Original Article

Evaluation of the Efficacy and Safety of Topical Procyanidin B2 and Placebo in the Treatment of Androgenetic Alopecia in Men; A Randomized, Double-blind, Placebo-controlled Study

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Abstract

Objective: Androgenetic alopecia (AGA) is a common type of alopecia characterized by the shortening of the anagen phase of hair growth and the miniaturization of hair follicles. TGF-β is a well-known hair cycle catagen phase inducer and is involved in the catagen phase in AGA. Inhibition of TGF-β is recognized as a therapeutic option in the treatment of AGA. Procyanidins are a type of polyphenol that has been shown to inhibit TGF-β activity *in vivo*, but there haven't been many studies on their effectiveness. In this study, we aimed to evaluate the efficacy and safety of topical procyanidin B2 in the treatment of male AGA. **Materials and Methods:** Patients aged between 18 and 50 years who applied to our dermatology outpatient clinic with the complaint of AGA and had Hamilton-Norwood type II-V AGA were included in our study. Those who had received 5-reductase inhibitor or isotretinoin treatment in the previous year, those who had used any medicinal or herbal product that stimulated hair growth, particularly topical minoxidil, in the previous six months, those who had used systemic steroids for more than two weeks in the previous three months, those who had undergone a transplant or scalp reduction, and those who had received radiotherapy or chemotherapy at any point in their lives were excluded from the study. A total of 40 patients who met the current criteria were included in the study. Patients were randomized into two groups to receive 16 weeks of topical procyanidin B2 (n = 20) or placebo (n = 20) therapy. At the end of the treatment, the patients were called for control. The efficacy of topical procyanidin B2 after treatment was evaluated by trichoscan and global photographic evaluation. **Results:** A total of 40 male patients (mean: 33.32, range: 21–44) with AGA type II-IV were included in the study. There was no significant difference between the two groups in terms of age, duration of hair loss, and AGA type (P > 0.05). At the end of the study, there was a significant increase in total hair count in the topical procyanidin B2 group compared to the placebo group compared to baseline (P < 0.05). Anagen hair count was also significantly increased in the topical procyanidin B2 group (P < 0.05). **Conclusion:** In this placebo-controlled study, we think that topical procyanidin B2 is an effective and safe treatment option in the treatment of AGA patients.

Keywords: Alopecia, androgenetic alopecia, cosmetics, finasteride, minoxidil, procyanidin

Introduction

Androgenetic alopecia (AGA) is a type of alopecia with miniaturization of hair follicles in the frontal and parietal areas, and it is the most common cause of hair loss in men today. The reduction of hair, which is an important part of people's external appearance, significantly affects people's social relationships and significantly reduces their quality of life.[1] Therefore, even if it is not causing any health problems, the search for an effective and reliable method for the treatment of AGA continues.

The two most important factors contributing to AGA are increased androgen sensitivity in hair follicles and genetic predisposition.[2] In individuals with a genetic predisposition to AGA, 5α-reductase activity in hair

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follicles is increased and testosterone is converted to its more active form, dihydrotestosterone. Dihydrotestosterone binds to androgen receptors in hair follicles, resulting in a shortening of the anagen phase and a prolongation of the telogen phase. As a result, miniaturization is triggered in hair follicles.[3] Apart from these two main factors, the factors that play a role in the development of AGA are defined as environmental pollution, smoking, ultraviolet rays, decrease in microcirculation, follicular microinflammation, and aging process.[4-9] Although the quality of life of patients with AGA is significantly affected, the only treatments approved by the FDA for AGA are oral finasteride and topical minoxidil. In addition to the effective clinical results of these treatments, there are a few disadvantages. The positive effect on the hair follicles cannot exceed a certain level over the years. They have also been associated with side effects, including skin irritation and sexual dysfunction.[10]

Today, effective and reliable dermatocosmetic products have been introduced to be an alternative to FDA-approved drugs in the treatment of AGA, but clinical studies on these products are insufficient. One of the important molecules in dermatocosmetic products recommended for the treatment of AGA is procyanidin oligomers. There are not enough clinical studies on the efficacy of procyanidin, which has been shown to induce the anagen phase in addition to its antioxidant and anti-inflammatory effects.[11,12] In this study, we aimed to evaluate the efficacy and safety of topical procyanidin B2 treatment in male AGA.

