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PLATELET-RICH PLASMA (PRP) THERAPY VS MINOXIDIL IN MEN WITH ANDROGENIC ALOPECIA: SYSTEMATIC REVIEW

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ABSTRACT
Androgenic Alopecia is characterized by progressive, patterned hair loss due to excessive sensitivity to androgens in genetically predisposed individuals. It is characterized by the gradual thinning of scalp hair in a specific pattern, causing a significant decrease in the individual's self-esteem and psychological well-being. Currently, there are several therapies for patients with androgenic Alopecia. One of them is platelet-rich plasma (PRP) and Minoxidil. This systematic review aims to compare PRP and minoxidil therapy use in men with androgenic Alopecia. This systematic review was prepared based on the references contained in the Priority Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This systematic review was prepared by searching research articles using three databases, namely PubMed, ScienceDirect, and Cochrane. Data was extracted from each study included in this systematic review using a pilot-tested data extraction form. The data that has been collected is then interpreted qualitatively and quantitatively. Based on the six studies reviewed in this systematic review, the majority stated that therapy with PRP on the scalp effectively treats androgenetic Alopecia in men. All studies in this review reveal PRP use's benefits and positive impacts.

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INTRODUCTION

Androgenic Alopecia is characterized by patterned and progressive hair loss due to excessive sensitivity to androgens in genetically predisposed individuals. Androgenic Alopecia occurs due to the role of androgens in mediating the conversion of terminal hair into vellus hair. Generally, this type of Alopecia begins at 20 years, and almost 50% of men suffer from androgenic Alopecia by the age of 50. Various literature reveals increased severity and frequency of androgenic Alopecia with increasing age. This disease is characterized by the gradual thinning of scalp hair in a specific pattern, leading to the individual's psychological well-being and a significant decrease in self-esteem. (Stevens & Khetarpal, 2019)

Until now, there have been several therapies for patients with androgenic Alopecia. One of them is platelet-rich plasma (PRP). Platelet-rich plasma (PRP), or platelet-rich growth factor or platelet concentrate, is a platelet-rich plasma protein concentrate derived from whole blood and centrifuged to remove red blood cells. (Magalon et al., 2016) Platelet-rich plasma (PRP) is a treatment modality currently widely used in androgenic Alopecia because of its autologous nature, minimal side effects and minimal invasiveness so that the risk of infection and immune rejection can be reduced. PRP therapy also offers more affordable costs compared to hair restoration surgery. PRP therapy is a

preparation of autologous platelets in concentrated plasma, generally above 1,000,000 platelets/μL or 2-7 times the original concentration of whole blood (Stevens & Khetarpal, 2019).

A meta-analysis of six studies consisted of four randomized controlled trials. At the same time, the other two were retrospective studies with 177 patients. The study showed a significant increase in the number of hairs per cm2 after PRP injection compared with controls (mean difference (MD) 17.90; 95% CI 5.84–29.95, P=0.004) and a trend towards an increase in the percentage of thickness hair and amount of hair (Giordano et al., 2017).

Apart from PRP, Minoxidil is also a therapy for patients with androgenic Alopecia. Minoxidil is a pro-drug converted into its active form, minoxidil sulfate, by the sulfotransferase enzyme expressed in the outer root sheath of hair follicles. Minoxidil sulfate is an active metabolite that stimulates increased hair growth (Suchonwanit et al., 2019). A meta-analysis showed that topical Minoxidil applied to all samples provided better results than those in the placebo group. Compared with the placebo group, the study showed a mean difference of 8.11 hairs /cm^2 and 14.90 hairs/cm^2 associated with 2% and 5% minoxidil treatment. Meanwhile, a comparison of the 2% minoxidil and the placebo groups in female patients showed an average difference of 12.41 hair strands/cm^2 (Adil & Godwin, 2017). In men with AGA, minoxidil sulfate 5% showed a significant improvement in the difference in mean hair density compared with minoxidil sulfate 2% and placebo treatment. Gentile and Garcovich's study evaluated the use of PRP in androgenic Alopecia compared with minoxidil, finasteride, and adult stem cell-based therapies. The study found that compared with Minoxidil, finasteride, and adult stem cell-based therapies, 84% of all studies reported a positive effect of PRP, and 50% showed a statistically significant improvement. In comparison, 34% showed an increase in hair density and thickness, although no values P or statistical analysis were described (Gentile & Garcovich, 2020).

