summarizing literature search results

Figure 1: Flowchart summarizing literature search results.

3. RESULTS

Table 2: Studies with positive effective and studies which showed no change.

<i>Studies with positive results</i>	<i>Studies which showed no change</i>
Ince et al, 2017 ^[1]	Aythollahi et al, 2017 ^[3]
Ferrando et al, 2017 ^[4]	Puig et al, 2016 ^[5]
Farid et al, 2016 ^[6]	Mapar et al, 2016 ^[9]
Alves et al, 2016 ^[7]	
Mahapatra et al, 2016 ^[8]	
Navarro et al, 2016 ^[10]	
Gentile et al, 2015 ^[11]	
Singhal et al, 2015 ^[12]	
Cervelli et al, 2014 ^[13]	
Gkini et al, 2014 ^[14]	
Khatu et al, 2014 ^[15]	
Schiavone et al, 2014 ^[19]	
Yong Miao et al, 2013 ^[17]	

Table 3: Characteristics of the selected studies.

Sr. No	Author Year	Objective	Conclusion
1	Aythollahi et al ^[3] 2017	PRP using single spin process in male pattern AGA as an effective tool	Injection of PRP has no significant effect on male pattern AGA and showed no clinical improvement in the condition.
2	Ince et al ^[1] 2017	Comparison of the efficacy of homologous and autologous PRP for treating AGA	Increase in hair density with homologous-PRP was greater than in a-PRP. Therefore, h-PRP can be used in treatment of AGA.
3	Ferrando et al ^[4] 2017	A proposal of an effective PRP protocol for the treatment of AGA.	PRP can be considered as an effective co-adjunctive therapy with minimum side effects.
4	Puig et al 2016 ^[5]	Double- blind, placebo-controlled pilot study on the use of PRP in women with female AGA	There was no significant improvement in terms of hair count and hair mass index on treatment with PRP although patients perceived some improvement. Improvements perceived was purely due to placebo effect.
5	Farid et al ^[6] 2016	PRP micro needling versus 5% Minoxidil in the treatment of patterned hair loss	Minoxidil remains first line of treatment. However, PRP micro needling can be used as an adjunct therapy.
6	Alves et al ^[7] 2016	Randomized, placebo-controlled, Double-blind, half-head study to assess the efficacy of PRP in treatment of AGA	PRP therapy can be used as a treatment option for AGA. PRP does not produce significant growth as compared to hair follicle transplant
7	Mahapatra et al ^[8] 2016	Study on the efficacy of PRFM in hair follicular unit transplantation in AGA patients	PRFM injection is an excellent adjuvant therapy to Hair Follicular Transplantation
8	Mapar et al ^[8] 2016	Efficacy of PRP in the treatment of AGA(male pattern); randomized controlled trial	PRP was found to be ineffective in the therapy of AGA.
9	Navarro et al ^[10] 2016	A comparative clinical study between PRGF and topical Minoxidil	PRGF is a safer, inexpensive and effective treatment for AGA.
10	Gentile et al ^[11] 2015	Effect of PRP in hair regrowth-randomized placebo-controlled trial	Injection of PRP has shown positive clinical improvements in patients with no major side effects and therefore can be used as an adjuvant therapy for AGA.
11	Singhal et al ^[12] 2015	Efficacy of PRP in the treatment of AGA	PRP was, therefore, seen as an inexpensive, effective and promising therapy in the treatment of AGA with minimum side effects.
12	Cervelli et al ^[13] 2014	PRP injection in pattern hair loss; Clinical and histomorphometric evaluation	Injection of Autologous Activated-PRP has a Positive effect on patients with Male Pattern Hair Loss. No major side effects were observed.
13	Gkini et al ^[14] 2014	Study of PRP injections in the treatment of AGA through a one-year period	PRP therapy shows clinical improvements in patients with AGA and therefore, can be used as an adjuvant therapy.
14	Khatu et al ^[15] 2014	Use of PRP in AGA	PRP is a simple, cost effective treatment option for AGA with minimum side effects.
15	Schiavone et al ^[16] 2014	injecting Platelet Rich Growth Factors into the scalp of patients using a specific autologous blood concentrate.	Only provides some preliminary evidence as to the clinical improvements seen in PRP therapy.
16	Yong Miao et al ^[17] 2013	Promotional effects of PRP in Hair Follicle Reconstitution in vivo	Significant improvement was noted on the administration of PRP in the hair formation and hair follicle reconstitution.

Table 4: Treatment protocol and outcome of the selected studies.

