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Original Article

Combining topical minoxidil with procapil; an assessment of their comparative efficacy in androgenetic alopecia: A randomized control trail

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Abstract

Introduction Androgenetic alopecia (AGA) is a commonly prevalent form of non-scarring alopecia mostly involving men. It involves 50% of men, and the prevalence increases with age. Its scalp involvement ranges from mild (I) to severe (VII) based on the Norwood scoring system. Multiple modalities have been tried for its treatment, including oral and topical minoxidil and finasteride. These treatment modalities have been successful in treating androgenetic alopecia up to a certain extent but are also associated with adverse effects. Very few studies are available on the efficacy of topical procapil, and none have compared it with minoxidil on a head to-head basis. The purpose of this study was to assess the efficacy of procapil in combination with minoxidil vs. minoxidil alone in the treatment of androgenetic alopecia.

Methods Using randomized sampling technique, 140 patients were enrolled in this study. Patients were divided into two groups, with 70 patients in each group. One-half of the patients used 5% minoxidil on a twice-daily basis (Group A), while the other half used procapil 5% alternated with minoxidil for 12 months (Group B). Both subjective and objective assessment tools were for hair regrowth evaluation in the form of an increase in the mean hair count as well as patients' satisfaction and dermatologist assessment scores.

Results The mean age was 32.6±6.7 and 31.5±7.4 years in groups A and B, respectively. The baseline line hair count and grads of AA were also comparable in both groups. As compared to minoxidil alone, the combination therapy showed better results in terms of an increase in hair count (p value=0.0001), Patient satisfaction (p value=0.011), and Dermatologist assessment scores (p value=0.0054).

Conclusion The addition of procapil to minoxidil is more efficacious than minoxidil alone for the treatment of androgenetic alopecia.

Key words
Androgenetic alopecia; Minoxidil; Procapil.

Introduction

Androgenetic alopecia (AGA) is the most prevalent kind of baldness, characterized by gradual, non-scarring hair loss.[1] AGA can affect all races and both genders, but the prevalence rates vary, being highest in Caucasians, with involvement rates for men in their 30s as 30%, in 40s as 40%, and 50% for men in 5th decade.[2] Similarly, up to 36% of men over 50 are

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involved in AGA, according to Pakistani studies. In other ethnic groups, prevalence is comparatively lower, at only 21% in Chinese.[3]

The severity increases gradually in all patients, regardless of age at onset or initial presentation. Various patterns of hair loss are seen both in men and women. In order to classify the disease according to the extent of scalp involvement, various assessment tools have been described, but the Norwood classification system is commonly applied. It has seven stages, with stages 2 and 3 being common in Asian populations.[4]

Multiple pathogenetic factors are described for the development of AGA alopecia, including genetic and hormonal factors. Candidate genes associated with androgen production and androgen conversion to dihydrotestosterone (DHT) are involved in this process.[5] Regarding the onset and progression, the hallmark of androgenetic alopecia (AGA) is the gradual miniaturization of the hair follicle, which is brought on by a changes in the dynamics of the hair cycle and results in the conversion of the terminal hair follicle to vellus one.[6] The normal hair cycle has an active growth phase (anagen), which can last for many years and contribute to the overall length and shape of the hair shaft. This is followed by a brief stage of regression called the catagen phase, where a burst of cellular death occurs in a majority of follicular keratinocytes resulting in vellus hair formation. After brushing and washing, the hair finally sheds, and the anagen phase restarts.[7] In AGA there is a steady decrease in the anagen phase and increase in telogen phase duration leading to miniaturization and bald appearance.[8] This whole process of abnormal hair follicle dynamics results from the abnormal sensitivity of hair follicles to circulating androgens. DHT is more potent in regulating hair growth, and it needs the 5-Alpha Reductase enzyme for its synthesis from testosterone. Genetic deficiency of this enzyme leads to the non-occurrence of AGA in such patients.[9] Dermal papilla cells (DPCs) are prevented from inducing hair follicle stem cell development by DHT via blocking the Wnt/catenin pathway, which in turn prevents GSK-3 activity.[10] The use of oral and topical finasteride in AGA is based on this pathogenesis.