Based on this background, until now, few studies have reviewed and compared PRP and minoxidil therapy in androgenic Alopecia. More studies need to be evaluating its use in men with androgenic Alopecia. This prompted the authors to compile a systematic review regarding the differences in PRP and minoxidil therapy use in men with androgenic Alopecia.

The aim of this study is to holistically evaluate and compare the effectiveness of Platelet-Rich Plasma (PRP) Therapy and Minoxidil in addressing androgenetic alopecia in men. The study will detail and assess previous research data, investigate the safety and side effects of both, analyze the research methodologies used, establish success parameters, and finally draw up recommendations for clinical practice. As such, this study is expected to provide healthcare practitioners with a comprehensive insight into the most effective and safe therapeutic options for managing androgenetic alopecia in the male population.

METHOD

This systematic review was organized based on references contained in the Priority Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Literature Search Strategy and Selection of Inclusion Studies. This systematic review was organized by searching for research articles using three databases, namely PubMed, Science Direct, and Cochrane. Other articles, such as previous reviews and systematic reviews, were used as additional data and comparison studies in the discussion. Data were extracted from each study included in this systematic review using a pretested data extraction form. Data from each study included in this systematic review included country, sample size, method, sample type, age range, and outcome in each study. The collected data were then interpreted qualitatively and quantitatively by analyzing each result obtained in each included study and looking at the trend of results from each study so that conclusions could be drawn regarding the comparison of the effects of Minoxidil vs PRP therapy in male patients with Alopecia.

RESULTS AND DISCUSSION

A total of 464 patients were subjects who met the inclusion criteria in this study. The treatment protocols used in this study varied from 3-4 procedures (average of three procedures), and the duration of the examination ranged from one month to twelve months. The age range used in this study ranged from 18-60 years old, with all the studies being men.