Sr. No	Authors	Patients included	Treatment done	Results
1	Aythollahi et al ^[3] 2017	15 male patients with male pattern AGA.	5 injections of 2-4ml PRP, prepared by using single spin process, were injected every 2 weeks. Std. photographs, trichogram, hair density and diameter measurement	There was a slight increase in the number of hairs but on the contrary, a decrease in thickness of hairs. The anagen/telogen ratio was also significantly decreased.
2	Ince et al ^[1] 2017	20 patients in each group.	Group 1 received non-activated-PRP, Group 2 received autologous activated-PRP, and Group 3 received homologous-PRP.	The increase in hair density was statistically significantly greater in Group 1 than in Group 2 and more so in Group 3 than in both groups among all controls
3	Ferrando et al ^[4] 2017	78 patients, 19 men and 59 men with AGA grade II-IV (Ebling's scale), who were then on Minoxidil and/or Finastaride for more than a year without results	PRP was prepared using single spin process, and injected in the affected areas for 3 monthly sessions followed by 3 bi-monthly sessions. A decrease of at least 1 grade in Ebling's scale was considered a success.	Only 63 concluded the study, 14 men and 49 women. After the 6 th session, 10/14(71.4%) of MAGA(male pattern baldness) and 36/49(73.4%) of FAGA(female pattern baldness) patients got successful results but 3/14(21.4%) and 8/49(16.3%) remained without changes. 1/14(7.1%) and 5/49(73.4)% experienced worsening of condition.
4	Puig et al 2016 ^[5]	A randomized sample of 26 women (treatment group, n = 15; placebo group, n = 11)	To compare the effects of PRP and that normal saline placebo as scalp injections. The end points were hair numbers and hair mass index (HMI) and a patient satisfaction survey. PRP was prepared using Angel PRP method with patient's blood.	No significant difference was seen between the PRP and placebo group in terms of hair count and HMI. 13.3% of the subjects noted improvements and 26.7% noted increase in coarseness and heaviness of hairs post treatment.
5	Farid et al ^[6] 2016	40 patients with patterned hair loss were enrolled.	Group 1 was treated with 2ml 5% topical Minoxidil and the other group received PRP injections in monthly sessions. (12-28 weeks)	Both treatment modalities were comparable in improving hair density and alopecia grade. Patient satisfaction was also comparable. Onset of action was faster in Minoxidil.
6	Alves et al ^[7] 2016	Randomized, double blind, placebo-controlled study in 25 patients with AGA.	Half the head was injected with PRP, The other half was injected with a placebo. 3 PRP treatments were given to each patient, with a gap of a month between each treatment.	Only 22 patients completed the study. 3 months after first treatment the mean hair density showed an increase of 14.8 ± 32.1 hairs/cm ² Whereas control showed a decrease of 0.7 ± 32.7 hairs/cm ² . After 6 months of PRP therapy, an increase of 12.8 ± 32.6 hairs/cm ² was seen compared to control are which had a decrease of 2.1 ± 32.3 hairs/cm ² . Injection of PRP led to increase in mean anagen hairs, telogen hair, hair density and terminal hair density compared to baseline.
7	Mahapatra et al ^[8] 2016	10 male patients between the ages of 18-50 were included in the study.	The PRFM was prepared by drawing 10ml of blood 3000 rpm for 10 minutes. The PRFM was injected intra dermally, 3 times. 1 st before Follicle Unit Transplant (day 0), then after FUT in the second month and then the third month. Equal number of FUs were implanted in 1×1 cm ² on both left and right temporal region.	There was a significant increase in the number of hair follicles. The calculated difference between hair follicle numbers in right and left side was 25.60 ± 3.30 , $P < 0.001$ after 1 month, 21.50 ± 5.09 , $P = 0.002$ after 2 months, 26.00 ± 4.63 , $P = 0.005$ after 6 months. The effect of hair retention was also observed from day 0 to 6 months. A significant improvement was seen in hair retention.
8	Mapar et al ^[8] 2016	19 men with AGA were enrolled, but	At first areas of 2.5×2.5 cm in size, 3cm apart from each other were	In case squares, the mean number of terminal and vellus hairs which was 87