Materials and Methods

Forty patients aged 18–50 years who applied to the Gülhane Training and Research Hospital Dermatology Outpatient Clinic and were clinically diagnosed with Hamilton-Norwood type II–V AGA were included in our study. The patients were randomly divided into two groups, and 20 patients were included in the topical procyanidin B2 treatment group, while the remaining 20 patients were included in the placebo group. Exclusion criteria in the study included: using any medical or dermatocosmetic product that stimulates hair growth, particularly topical minoxidil, in the previous six months; using systemic steroids for more than two weeks in the previous three months; having a history of hair transplantation or scalp reduction, and receiving radiotherapy or chemotherapy at any time in his life. Our study was carried out with the permission of the Gülhane Training and Research Hospital Medical Ethics Committee. Each patient was informed about the content of the study, and their written consent was obtained.

Treatment and placebo groups were followed for 16 weeks to evaluate the efficacy and safety of topical procyanidin B2. The treatment product we used in our study, 1% procyanidin B2 dimer obtained from apple (malus pumila), was prepared in 100 cc spray cans containing biotin and dexpanthenol. The placebo product was prepared in the same way, but the active ingredient, the procyanidin B2 dimer, was not added. It was stated that both groups should apply the treatment with 2 × 9 puffs (each puff 0.2 ml) per day. Patients' vertex photographs and trichoscan records that were taken before the treatment and at the end of the 16th week were evaluated.

Trichoscan evaluation

The amount of hair in the target area, percentage of anagen hair, percentage of telogen hair, and anagen/telogen hair ratio were evaluated and recorded with the help of the trichoscan device before the treatment and at the 16th week. Trikoscan evaluation is applied to a circular area on the front or side of the vertex where hair loss is observed. In the trichoscan process, a temporary tattoo that shows the target area is applied, and the length of the hair in the target area is cut to 1 mm. The patient was called for trichoscan evaluation three days after the procedure. Before trichoscan, the hair in the target area is dyed with the help of a special hair dye, and the dye is kept on the hair for 10–15 minutes. After cleaning the hair dye with the help of alcohol, the hair parameters are evaluated with the trichoscan device.

Evaluation of patients

Patients were asked to evaluate their hair loss status after treatment. Evaluation was made on a 7-point scale, and on this scale: -3 = significant worsening, -2 = moderate worsening, -1 = minimal worsening, 0 = no change, +1 = minimal improvement, +2 = moderate improvement, +3 = significant improvement. Standardized photographs of the vertex region, taken before treatment and at week 16, are shown to help patients respond. To standardize the photographs, the vertex region of all patients participating in the study was recorded with the help of a stereotactic photographing device [Figure 1].

Global photographic assessment

The global photographic assessment was made by examining the vertex photographs recorded with the aid of the stereotactic photographing device before the treatment and at week 16 by three dermatologists (HY, ST, ŞH) who were blind to the study. The change observed in the hair compared to pre-treatment by dermatologists was evaluated on the 7-point scale used by the patients. The scores obtained as a result of the evaluation were compared. If two of the scores are equal, the score is valid, while if all three scores are different from each other, the scores are averaged.

Safety assessment

During the treatment and at the 16th week, the patients were asked if they had any signs of irritation and were