Various treatment modalities have been tried in the past to treat AGA. Importantly, oral and topical minoxidil, 5 alpha-reductase inhibitors, platelet-rich plasma, and hair transplantation.[11] Minoxidil is a piperidino-pyrimidine derivative, and its active metabolite minoxidil sulphate is primarily responsible for hair growth related pharmacodynamics. The enzyme sulfotransferase, which catalysis the conversion into this active metabolite, is found in hair follicles and varies in activity among individuals, which is why its response is variable among patients.[12]

Androgens and androgen receptors (AR) are the main factors contributing to the development of AGA, and inhibition of AR leads to the reversal of hair growth. Among many hypothesized mechanisms for hair growth, Minoxidil also reduces AR-related functions, lowering AR transcriptional activity in reporter assays and lowering the expression of AR targets at the protein level. It also binds directly to AR receptors and decreases and destabilizes AR protein in dermal papilla cells.[13]

Secondly, continued hair growth needs unprohibited blood supply to DP cells, which in turn is dependent on good vascularization. A dose-dependent increase in VEGF mRNA expression is caused by minoxidil, which leads to enhanced perifollicular vascularization, especially during the anagen phase.[14] The dermal papilla also contains potassium channels, and minoxidil acts by opening these channels, leading to depolarization and relaxation of

vascular smooth muscles. This results not only in increased blood supply to the dermal papilla but also in the maintenance of hair-specific genes and continued proliferation of follicular cells.[15]

Thirdly, minoxidil affects various pathways that are important for cellular growth and differentiation. It increases catenin activity and follicular proliferation and differentiation, which prolongs the anagen phase. This results in an increase in follicle size histologically, and hair shaft elongation clinically.[16]

Finally, prostaglandin endoperoxide synthase-1 (PGHS-1)'s cytoprotective isoform is mainly expressed in hair follicles. It is necessary for cellular growth and metabolism. Minoxidil activates PGHS-1 in a dose-dependent manner, leading to increased prostaglandin E2 production and higher oxygen consumption by follicular cells.[17]

Very little data is available on Procapil, its precise mechanism of action, and its efficacy in androgenetic alopecia. Procapil is basically composed of three active plant-derived substances, all of which contribute to hair growth at different stages. These include oleanolic acid, which inhibits 51 and 52 reductase enzymes, resulting in decreased conversion of testosterone into DTH; apigenin, which is involved in vasodilation; and biotinyl GHK, which contributes to enhanced anchoring of the hair with the strengthening of inner and outer root sheaths. Similarly, procapil is involved in regulating many genes affecting cellular metabolism, inflammation, antioxidant activities, matrix remodeling, and angiogenesis.[18]

Methods

This was a randomized control trial consisting of 140 patients, 70 in each group. After receiving approval from the hospital administration, patients were divided into two groups based on randomized sampling technique. Written consent was obtained from all patients and they were given explanation of the study procedure and possible drug adverse effects and complications.

Group A received minoxidil solution (5%) twice a day, while group B applied minoxidil (5%) and procapil (5%) on alternate days, 7 days a week, for 12 months consecutively. Basic demographic data like age, gender, duration of disease, and age of onset were taken along with the baseline hair count per centimeter square, and the modified Norwood-Hamilton score. The results were finalized after 12 months based on hair counts, dermatologist assessment, and patients' satisfaction scores, keeping a p-value of <0.05 as significant.

Inclusion criteria: In this study, all male patients with Norwood-Hamilton stages II–V AGA, between the ages of 18 and 55, who had signed a written consent form and desired to maintain their hair's style and length were included.

Exclusion criteria: Patients with scalp skin conditions contributing to hair loss other than AGA and those with significant heart, kidney, liver, medication hypersensitivity, or lung conditions were eliminated from this study. Individuals who wore wigs or had used any form of hair loss treatment during the previous six months or had used androgens or antiandrogens for other indications were also excluded.

Norwood-Hamilton classification[19]

1. There is either no recession or very little recession in the frontotemporal hairline region.

2. The hairline in the frontotemporal region shows a symmetrical, triangular recession.

Even though the middle of the frontal region exhibits some hair thinning or loss, it is less pronounced than in the frontotemporal region.

3. Hair thinning becomes obvious. It becomes evident that there is a significant frontotemporal recession.
4. There is severe frontal and frontotemporal hair loss. The vertex has a noticeable thinning.

There is a distinct band structure that separates these two zones.

5. In type 4, the hair band gets thinner. Vertex and frontotemporal regions show a greater percentage of hair-free areas.
6. Even in the band region, the hair loss is more obvious. Hair-free areas in the frontotemporal region converge with those in the vertex.
7. The is the most severe form. It extends rearward from the front of the ear. There is now only a horseshoe-shaped patch of hair covering the rear area.

In order to standardize the evaluation, a specific point selection for the hair count calculation was necessary. To accomplish this, two lines are drawn from the mid-pupillary region and tragus onto the scalp, and the intersection of these lines is taken as a standard for hair count calculation.

Photographs were taken and analyzed by 2 dermatologists independently, and then the average of all observations were taken as the final count. This was done at baseline and after 12 months.

A 7-point patient self-evaluation questionnaire was given to the patients in both groups to fill out according to their own perception of hair regrowth after 12 months. Patient satisfaction with the treatment modalities is classified as very satisfactory, moderately satisfactory, slightly satisfactory, slightly unsatisfied, moderately unsatisfied, and very dissatisfied.

