A Comparative Study Between Topical Minoxidil 5% and Topical "Redensyl, Capixyl, and Procapil" Combination in Men with Androgenetic Alopecia

Abstract

Introduction: Androgenetic alopecia (AGA) is one of the three most common forms of the noncicatricial alopecia characterized by hair loss in both men and women. It is found in 50% of the men above their 50s. Currently, two effective treatments for AGA are used in men: topical minoxidil and oral finasteride. Several clinical studies showed that minoxidil and finasteride are two most effective methods showing positive therapeutic outcomes.

Aim: This study aimed to compare the safety and effectiveness of Redensyl, Capixyl, and Procapil (RCP) and minoxidil 5% solution in adult male patients suffering from AGA.

Material and Methods: This randomized controlled study was conducted on patients who used either RCP or minoxidil 5% for 24 weeks. The patients applied 1 mL of each solution to their head skin twice a day, in the morning and evening.

Results: It has been shown that the patients treated with RCP had a significantly higher researcher score (minoxidil 26% vs. RCP 65%), higher global photographic evaluation score (minoxidil 60% vs. RCP 89%), and higher self-evaluation score on comparing the RCP group with the minoxidil group.

Conclusion: The RCP group showed a significantly better clinical recovery in terms of hair growth.

Key words: Alopecia; androgenetic hair loss; finasteride; minoxidil; Redensyl, Capixyl, and Procapil

Introduction

The most common three types of noncicatricial alopecia are androgenetic alopecia (AGA), telogen effluvium, and alopecia areata. AGA causes hair loss, which starts with bitemporal recession in the frontal hair line and progresses with a severe thinning on the top of the head [1]. The hair loss is a general problem related to AGA, which is seen in 95% of men above their 50s [1]. In females, the male-type AGA is usually seen in individuals who suffer from postmenopausal hair loss; however, it may be seen in young individuals as well. The alopecia starts with hair follicle miniaturization because of the stimulation of the conversion of testosterone into dihydrotestosterone (DHT) by the 5a-reductase (5-AR) enzyme and progresses gradually. It has been reported that AGA does not occur in males who are genetically deficient in the a5-AR type 2 enzyme that converts testosterone into DHT. Therefore, AGA occurs due to androgen-dependent hair follicle miniaturization stimulated by the a5-AR type 2 enzyme [2]. Depending on the severity of AGA, different levels of hair loss are seen on the frontotemporal and top areas of the head skin in men with AGA [1]. A model for AGA pathogenesis has been suggested to explain these clinical aspects with a variety of factors such as miniaturization of hair follicles, increase in the telogen/anagen ratio, systemic and local effects of the androgens that trigger the disease, and finally familial susceptibility. The candidate genes are related to androgen production and conversion of androgen into DHT. AGA occurs because of an autosomal dominant gene showing an altered penetrance. Also, AGA is also known to have a polygenetic inheritance. However, the pathogenesis of this clinical condition is still complex [3].

Since AGA is a common problem especially in the male population, some topical and oral treatment strategies or implants have been used to deal with this issue. Also, only two drugs have been approved by the US Food and Drug Administration (FDA): minoxidil and oral finasteride.

Minoxidil is a biological response regulatory drug that stops hair loss in AGA and helps in hair growth. No antiandrogenic effects of this drug were reported. Although it was developed as an antihypertensive drug, its effect on hair growth was discovered later. Minoxidil opens potassium channels and decreases intracellular calcium. The role of vasodilation in AGA treatment should be discussed. The calcium inhibits epidermal growth factor–induced stimulation of the growth of the hair root. Minoxidil is suggested to stimulate hair growth by inhibiting the drop in calcium levels in the cells [4,5].

Finasteride is an inhibitor of a5-AR that causes the inhibition of miniaturization of hair follicles and an increase in DHT formation. Oral finasteride was suggested to have some potential risks such as gynecomastia, feminization, and impotence [3]. It was reported that 1 mg oral finasteride and 5% topical minoxidil are safe and effective. Oral finasteride was found to be more effective than minoxidil in patients with moderately severe AGA [6]. A combination of minoxidil and finasteride showed better outcomes than their individual use [7-9].