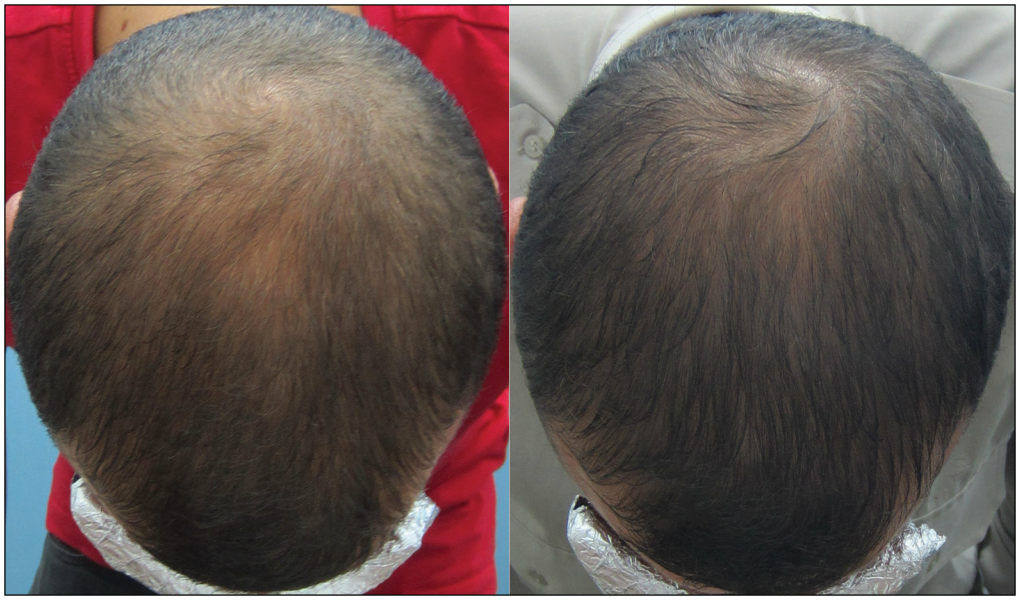

Figure 1: Vertex photographs taken before treatment and at week 16

examined by the investigators for signs of dermatitis. Irritation signs (stinging, burning, itching) were evaluated by patients as absent, mild, moderate, or severe; dermatitis symptoms (erythema, dryness/scaling, folliculitis) were evaluated by the researchers as absent, mild, moderate, or severe, and recorded in the patient files.

Statistical analysis

Statistical analysis was performed using the SPSS (IBM Corp. IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, NY, USA) program. In the treatment and placebo groups, the hair parameters obtained with the help of trichoscan before the study and at the 16th week were compared by analyzing the changes with the help of the SPSS program. A Kolmogorov-Smirnov test was performed to determine whether continuous variables fit the normal distribution. In the analysis of variables with a normal distribution, the T-test was used for dependent groups, and the Wilcoxon test was used for variables that did not fit the normal distribution. A descriptive analysis was used to evaluate the safety parameters.

Results

Initial status

A total of 40 male patients (mean: 33.32, range: 21–44) between the ages of 21–44 who were diagnosed with AGA participated in our study. The patients were randomly divided into two groups: treatment and placebo groups. There was no significant difference between the two groups in terms of age, duration of hair loss, and type of AGA ($P > 0.05$). The mean age of the patients in the treatment group was 32.80 ± 6.38 years. A Hamilton-Norwood hair loss pattern was observed in 4 patients with Type II, 8 patients with Type III, 6 patients with Type IV, and 2 patients with Type V. The mean age of the patients in the placebo group were 33.85 ± 6.96 years. A Hamilton-Norwood hair loss pattern was observed in 5 patients with Type II, 7 patients with Type III, 5 patients with Type IV, and 3 patients with Type V. [Table 1]

Table 1: Demographic characteristics of patients and trichoscan findings

	Placebo Group	Procyanidin B2 Group
Number of patients	20	20
Age	33,85 ± 6,96	32,80 ± 6,38
Hair loss time	10,65 ± 6,08	12,63 ± 6,39
Hamilton Norwood Pattern (n, %)		
Type II	5 (25,0)	4 (20,0)
Type III	7 (35,0)	8 (40,0)
Type IV	5 (25,0)	6 (30,0)
Type V	3 (15,0)	2 (10,0)
Trichoscan characteristics (mean ± SD)		
Total hair count	145,35 ± 17,13	141,65 ± 16,18
Terminal hair count	60,80 ± 7,12	57,55 ± 6,79
Non-terminal hair count	84,55 ± 12,48	84,10 ± 12,57
Anagen hair count	91,10 ± 11,81	86,90 ± 10,14
Anagen/telogen ratio	1,69 ± 0,19	1,60 ± 0,16