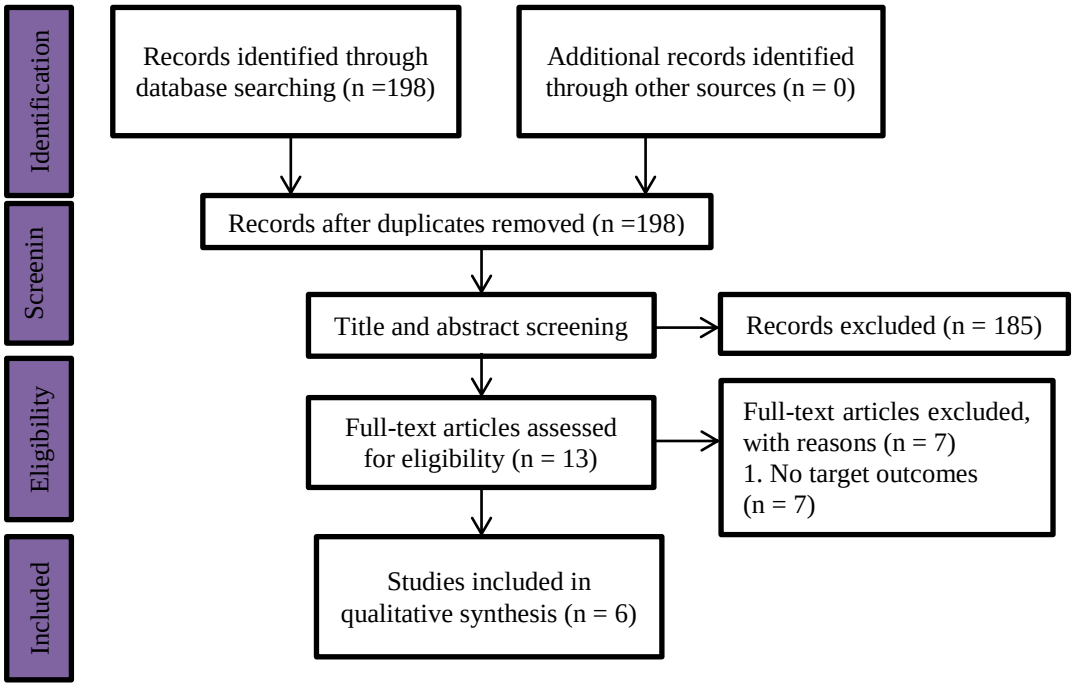

Figure 1. PRISMA Flow Diagram in Literature Search

Based on the analysis of studies carried out, four studies analyzed PRP treatment, which was then evaluated based on the hair density of the patient. Previous studies found that patients who received PRP had a significant increase in hair density compared to controls ($p<0.05$) (Cervelli et al., 2014; Gentile et al., 2015; Rodrigues et al., 2019; Sultana & Kumar Paul, 2020). Furthermore, two studies compared the administration of PRP and Minoxidil, which resulted in significant improvements. Significant when compared with Minoxidil monotherapy ($p<0.05$) and ($p<0.001$) (Pakhomova & Smirnova, 2020; Singh et al., 2019).

This study also analyzed immunohistochemistry to evaluate cell proliferation activity in the hair of research subjects. Several studies analyze cell proliferation activity via Ki-67. In previous studies, it was found that there was a significant increase in Ki-67 in patients before and after receiving PRP intervention ($p<0.05$) (Cervelli et al., 2014; Gentile et al., 2015; Pakhomova & Smirnova, 2020).

Androgenic Alopecia is one of the most common causes of hair loss, affecting up to 80% of men and 50% of women. The main goal of androgenic alopecia therapy is to stop hair loss and prevent further hair thinning. Pharmacological therapy for this disease targets reducing levels of dihydrotestosterone (DHT) and stimulating hair follicles through the use of Janus kinase (JAK) inhibitors and 5-alpha reductase (5AR) inhibitors. Due to the limitations of available pharmacological therapy modalities, ongoing research is carried out regarding the effectiveness of the newest modalities, one of which is PRP therapy (Kelly et al., 2016).

PRP has been developed in dermatology and is widely used in therapies such as skin rejuvenation, acne scarring, and vitiligo. PRP contains chemokines, growth factors, cell signaling molecules, and cytokines. The mechanism of PRP in managing AGA has yet to be fully discovered.

However, it is thought to be due to hair growth stimulation and immune system improvement. PRP is a small portion of blood plasma with a higher platelet content. Platelets are no longer only associated with the hemostasis system. Platelets are a source of growth factors (GF) released during platelet degranulation. They will cause cell proliferation, differentiation, migration and angiogenesis. Some of the GFs released by platelets are in the form of platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), Fibroblast Growth Factor (FGF), and Epidermal Growth Factor (EGF) (Alves & Grimalt, 2016).

PRP is known to have more than 20 growth factors and affects wound healing and hair growth. PRP works by activating platelet a-granules, transforming growth factor (TGF), PDGF, VEGF, epidermal growth factor (RGF), insulin-like growth factor, and interleukin-1 (IL-1) (Donovan, 2015). Plasma components containing growth factors can increase skin growth spe, speeding up the wound healing process and increasing the elasticity of collagen tissue, which has a big role in cell regeneration. In treatment with PRP, a portion of whole blood must contain more than four times the number of platelets or an absolute 1,000,000/mL in 5 mL of PRP (Hesseler & Shyam, 2019).

In other pathways, PRP also plays a role in the WNT/catenin pathway. This pathway functions in the process of hair morphogenesis during the embryonic phase. However, other research also states that this pathway is activated during adult hair growth, especially during anagen activation. The catenin pathway is essential for converting telogen hair to anagen hair and deleting the WNT-less gene, whose function is to arrest hair follicles in the telogen phase (Myung et al., 2013).

Several studies assess the effectiveness of PRP as a single modality, including Qu et al. and Butt et al . Qu et al.'s research using a randomized controlled trial (RCT) method assessed the effectiveness of PRP as a treatment modality for androgenic Alopecia with a sample of 32 men with grades II-V (Norwood-Hamilton scale) and 20 women with grades I-III (Ludwig scale). PRP is injected subdermally into half of the patient's scalp while the other half is injected with saline solution. The injection is carried out three times at one-month intervals. PRP significantly increased hair density after three months compared to before therapy (124.9 ± 11.7 versus 143.8 ± 12.0 hairs/cm^2, $p < 0.001$). There was also a significant increase in hair number ($p<0.001$), diameter ($p<0.05$), and anagen hair ratio ($p<0.05$) after six months (Qu et al., 2021).