Hair regrowth was assessed by 2 dermatologists, by filling the proforma at the end of the study. Global photography was used as a marking system. Each patient was evaluated based on 7-point scoring system. Excellent, moderate and slight hair regrowth was defined by hair growth almost similar to normal areas of the scalp, good recovery but not equivalent to non-involved regions, and minimal recovery of hairs with bald areas still clearly visible respectively. On the other side no change, slight hair loss, moderate hair loss and extreme hair loss were defined by, no change in hair growth, a slight increase in hair loss from the baseline but not clearly visible, clearly visible worsening of hair loss and 1 step downgrading on Norwood's scale, respectively.

Data analysis

Statistical software for social science (SPSS Version 24) was used to enter and analyze the data. The mean and SD were calculated for age and hair count per cm2 score at baseline and 12 months after treatment. Both groups were compared by age, hair count, the modified Norwood-Hamilton score, patient satisfaction, and Dermatologist Assessment scores. A chi-square test was applied to compare the efficacy in both groups, using a two-sided $P < 0.05$ as significant. For statistical purpose; excellent, moderate and slight hair regrowth in Dermatologist Assessment scores and very, moderately and slight satisfaction in-patient satisfaction score were considered as significant.

Results

A total of 140 patients participated in this randomized control trial, 70 in each group. The basic demographic data and clinical profiles of patients are shown in **Table 1**. The mean age±SD in the minoxidil group (A) was

Table1 Clinical and demographic data of patients.

Parameter	*Minoxidil (A)*		*Minoxidil+procapil(B)*		*P value*
Number of patients	70		70		
AGE (mean &SD)	32.6±6.7		31.5± 7.4		0.3582
Norwood-Hamilton classification					
Stage 1	13		11		0.65
Stage 2	12		14		0.662
Stage 3	17		12		0.298
Satge4	15		13		0.6744
Stage5	11		20		0.672
Hair count	Baseline 51.28±10.4	At 12 months 67.34±11.72	Baseline 44.63±10.31	At 12 months 81.55±14.32	0.0001

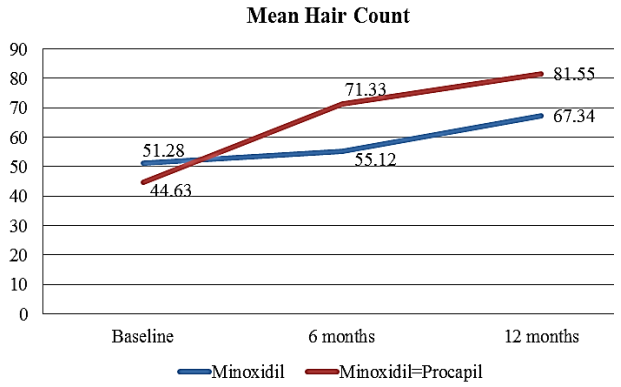

Figure 1 Changes in hair count over time.

32.6±6.7 years, while in the minoxidil/ procapil combination group (B) it was 31.5±7.4 years. Both groups had a comparable number of patients according to the Norwood classification of androgenetic alopecia. The baseline mean hair count in groups A and B was 51.28±10.4 and 44.63±10.31, respectively. While at the end of 12 months, the hair count increased to 67.34±11.72 in Group A and 81.55±14.32 in Group B (pvalue=0.0001), as shown in **Figure 1**. The patient's own satisfaction and the researcher's perception scores are shown in **Figures 2, 3** respectively (p value <0.05)

Discussion

Androgenetic alopecia (AGA) is the most prevalent type of non-scaring alopecia affecting adult men and women. Its severity varies, and staging is based on the Norwood scoring system.[20] The mean age of onset is 30 years. Many treatment modalities have been used in the past, namely topical and oral minoxidil, topical and oral finasteride, and PRP.[21] Very limited data exists about the role of procapil to treat AGA, and according to our knowledge, no study has been carried out to directly evaluate its efficacy in combination with minoxidil. This study was conducted in order to fill this research gap.

In this study, a total of 140 male patients with different stages of androgenetic alopecia were enrolled. One group (A) used 5% minoxidil solution twice daily, while the other group (B) used minoxidil solution alternating with procapil 2% twice a day for 12 months. In the end, groups A and B achieved an increase in mean hair count of 16.06 and 36.92, respectively, with p value <0.0001. Similarly, in terms of dermatologist's assessment and patient satisfaction, combination therapy was better than minoxidil alone with p values of 0.0054 and 0.011, respectively. The lower satisfaction score may be attributable to the patient's own perceptions and expectations, as well as the extra cost of procapil solution in addition to minoxidil in the combination group.

A post-marketing study of patients in Germany showed favorable results for minoxidil in male patients with androgenetic alopecia.