Redensyl is made from a combination of botanical ingredients. It contains dihydroquercetin glucoside (DHQG: 0.005%), epigallocatechin gallate glucoside (EGCG2: 0.0009%), glycine (0.005%), zinc chloride (0.002%), metabisulfite (0.015%), and glycerin (50%). Redensyl is formed from patented molecules that target and stimulate fibroblasts in the outer root sheath stem cells and dermal papilla (DHQG and EGCG2: two stabilized polyphenols). Glycine and zinc are required for hair metabolism [10]. Glycine is one of the main compounds for specific hair proteins called keratin-related proteins (KAP) [11]. Zinc is also an essential element for holding cysteine to keratin [12].

Another compound Procapil contains three extremely effective plant-derived substances: oleanolic acid, which inhibits 5α1 and 5α2 reductase enzymes (extracted from olive leaves); apigenin for vasodilation (a flavonoid that is extracted from citrus peel); and glycine–histidine–lysine peptides, which are required for pro-matrix metalloproteinase activity to be able to meet the metabolic needs of hair follicles [13]. Also, Biotinyl-GHK (vitamin-carrying peptide) is formed from biotin (vitamin H). The deficiency of this vitamin leads to thin hair, alopecia, loose skin, and dermatitis [14].

Capixyl is a biomimetic peptide complex that is mixed with red clover extract. It has been demonstrated to cause an increase in hair width and density [15].

These three compounds are mixed and used as a topical spray to inhibit hair loss and stimulate the growth of new hair follicles.

Moreover, the topical formulation of finasteride is not commercially available. Minoxidil is usually well tolerated; however, it has several side effects including burning/irritation and itching in the eye, irritation in the application area, and the growth of unwanted hair in different parts of the body. The flaming was also reported in hair loss/alopecia [16]. The most common minoxidil-dependent side effect is irritant contact dermatitis. It is more related to propylene glycol contained in minoxidil. In some cases, allergic contact dermatitis can also be seen. A small amount of minoxidil passes through the systemic circulation [16].

Redensyl, Capixyl, and Procapil (RCP) combination was prepared according to the criteria for cosmetic products to develop a more effective treatment option for patients without side effects. This formula is available for long-term use due to no side effects. This study was performed to evaluate whether this combination was more effective than minoxidil.

Material and Methods

Redensyl was obtained from Induchem Laboratories (Switzerland and USA). Capixyl was obtained from International Flavors and Fragrances Laboratories (France), and Procapil was obtained from Sederma Laboratories (France). Topical minoxidil (5%) was procured from a local drug company in Turkey. The products were formulated at the Cosmetic Studies Unit R&D Department, Faculty of Pharmacy, Yeditepe University, and all the rights of this combination were reserved by the Turkish Patent Institute with the name Procare. After receiving the ethical board approval (16/2016, in 31.01.2016) of Istanbul Anatolia–North Region Public Hospitals Trust, this study was conducted according to the Good Clinical Applications guide of Helsinki Declaration and Central Drugs Standard Control Organization.

A total of 120 patients were included in this study. All the patients who desired to participate were evaluated by taking all inclusion and exclusion criteria into account, and their suitability was screened before the study.

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According to the modified Norwood–Hamilton classification [17], all the male patients, 18–55 years of age, who had stages II–V AGA, wanted to preserve the style, length, and color of their hair during the study, and signed the written consent, were included in this study.

Table 1. Norwood–Hamilton classification

Type 1	No recession in the frontotemporal hairline region is observed or the recession is minimal.
Type 2	A symmetrical and triangle-shaped recession is observed on the frontotemporal region hairline. Although some hair loss or thinning is seen in the middle of the frontal region, it is less than that in the frontotemporal region.
Type 3	Hair loss becomes evident. A clear
Type 4	Severe frontal and frontotemporal hair loss is observed. A clear thinning is observed in the vertex. These two regions get apart from each other with a clear hair band structure.
Type 5	The hair band in type 4 gets thinner. Hair-free regions increase in the vertex and frontotemporal region.
Type 6	The hair loss becomes clearer even in the hair band region. Frontotemporal hair-free regions get together with the vertex.
Type 7	This is a severe form. It starts from the front of the ear and extends backward. Only a horseshoe-shaped band of hair is left that surround the posterior region.