In another clinical trial by Butt et al. in 2019, the effectiveness of PRP in androgenic alopecia therapy was assessed with a sample of 20 men with grade III-IV (Norwood-Hamilton scale) and ten women with grade I-III (Ludwig scale). All samples received PRP injections twice with an interval of 4 weeks. From the study results, most patients experienced an increased ratio of terminal to vellus hair. Hair density also increased significantly within six months after the first injection. The average hair density of the samples at the first visit was 34.18±14.36/cm^2 at the final visit, it was 50.20±15.91/cm^2 ($P<0.05$). From these two studies, PRP has a significant effect as an androgenic therapy for Alopecia, both in men and women (Butt et al., 2019).

The side effects of PRP therapy are very minimal, except for an infection. On sensitive scalp, these side effects usually appear. PRP should be avoided in patients with malignancies, platelet disorders, anemia, bleeding, pregnant patients, and immunocompromised conditions (Singhal et al., 2015).

One modality that has long been used for androgenic alopecia therapy is Minoxidil. This modality is available in topical form and in oral form, where the drug in topical form is more effective in treating androgenic Alopecia. In contrast, the oral preparation is more effective in treating a condition of refractory hypertension (Ramos et al., 2020; Randolph & Tosti, 2021). This Minoxidil topical preparation is available in liquid or foam form with different contents. The liquid preparation consists of alcohol and propylene glycol. These two important molecules can help dissolve the drug in the patient's body so that the drug can be absorbed into the tissue properly. There are also two types of

available doses of Minoxidil, namely in a concentration of 2% minoxidil and 5% minoxidil, which is usually used to treat androgenic alopecia patients under 18 years of age and has been approved by the Food and Drug Administration (FDA) (Gajjar et al., 2019).

For androgenic alopecia therapy, Minoxidil 5% is generally used twice a day for male patients and once a day for female patients. However, female patients can also use the 2% preparation twice daily. When using this medicine, it is not recommended to massage the patient's scalp. The use of this drug in patients with liver disease, kidney disease, and pregnant patients is not recommended. Minoxidil has a hair growth function with the empirical formula $C_9 H_{15} N_5 O$. The sulfotransferase enzyme found in the human scalp can convert Minoxidil into minoxidil sulfate, which is the active form of the drug. Differences in sulfotransferase enzyme levels between individuals can affect this drug's activity, so not all therapies show satisfactory results. This drug can shorten the hair's telogen phase so inactive hair follicles will prematurely transition to the anagen phase. Shortening of this phase can cause a condition of telogen effluvium. Namely, the anagen phase of the hair itself will lengthen, which will have the effect of increasing the length and thickness of the hair, where usually the effect of using topical Minoxidil can be seen within eight weeks of treatment, with the maximum effect being seen within four months. This drug works by opening potassium channels found in smooth muscles and hair. Opening these potassium channels will cause stimulation of microcirculation around the hair follicles, which affects the vasodilation of the arteries, which in turn will impact better hair growth. Apart from that, this drug works by stimulating vascular endothelial growth factors, increasing vascularization around the hair follicles to increase and improve hair growth (Verma et al., 2019).

Opening the potassium channels will also cause activation of the enzyme prostaglandin endoperoxide synthase-1, which can cause increased hair growth. This drug can also stimulate directly from the hair follicle itself, which acts as an epidermal growth factor on matrix cells and prolongs the anagen phase that can be achieved by activating the beta-catenin pathway (Suchonwanit et al., 2019).