Efficacy

The trichoscan values obtained from the treatment and placebo groups before the study, including total hair count, terminal hair count, anagen hair count, and anagen/telogen hair ratio, are summarized in [Table 1]. In the placebo group, there was no significant change observed in trichoscan values before and after

Table 2: Trichoscan findings of the patients before and after the study

Trichoscan features	Placebo Group			Procyanidin B2 Group		
	Week 0	Week 16	*p*	Week 0	Week 16	*p*
Total hair count	145,35 ± 17,13	142,50 ± 19,64	>0,05	141,65 ± 16,18	155,40 ± 21,01	<0,05
Terminal hair count	60,80 ± 7,12	58,90 ± 9,57	>0,05	57,55 ± 6,79	67,20 ± 9,04	<0,05
Non-terminal hair count	84,55 ± 12,48	83,60 ± 15,34	>0,05	84,10 ± 12,57	88,20 ± 12,68	<0,05
Anagen hair count	91,10 ± 11,81	92,93 ± 12,99	>0,05	86,90 ± 10,14	97,10 ± 12,20	<0,05
Anagen/telogen ratio	1,69 ± 0,19	1,72 ± 0,29	>0,05	1,60 ± 0,16	1,69 ± 0,18	<0,05

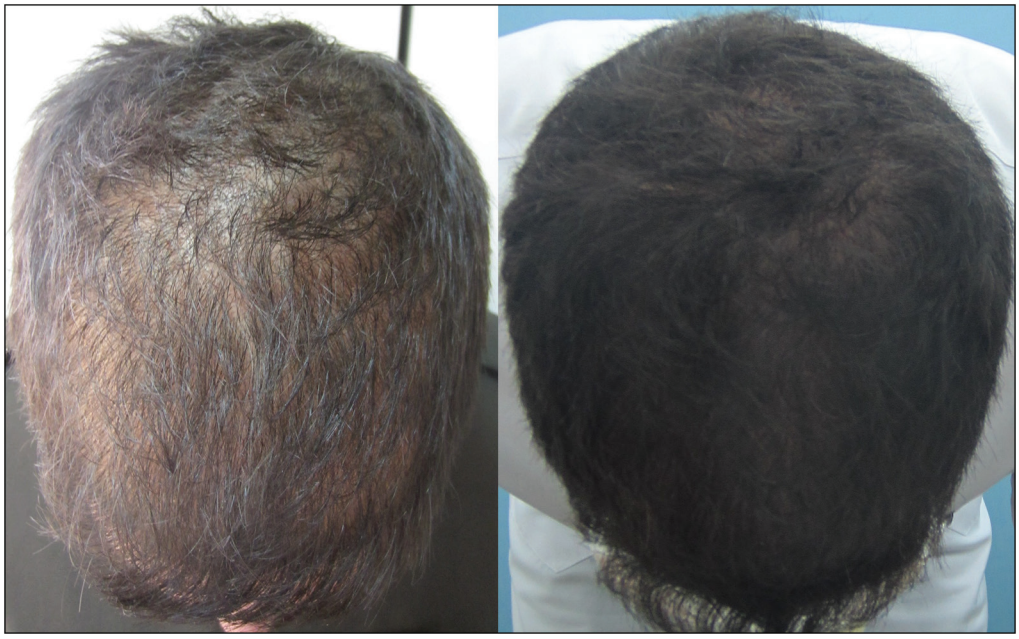

Figure 2: Vertex photographs taken before treatment and at week 16

Table 3: Post-treatment efficacy evaluation of the patients and experts

Response to treatment	Patient Opinion	Expert Opinion
-3 = significant worsening	0	0
-2 = moderate worsening	1	0
-1 = minimal worsening	3	2
0 = no change	4	4
+1 = minimal improvement	4	5
+2 = moderate improvement	5	6
+3 = significant improvement	3	3

treatment. [Table 2] In the procyanidin B2 treatment group, there was a statistically significant increase in total hair count, terminal hair count, anagen hair count, and anagen/telogen hair ratio compared to baseline ($P < 0.05$). [Table 2]