All patients applied minoxidil 5% solution to the scalp twice daily for 12 months. 15.9%, 47.8%,

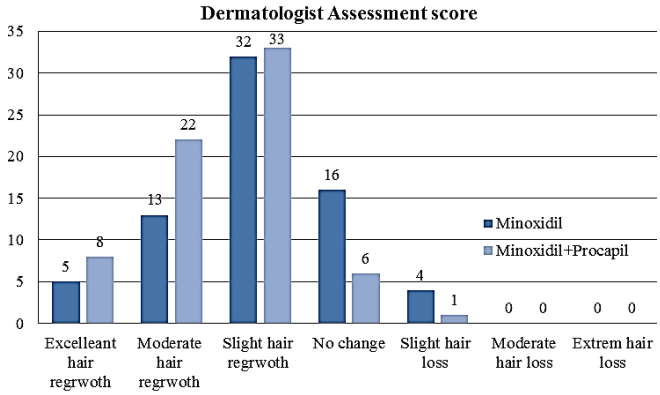

Figure 2 7-point dermatologist evaluation score based on physical examination.

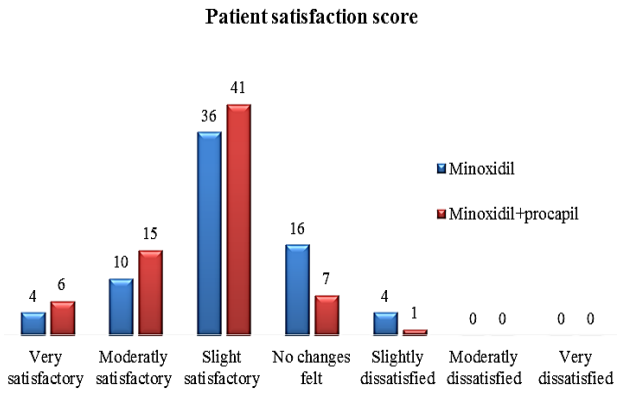

Figure 3 7-point patient satisfaction score based on patient own perception of hair regrowth.

20.6% and 15.7% of patients with overall good tolerability achieved very effective, effective, moderately effective, and ineffective hair regrowth respectively.[22]

Another study of 90 male patients with androgenetic alopecia was carried out in Egypt. Patients were divided into 3 groups. The first and second groups used 5% and 10% minoxidil solutions for 9 months, respectively, while the third group used the placebo. In the end, 5% minoxidil was superior to 10% minoxidil in terms of hair growth, changes in the hair pull test, and a lower adverse effect profile.[23]

A study by Ercan Arca *et al*. compared the efficacy of minoxidil vs. finasteride in men with AGA. 40 patients used 1mg finasteride tablets, while 25 patients used 5% minoxidil twice daily. After 1 year, finasteride came to be superior to minoxidil in terms of hair regrowth (80% vs. 52%) with a p-value of <0.05. This was associated with a transient but greater number of adverse effects in finasteride group.[24]

An Indian study of 64 patients compared the efficacy of minoxidil with platelet-rich plasma. Patients were divided into 2 groups, each comprising 32 patients. One group applied minoxidil solution twice a day, while the other group received PRP injections in the involved areas of the scalp at 3-monthly intervals. At the end of 3 months, both groups had achieved significant hair density (p values 0.05), but there was no statistically significant intergroup difference in total terminal hair count. (p-value= 0.47).[25]

A study comprising of 20 male patients in each group compared the efficacy of 2% minoxidil with a cocktail solution (Trust Tonic) composed of capixyl, procapil, and rosemary extract. Patients in both groups applied the respective formulas twice a day continuously for 24 weeks. At the end of the study, Trust Tonic results were superior to minoxidil in terms of self-assessment (64% vs. 36%), staff assessment (60% vs. 30%), and photographic evaluation (57% vs. 8%), with a p-value of < 0.05 in all cases.[26]

A specially formulated solution consisting of Redensyl, Procapil, and Capixyl (RCP) was compared to 5% minoxidil in a Turkish study by Nezih Karaca *et al*. Both solutions were applied twice a day to 54 and 52 patients in the RCP and minoxidil groups, respectively, for 24 weeks. RCP appeared to achieve better hair growth than minoxidil when results were summarized in terms of global photographic assessment (88.9% vs. 60%), researcher evaluation score (67.7% vs. 25.5%), and patient self-assessment (66.6% vs. 38.2%). The p-value was <0.05 in all categories.[27]

Conclusion

According to these results, Procapil combined with Minoxidil is superior to Minoxidil alone in treating Androgenetic Alopecia (AGA).

Limitations of the study As there was no long-term follow-up of patients, disease progression and relapse/ remission could not be anticipated in this study. The small sample size was another limitation. As there is very limited data available on the efficacy of procapil in androgenetic alopecia, therefore large centers studies enrolling greater number of patients are needed.

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