The clinical efficacy of topical Minoxidil in men was evaluated in one RCT study by Researchers. This study used a sample of 300 male patients aged ≥20 years who were given topical Minoxidil therapy 5% (n=150) and 1% (n=150) for 24 weeks. In both therapy groups, there was a significant increase in total hair number after 16 weeks, with an average of 22.3 ± 1.4 hairs/cm^2 for the group with 5% Minoxidil therapy ($p < 0.001$) and 17.2 ± 1.3 hairs/cm^2 for the group with treatment Minoxidil 1% ($p< 0.001$). The difference in therapy results in the two groups was also significant ($p= 0.020$). Meanwhile, from the safety aspect, the incidence of side effects in the Minoxidil 5% group was 8.7% (13/150), and Minoxidil 1% was 5.3% (8/150). There was no significant difference in the two groups regarding the incidence of side effects ($p= 0.258$). The FDA does not currently approve Minoxidil oral preparations, so few studies assess the clinical efficacy of oral Minoxidil. The oral pharmacological modality that the FDA has approved is Finasteride 1 mg. A prospective study by Panchaprateep et al. assessed the clinical efficacy and safety of Minoxidil 5 mg administered orally once daily. The study used 30 men aged 24-59 years with androgenic alopecia grade III vertex-V (modified Norwood-Hamilton scale). The study results showed a significant increase in the total number of hairs after 12 weeks (182.5-208.5 hairs/cm^2, $p= 0.023$) and 24 weeks (182.5-217.6 hairs/cm^2, $p=0.003$) of therapy. Hair diameter increased significantly by 10.6% from baseline before therapy ($p<0.001$). After 12 weeks, the diameter increased from 58.5±11.8 to 64.7±15.2 µm, and after 24 weeks, it increased from 58.5±11.8 to 67.4±14.5 µm. The most common side effects from using oral Minoxidil are hypertrichosis (93% of total patients) and leg edema (10% of total patients). This oral preparation must also be cautiously given to patients with hypertension and at risk of cardiovascular disorders (Panchaprateep & Lueangarun, 2020).

Based on other studies, the side effects that this drug can cause include excessive hair loss in sufferers of androgenic Alopecia because Minoxidil works by stimulating telogen effluvium. The telogen phase will shorten. Also, scalp irritation can occur, such as erythema and a burning sensation. Itching of the scalp, allergic contact dermatitis, and hypertrichosis or excessive hair growth due to a prolonged anagen phase (Rica Echevarría et al., 2020).

Several studies have shown sound therapeutic effects of using PRP and Minoxidil separately. Several studies compare the two therapeutic agents' effectiveness to determine which type of therapy is more effective, safe and efficient for androgenic alopecia patients. The study by Balasundaram et al. is one of the comparative studies that assess the efficacy and safety of PRP with standard androgenic alopecia modalities, namely topical Minoxidil. This study used a sample of 64 men aged 20-50 years with grades III, III vertex, and IV (modified Hamilton-Norwood scale) who were randomized to receive 5% Minoxidil therapy (2 times a day for six months) and PRP injections (3 times a month). The increase in the number of hairs (basal and terminal) and hair density was significant in the Minoxidil group (all groups with $p<0.001$) and the PRP group ($p= 0.014$, $p= 0.001$, $p= 0.029$, and $p=0.046$ in each group) after 12 weeks. There was no significant difference in therapeutic results between the Minoxidil and PRP groups. However, the increase in hair density in the PRP group after 12 weeks was better than in the Minoxidil group, although not significant ($p= 0.713$). The incidence of side effects in the Minoxidil group was 37%, and PRP was 53% ($p= 0.21$). The most common side effects were mild headache (n=4) and itching of the scalp (n=4). In terms of clinical efficacy, both modalities have the same effect. In contrast, concerning safety, using PRP causes more side effects (Balasundaram et al., 2023).

In another comparative study, PRP showed promising clinical efficacy as an androgenic therapy for Alopecia but was not better than Minoxidil. Farid et al.'s study reported that patients experienced faster therapeutic results and a higher average increase in hair count after receiving Minoxidil therapy compared to the combination group of PRP and micro-needling therapy (16 hairs versus five hairs/cm^2) (Farid & Abdelmaksoud, 2016). Meanwhile, Bruce et al.'s study showed that patients' quality of life with PRP therapy was better than with Minoxidil therapy (Bruce et al., 2020). PRP side effects are generally mild, and pain is a frequently reported complaint. The subdermal PRP injection technique causes less pain, so it will be considered an injection technique in the future (Hausauer & Jones, 2018).

CONCLUSION

Androgenetic alopecia is one of the most common causes of hair loss, affecting up to 80% of men and 50% of women. Androgenetic alopecia therapy primarily aims to stop hair loss and prevent further hair thinning. While both PRP and Minoxidil have shown effectiveness in the management of androgenetic alopecia, some comparative studies paint a mixed picture. Studies show that both PRP and Minoxidil have positive effects on improving hair density and hair growth, with variations in results depending on the specific study. In addition, both therapeutic modalities have a good safety profile, with minimal side effects. Therefore, the choice between PRP and Minoxidil can be tailored to patient preference, individual response, and specific safety considerations. Further studies and careful comparative research are needed to confirm these findings and provide clearer guidance in choosing the most suitable therapeutic modality for androgenetic alopecia patients.

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