With the help of standardized vertex photographs, patients and experts evaluated the hair loss status at the end of the study [Figure 2]. In the evaluations made by the patients, 60% of the patients found improvement in hair loss, while 20% stated that there was no change. In the experts' evaluation, improvement was detected in 70% of the patients, while no change was detected in 20% of the patients. [Table 3]

No significant adverse effects were observed in the placebo group or the procyanidin B2 treatment group during the study. Mild erythema and scaling were observed in 3 patients who had itching and stinging complaints.

Discussion

The reduction of hair, which is an important part of people's external appearance, significantly affects people's social relationships and significantly reduces their quality of life.[1] Currently, a wide spectrum of treatments, including topical therapies (topical minoxidil, topical finasteride), oral therapies (oral finasteride, oral dutasteride, oral minoxidil), hormonal therapies (spironolactone, flutamide, bicalutamide, cyproterone acetate), light therapies (low-level laser therapy, light-emitting diode devices), injectables (platelet-rich plasma, exosomes, microneedling), supplements, and over-the-counter treatments (oral nutraceutical supplements, topical saw palmetto, plant-based oils, ketoconazole) are commonly utilized by physicians.[13] Among them, only oral finasteride and topical minoxidil have been approved by the FDA for the treatment of AGA.

With the help of the sulfotransferase enzyme, minoxidil is converted to its active metabolite, minoxidil sulfate, which opens ATP-sensitive potassium channels, leading to relaxation of vascular smooth muscles. Minoxidil shows its effect by increasing cutaneous blood flow with this mechanism.[14] Studies on the efficacy of minoxidil treatment have shown that it provides a significant increase in the number of non-vellus hairs.[15,16] Although the topical formulation of the drug is safe in terms of side effects, contact dermatitis can be observed in some patients due to the propylene glycol contained in its content.[17] In addition to this, it has been reported in the literature that important side effects observed, such as chest pain, palpitations, and myocardial infarction, may develop due to systemic absorption of minoxidil.[18]

Finasteride, the second drug approved by the FDA for the treatment of AGA, inhibits the 5α-reductase enzyme. In this way, it stops the conversion of testosterone to dihydrotestosterone, a potent androgen, and prevents the miniaturizing effects of androgens on hair follicles.[19] A total of 212 patients were evaluated in a placebo-controlled study on the efficacy of finasteride treatment, and 106 patients in the treatment group were given 1 mg/day of oral finasteride for 48 weeks. As a result of the study, it was reported that there was a statistically significant increase in the total hair count, anagen hair count, and anagen/telogen hair ratio in the treatment group compared to the placebo group.[20] In studies on drug safety, it was reported that transient sexual dysfunction occurred in some of the patients during the 5-year follow-up period.[21] However, it is stated that sexual dysfunction may be permanent in some patients.[22]

Although 5α-reductase enzyme inhibitors come to the fore as an effective treatment option in the treatment of AGA, their systemic side effects limit their use. In addition, its positive effect on hair follicles can not exceed a certain level over time.[10] Although many dermatocosmetic products with herbal ingredients that can be alternatives to these drugs have been introduced, there is a lack of clinical studies with adequate evidence on the efficacy and safety of these products.