The patients having other dermatological diseases except for AGA on their head skin and the ones having serious cardiovascular, kidney, liver, drug hypersensitivity, and lung diseases were excluded from the study. Additionally, the ones who used wigs, had a hair-loss-related treatment history, or had shaved head skin were also excluded from the study.
All the volunteer patients who satisfied these suitability criteria were registered with a randomization ID. Four of these test compounds were provided to these patients in one visit. These patients attended a training session to be able to apply these test compounds to the hairless area topically. The start date of the study was considered as the first day for all registered patients, and all other time points for the evaluation (e.g., visit days) were planned accordingly. The patients were randomized to take only RCP and minoxidil. These two compounds were applied to hair with an injector in the mornings and evenings, 1 mL each time. This amount was labeled on the injector and shown during the training session. At each time point of the evaluation [start of the study, follow-up (after every 4 weeks), and end of the study (in total 24 weeks)], the patients were expected to visit the clinic and the condition of their hair, the follow-up plan of their topical serum treatment, and adverse effects, if any, were recorded in the case record form (CRF). Also, the researcher used a 5-point evaluation for the increase in hair density, and the scaling criteria were as follows:

- A significant recovery: Intensive hair growth (the hairless area has almost similar intensity with the nonhairless area, and the skin is almost covered with hair).
- A moderate recovery: Average hair growth (the hairless area has less intensity than the nonhairless area and is partially covered with the newly grown hair).
- A slight recovery: Minimum hair growth (besides hair growth, the hairless area can be seen clearly).
- No change: No hair growth with a naked eye.
- Worsening: Decreasing hair growth.

In addition to the visit at the beginning of the study, the effect of the test compounds on hair growth was evaluated using a self-evaluation form (Table 2). The related scores were recorded in the CRF. Detailed global photographic evaluations [18] were performed at the beginning of the study and at the end of 12th-week and 24th-week visits by the researcher.

The comparison of the change in the researcher evaluation score in terms of hair growth and intensity-dependent head skin coverage was used as primary activity criteria.
To evaluate secondary activity criteria, the change in the hair condition was analyzed using the self-evaluation questionnaire and 7-point global photographic evaluation. Single-variable SAS was used to test normality assumption, and the Shapiro-Wilk test was used for the normality evaluation of both the groups.

Table 2. Self-evaluation form of the patient

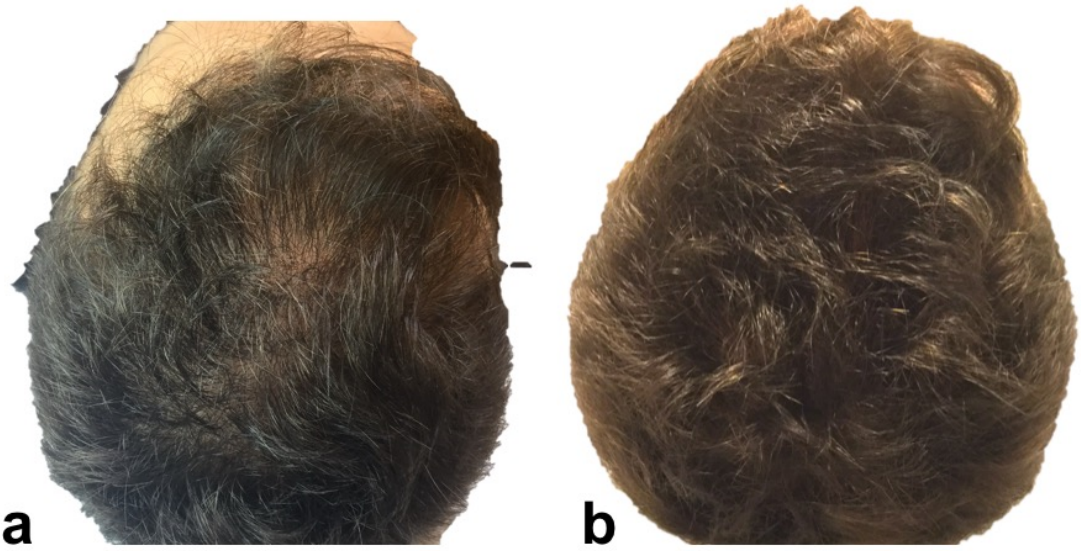
Question	Score
1. **My bald area shrank.**	
Strongly agree	1
Agree	2
No idea	3
Disagree	4
Strongly disagree	5
2. **The view of my hair after the treatment**	
Much better	1
Better	2
Same	3
Worse	4
Much worse	5
3. **New hair growth**	
Perfectly increased	1
Moderately increased	2
Not changed	3
Moderately decreased	4
Clearly decreased	5
4. **Satisfaction with the look of my hair**	
A. **Frontal (frontal area)**	
B. **Vertex (top of the hair)**	
Very satisfactory	1
Satisfactory	2
Average	3
Not satisfactory	4
Very bad	5