		only 17 completed.	selected on the scalp of each as case and control. 1.5ml PRP was injected at the case site and 1.5ml normal saline, at the control site. Injections were given in 2 sessions, 1 month apart. The terminal and vellus hair were counted in each square at the beginning and then 1, 3 and 6 months after injections.	and 43 at the beginning, was found to be 85 and 42 at the end of 6 months. Therefore, no clinical improvement was noted.
9	Navarro et al [10] 2016	A retrospective case control design was followed. 379 patients were enrolled who were either treated with PRGF or minoxidil.	In the 282 patients PRGF was injected in the affected areas followed by a pressure-based Craniosacral massage. This was done monthly in 2 sessions. In 97 patients, 3% topical minoxidil was to be applied with certain directions given This was for 6 nights a week for 4 months.	PRGF patients showed an increase in Anagen hair % of 56±5 to 63±3%(6.9±0.4%) compared to minoxidil patients who had 59±4 to 63±4%(4.6±0.5%). Telogen hairs decrease was seen as Side effects noted were transient erythema and local edema.
10	Gentile et al ^[11] 2015	The study includes 23 male patients with pattern hair loss.	The scalp was divided into 4 areas; frontal, vertex, parietal, occipital. The affected adjacent areas were injected with autologous PRP and placebo alternatively. The treatment was given thrice at an interval of 30 days for each patient. The patients were evaluated at 6 stages; At the beginning, after 2 months, after 6 months, after 12 months, after 16 months and after 24 months.	After 3 months, the patients presented with an increase in mean number of hairs with increase in 33.6, mean increase in total hair density as compared to baseline values of 45.9 hairs/cm ² . Relapse of AGA not evaluated until 12 months after treatment. 4 patients showed progressive hair loss after 16 months. These 4 were re-treated.
11	Singhal et al ^[12] 2015	10 patients were included in the study.	Each was given autologous PRP in the area affected with alopecia over a period of 3 months at an interval of 2-3 weeks and the results were assessed.	After 3 months, the patients presented with clinical improvements in hair count, thickness, hair root strength and overall alopecia.
12	Cervelli et al ^[13] 2014	Total of 10 male patients with MPHL were treated.	18cc of blood was taken from each to prepare AA-PRP. The scalp was divided into 4 parts, the frontal, parietal, the vertex, the occipital and the areas affected with MPHL were injected with AA-PRP and the adjacent affected area was injected with the placebo. The patients were evaluated at 4 stages; At the beginning, after 3 months, after 6 months and after 12 months.	Improvement was seen in terms of mean number of hairs, mean increase of 18.0 hairs in target area, mean increase in hair density of 27.7(number of hairs/cm ²) compared to baseline values. Increase in epidermis thickness and number of hair follicles was also noted two weeks after, compared to baseline.
13	Gkini et al ^[14] 2014	22 AGA patients were enrolled into the study of which 20 concluded the study (18 males and 2 females).	PRP was prepared using single spin method and once activated, was injected in the androgen-related areas of the scalp. 3 therapy sessions were performed with an interval of 21 days and a booster session of 6 months after the onset of the therapy.	Hair loss reduced and at 3 months, was brought down to normal levels. After 3 months, hair density reached its peak. At 6 months and a year, it was significantly increased respectively compared to baseline. No major side effects were noted.
14	Khatu et al ^[15] 2014	11 patients with AGA, not responsive to 6 months therapy with minoxidil and finasteride were enrolled.	Hair pull test was done before every treatment session. A total volume of 2-3 cc of PRP was injected into the scalp using an insulin syringe. The treatment was repeated every 2 weeks, 4 times. The outcome was seen after 3 months by hair pull test, clinical examination, macroscopic photos and patient's satisfaction.	A significant reduction in hair loss was observed between the first and the fourth injection. Hair count increased from an average of 71 hair follicular units to 93 hair follicular units. Therefore, there was an average increase in 22.09 cm ² . After the 4 th session, the pull test was negative in 9 patients.
15	Schiavone et al ^[16]	64 patients were enrolled in the study	2 injections of leukocyte rich PRP with the addition of plasmatic proteins were	Clinical improvements were seen in all 64 patients by the first independent evaluator

	2014	of which 42 were men and 22 were women.	injected at baseline and after 3 months (single spin at baseline and double-spin centrifugation at 3 months.). Macro photographs of the treated regions were taken at the beginning or the baseline and after 6 months, and 2 independent evaluators rated them using the Laeschke rating of clinical change.	and in 62 patients by the second independent evaluator. Overall mean change in clinical rating was 3.2 and the overall percentage of patients reaching clinical importance difference is 40.6% and 54.7% according to the two evaluators.
16	Yong Miao et al ^[17] 2013		Freshly isolated epidermal cells and cultured dermal papilla cells (DPCs) were mixed with different concentrations of activated PRP and transferred to the grafting chamber. This was later implanted into the dorsal skin of nude mice. Grafting chambers were removed one week later and Hair Follicle formation was monitored over 4 weeks.	Significant difference was formed in the number of newly formed follicles in the area of reconstituted skin. PRP was noted to have shortened the time of hair formation significantly. First hairs were observed in 18±1 days using 10% PRP and in 20±1 days without PRP.