The main active ingredient in the product we used in our study is procyanidin B2 dimer. Proanthocyanidins, a member of the polyphenol family and an oligomeric flavonoid containing flavon-3-ol, have antioxidant, antihypertensive, capillary protective, and elastase inhibitor effects.[23] In vivo studies on procyanidin B2 dimer, a proanthocyanidin obtained from apple extract, have been shown to stimulate growth in hair epithelial cells and induce the anagen phase.[24] It is considered that this effect is caused by cytokines that regulate the hair cycle. IGF-1, HGF, KGF, and VEGF are known to positively regulate hair growth in the hair cycle; TGF-β, FGF-5, TNF-α, IL-1α, and IL-1β are known to negatively regulate hair growth.[25] Among these cytokines, it has been shown that TGF-β1 induces apoptosis in keratinocytes, and TGF-β2 stimulates the transition to the catagen phase.[26,27] Procyanidin stops the growth inhibitory effect of TGF-β1 and TGF-β2 and saves cells from apoptosis. It was also stated that it provides MEK activation, which plays a role in cell proliferation and stimulates hair growth with its antioxidant effect.[23] However, it has been shown that the expression of protein kinase C, which is a negative hair growth factor, decreases *in vitro*.[28] In addition to the procyanidin B2 dimer in the treatment solution we used in our study, it also contains biotin and dexpanthenol to be included in the placebo solution. It has been reported that these molecules may have positive effects on hair growth.[29,30]

According to our study results, in the procyanidin B2 treatment group, the total number of hairs in the target area after the 16 weeks of procyanidin treatment significantly increased over the baseline value measured at the start of the trial by trichoscan (141,65 ± 16,18 (mean ± SD) vs 155,40 ± 21,01(mean ± SD), $P < 0.005$). In addition to this, the anagen/telogen hair ratio in the target area after the 16 weeks of procyanidin treatment significantly increased over the baseline value measured at the start of the trial by trichoscan (1,60 ± 0,16 (mean ± SD) vs 1,69 ± 0,18 (mean ± SD), $P < 0.005$). These results show that there is a marked improvement in the hair quantities and quality after procyanidin treatment. Unfortunately, there is no systematic review, but two studies in the literature on the efficacy of procyanidin B2 dimer in the treatment of AGA. In a double-blind, placebo-controlled study conducted by Takahashi *et al.* on 29 patients, they gave treatment for 4 months and emphasized that there was a significant increase in hair diameter and total hair count at the end of the treatment compared to placebo treatment.[31] In another study, Kamimura *et al.* reported that after 6 months of treatment, there was a significant increase in the total hair count in the treatment group compared to the placebo group. They also stated that after 12 months of treatment, the total hair growth was 23 hairs/cm2 and that the increase was the same as in the treatment of minoxidil and finasteride.[11,32,33] In our study, similar to two pioneering studies, procyanidin B2 dimer was effective in the treatment of AGA; we observed an average of 13.75 hairs/cm2 increase was achieved in the total number of hairs. We attribute the lower rate of increase in our study to the differences in the methods used, the differences in the Hamilton-Norwood hair loss patterns, and the use of the trichoscan device for hair analysis, unlike previous procyanidin B2 dimer studies. This device strengthened our study design by helping us acquire objective data such as total hair count, terminal

hair count, anagen hair count, and anagen/telogen ratio with the computer-aided identification system. The double-blind randomized controlled design of our study lead us to achieve unbiased data throughout the study. In line with the data obtained, we observed a statistically significant increase in the number of terminal hairs and anagen hairs, as well as the total number of hairs. In addition, while 60% of the patients found improvement in hair loss, in the evaluation made by the experts, improvement was found in 70% of the patients.

On the side of the safety of the drug, it was reported that procyanidin B2 dimer did not cause any side effects.[12] During the study, we observed that the topical procyanidin B2 dimer was well tolerated and no significant drug-related side effects occurred in any of the patients. In the evaluations, it was observed that mild erythema and scaling developed in 3 patients who described itching and stinging sensations. There is no definite evidence that this reaction is drug-related.

As a result of the study, we observed that the topical procyanidin B2 dimer is an effective and safe treatment option for the treatment of AGA. Although we designed a randomized double-blind controlled study, there are some limitations that we cannot prevent including the limited number of the patients due to the study budget and lack of long-term results of the treatment. We think that long-term randomized controlled studies or meta-analyses should be conducted in larger patient groups to reveal the efficacy of the procyanidin B2 treatment more clearly.

Statement of ethics

Throughout the study procedure, the principles of the 1975 Declaration of Helsinki were followed, and written informed consent was provided by all patients for the use of their photographs and medical records for the study. The study was approved by the Institutional Ethics Committee.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflict of interest

The authors have no conflicts of interest to declare.

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