Results

This randomized, prospective, and open-ended clinical study was scaled with the modified Norwood–Hamilton scale between stages II and V (Table 1). It was conducted on adult male patients with AGA. The suitable volunteers were randomized to take either RCP or topical minoxidil. For the activity evaluation of the compound, the data at the beginning and the end of the treatment were compared within groups and between groups. During the study, any absolute change in the evaluation of the researcher at each time point after the beginning date of the study, patient evaluation, and global photographic evaluation scores were reported.
In the end, 106 volunteers completed the study (54 patients in the RCP group and 52 patients in the minoxidil group). The researcher evaluation showed significantly better recovery in the group treated with RCP than in the group that received minoxidil treatment (minoxidil group 25.5% vs. RCP group 64.7%, $P = 0.006$) (Fig. 1).

In the patients with AGA, a 7-point global photographic evaluation scale was used to evaluate the head skin before and after the treatment by the photography of the top and superior frontal area. Evaluation of 106 patients who completed global photographic evaluation (54 in the RCP

group and 52 in the minoxidil group) was performed, which revealed significantly more recovery (slight, moderate, and high increase) in the group treated with RCP than in the group treated with topical minoxidil (88.9% in the RCP group vs. 60% in the minoxidil group) (Fig. 2). It was shown that topical RCP provided better recovery compared with 5% minoxidil and this recovery was statistically significant between the two groups ($P < 0.05$) (Picture 1).



Picture 1. (a) View of the alopecic areas before treatment (extending from the frontal area to the vertex)**. (b)** Recovery on the alopecic areas after 24 weeks of RCP treatment.

The results of the self-scoring questionnaire were also evaluated. Seventy patients (34 in the minodixil group and 34 in the RCP group) submitted their self-evaluation forms. In these forms, the number of patients who responded to "Did the bald area shrink?" by saying "strongly agree" or "agree" was 15 in the group using 5% minoxidil and 30 in the group using RCP; the results were found statistically significant. The results are shown in Table 3.
Patients treated with RCP showed a better recovery on their hair front line ($P = 0.023$) and general evaluation (0.0004). They also stated that they had better outcomes in terms of hair growth and hair loss. Tables 4 and 5 show that the self-evaluation scores of the patients were related to hair growth and hair loss retardation.

	Bald area scoring (gradual shrinkage of the bald area)				
Treatment	Strongly agree	Agree	Disagree	No idea	Total
RCP	9	21	2	4	36

Minoxidil	0	15	8	11	34
Total	9	36	10	15	70

Treatment	Hair growth scoring					
	Clearly increased	Moderately increased	Slightly increased	Not changed	Moderately decreased	Total
RCP	10	14	8	3	1	36
Minoxidil	3	10	13	7	1	34
Total	13	24	21	10	2	70

Treatment	Hair loss scoring				
	Very effective	Effective	Partially effective	No effect	Total
RCP	6	17	10	3	36
Minoxidil	3	16	13	2	34
Total	9	33	23	5	70

Discussion

Minoxidil is a biological response regulatory drug that stops hair loss in AGA and helps in hair growth. No antiandrogenic effects of this drug were reported. Although it was developed as an antihypertensive drug, its effect on hair growth was discovered later. Minoxidil opens potassium channels and decreases intracellular calcium. The role of vasodilation in AGA treatment needs to be discussed. Calcium inhibits epidermal growth factor–stimulated growth of the hair root. Minoxidil is suggested to stimulate hair growth by inhibiting the drop in calcium levels in the cells [19]. At the same time, minoxidil has been shown to be a mitogenic drug that prolongs the life of hair follicles [20]. *In vitro* studies showed that minoxidil stimulated the proliferation of hair follicles [21]. In 1998, 2% minoxidil and, in 1997, 5% minoxidil were approved by FDA. The dose of minoxidil should be 1 mL twice a day. It needs to be used at least for 6 months to evaluate its activity [22]. The clinical effectiveness of minoxidil has been shown by several studies. Minoxidil stimulates the conversion of villus-type hair to terminal hair. Therefore, it depends on the severity of AGA and the presence of these hair [23]. Moreover, topical minoxidil is not effective on the temporal area. A study showed that minoxidil stimulated new hair growth in 90% of the males and also strengthened the hair growth in 60% of the patients [24]. These

in 90% of the males and also strengthened the hair growth in 60% of the patients [24]. These percentages were considered as exaggerated results. Another study demonstrated new hair formation in 15% of the males who used minoxidil. In the same study, a delay in the hair loss was observed in 50% of the males and continuous hair loss was observed in the remaining 35% of the individuals [3]. Another study compared the effectiveness of 5% and 2% minoxidil and showed that the effect of minoxidil started earlier in the 5% minoxidil group and 45% stronger hair growth was observed [25]. After discontinuing the use of minoxidil, the newly grown hair were lost and the hair reverted to their original form [26]. Minoxidil can be combined with tretinoin. It has been reported that this formulation makes hair growth faster [27].