4. DISCUSSION

The present literature review, included 16 studies which included 732 patients. Majority of the articles provide a compelling evidence about PRP treatment for hair restoration in AGA. All the studies were prospective clinical studies whereas the study by Navarro et al was a retrospective study.

Most of the studies had a different methodology but the objective was the same to find the efficacy of PRP in ADA.

While the genetic involvement is pronounced but poorly understood, major advances have been achieved in understanding principal elements of the androgen metabolism involved.^[18] The beneficial effects of PRP in AGA can thus be attributed to various Platelet derived growth factors causing improvement in the function of hair follicle and promotion of hair growth. It is safe, cheap, and nonallergic, and it appears to be a useful adjuvant in the management of AGA.^[12]

There is no a standardized method for PRP preparation, therefore, there might be differences in product composition. This fact may lead to an altered PRP function, which might explain the controversy found into the literature.^[16] Differences in PRP composition result from differences in the samples retrieved from person to person. Differences in the manufacturing of the inoculate result, especially from the routine of centrifugation and whether either bovine thrombin or calcium chloride is used in activation.^[19] 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.^[19]

4.1 Studies with positive results

The meta-analysis done by Gupta et al, included 13 studies which investigated the use of PRP for treatment of AGA. The analysis encouraged the use of PRP for the

treatment of ADA.^[20] A review conducted by Cervantes et al, included 12 studies, in which most of the studies showed that platelet rich plasma was effective in increase of terminal hair density/diameter.^[2] In the systematic review by Giordano et al, 6 studies involving 177 patients were reviewed. A significant localized increase in hair numbers per cm² was noticed. Post PRP injection treatment patients were compared to control. Similarly, a significant increase in hair thickness cross section per 10 mm² was noted.^[19] In a study conducted by Ince et al, 6 studies involving 177 patients were reviewed. A significant localized increase in hair numbers per cm² was noticed.^[1] Ferrando et al, Gentile et al, Singhal et al, Cervelli et al, Gkini et al, Khatu et al, Yong Miao et al concluded that the use of PRP for AGA is effective and can be considered with minimal side effects.^[4,11-15,17] Alves et al, stated that PRP can be used for the treatment of AGA but it is not as effective as a hair transplant procedure.^[7] Platelet rich fibrin matrix (PRFM) was also used in conjugation with hair transplant surgery. It was found that PRFM injection is an excellent adjuvant therapy to Hair Follicular Transplantation.^[8] Navarro et al concluded that Platelet Rich Growth Factors found in PRP is a safer, inexpensive and effective treatment for AGA.^[10] Schiavone et al conducted the study involving 64 patients of which 42 were men and 22 were women. Provides some preliminary evidence as to the clinical improvements seen in PRP therapy.^[16]

4.2 Studies with no changes observed

Aythollahi et al conducted a study involving 15 male patients with male pattern AGA and concluded that there was no positive clinical improvement. This study showed that injection of PRP has no significant effect on male pattern AGA.^[3] Puig et al conducted a double-blinded multi-center placebo-controlled study that compared the effects of PRP and that normal saline placebo as scalp injections. There was no significant improvement in terms of hair count and hair mass index on treatment with PRP although patients perceived some improvement. Improvements perceived was purely due

to placebo effect.^[5] Farid et al conducted a study involving 40 patients with patterned hair loss. They were divided into two groups. The first group was treated with 2ml 5% topical Minoxidil and the other group received PRP injections in monthly sessions. Both treatment modalities were comparable in improving hair density and alopecia grade. Patient satisfaction was also comparable. Onset of action was faster in Minoxidil and no statistical improvements were observed when administering the PRP injections.^[6] In the study done by Mapar et al, 19 men with AGA were administered PRP injections, but only 17 completed the study. They conclude that PRP was ineffective in the therapy of AGA.^[9]

5. CONCLUSION

Most of the studies have shown a beneficial outcome. The data collected is suggestive of the positive effects; but more randomized, blinded, case control design studies are necessary to completely establish the efficacy of Platelet-Rich Plasma in the treatment of Androgenic Alopecia. A standardized protocol should be established for the usage and preparation of PRP. More in vitro studies should be conducted to determine the optimal type of PRF to be used. PRP injections are minimally invasive, easily available, less costly, biologically compatible and has tested to have minimal or none side effects. PRP therapy can be recommended to patients before the more invasive hair transplant surgery. The minimal invasive surgery is more acceptable by the patients. Long term randomized clinical control trials with long term follow up should be conducted in the future for the establishment of PRP as a treatment alternative for ADA.

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