Finasteride is a drug that inhibits the activity of the 5-AR enzyme. Thus, it inhibits the conversion of testosterone into DHT. This drug does not affect androgen receptors and cause any elevations in the testosterone levels. Therefore, it does not have any antiandrogenic effects and can be safely used in males. Its half-life is approximately 8 h, and any dose adjustment is not needed against kidney failure. In 1997, the usage of this drug for treating AGA was approved by FDA [28, 29]. The application of 1 mg finasteride is suggested. An increase in hair intensity was reported as 48% at the end of the first year and 66% at the end of the second year of treatment. This percentage was reported as 7% in the placebo group [22]. No significant difference was observed between finasteride and palace treatments in postmenopausal women with AGA [30]. Therefore, it is not suggested for women. This drug is usually well tolerated. Any cross-reaction with other drugs has not been reported. It rarely shows side effects. A decrease in libido (1.8%), erectile dysfunction (1.3%), and ejaculation volume (0.8%) are reported as side effects. Since it can cause feminization in the fetus, its usage in women in reproductive age is contraindicated. Finasteride use (1 mg/day) has shown a progression in the recession of the hair loss and an increase in hair growth in 2 years [31]. Some hair intensity–independent factors such as increased growth (length) and hair thickness contribute to the beneficial effects of finasteride [31].

Similarly, 23% improvement were observed in men who used placebo and 60% improvement was seen in the group treated with 5% topical minoxidil for 48 h. Also, 5% minoxidil treatment ended up with better hair growth compared with 2% minoxidil treatment [5].

In this study, Redensyl, made from a combination of botanical ingredients, was used in this study. It contains DHQG (0.005%), EGCG2 (0.0009%), glycine (0.005%), zinc chloride (0.002%), metabisulfite (0.015%), and glycerin (50%). Redensyl is formed from patented molecules that target and stimulate fibroblasts in the outer root sheath stem cells and dermal papilla (DHQG and EGCG2: two stabilized polyphenols). Glycine and zinc are required for hair metabolism [10]. Glycine is one of the main compounds for specific hair proteins called KAP [11]. Zinc is also an essential element for holding cysteine to keratin [12].
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Capixyl is a biomimetic peptide complex that is mixed with red clover extract. It has been demonstrated to cause an increase in hair width and density [15].

Instead of largely accepted topical minoxidil, which plays an important role in AGA treatment, the effectiveness of topical Redensyl, Procapil, and Capixyl (RCP) at an appropriate stoichiometric combination was compared with that of 5% minoxidil.

The researcher evaluation scores indicated that the percentage of volunteers with either "significant recovery" or "moderate recovery" was 64.7% in the RCP group and 25.5% in the 5% minoxidil group ($P = 0.0006$). At the end of 24 weeks, the recovery in the RCP group was 2.54 times higher than that in the minoxidil group, and this result was found to be statistically

significant.

The global photographic evaluation showed significantly more recovery (slight, moderate, and high increase) in the group treated with RCP than in the group treated with topical minoxidil (88.9% in the RCP group and 60% in the minoxidil group) (Fig. 2). It was shown that topical RCP provided better recovery compared with 5% minoxidil, and this recovery was statistically significant between the two groups ($P < 0.05$). Hence, the RCP group showed 1.5 times more improvement than the minoxidil group, and this result was consistent with the results of researcher evaluation scores.

No serious adverse effects were reported in this study except a slight minoxidil-related irritation. More effectiveness and patient satisfaction were observed with topical RCP and minoxidil combination compared with minoxidil. Since either topical or systemic treatments take extremely long time in AGA treatment, the combinational treatment of "topical minoxidil and topical RCP" can be an innovative and effective approach for patients who have concerns about the side effects of topical minoxidil. More large-scale, controlled studies need to be conducted on the difference between single and combinational usage with minoxidil to analyze the effectiveness of RCP treatment.