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Research Article

Efficacy of Oral Supplementation with *Serenoa Repens*, Pumpkin Seed Extract and Cysteine Combined with Topical Minoxidil 5% *Vs* Topical Minoxidil 5% Alone in Androgenic Alopecia A Randomised Assessor-Blinded 6-Month, Superiority Trial

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Abstract

Introduction: Topical minoxidil is an effective treatment for androgenic alopecia (AGA) in both men and women. However, satisfactory clinical responses are achieved in only 50-55% of patients. Inhibiting 5-alpha reductase with *Serenoa repens* and pumpkin seed may provide a safe and effective adjunctive treatment for minoxidil-treated AGA patients. We conducted a randomized, 6-month, assessor-blinded superiority trial comparing an oral supplementation product in capsule form (AGA-P: 320 mg *Serenoa repens* extract, 320 mg pumpkin seed extract, 425 mg cysteine; one capsule daily) combined with topical 5% minoxidil lotion (ML, applied twice daily) (Group A) against topical 5% ML alone (Group B). **Subjects and Methods:** Eligible participants included males and females aged 18-65 with a clinical diagnosis of AGA (for men: Hamilton scale III-IV-V vertex; for women: Ludwig Scale I-II2). A total of 50 subjects (40 men and 10 women, mean age 36 years) were randomized into Group A (N = 25) and Group B (N = 25). The treatment duration was 6 months. The primary outcome was the Global Photographic Assessment Score (GPAS) evaluated on a 7-point scale (from -3: severe worsening of AGA to +3: significant improvement) by an assessor blinded to group allocation. GPAS evaluations occurred after 12 and 24 weeks of treatment. Secondary endpoints included clinical global evaluation and tolerability assessed by both the investigator and subjects. **Results:** All subjects except 4 (one in group A and 3 in group B) concluded the trial. In comparison with baseline the GPAS, mean (SD), in group A was 1.4 (0.8) after 12 weeks and 2.3 (0.4) after 24 weeks of treatment. In group B, GPAS was 1.0 (0.7) and 1.8 (0.5), respectively. The GPAS score in Group A was statistically higher ($p = 0.0016$) in comparison with group B at week 24. At week 12 a trend in favour of combination treatments was observed ($p = 0.08$). Both regimens were well tolerated. Two subjects (1 in group A and 2 in group B) reported mild scalp dermatitis. **Conclusion:** Oral supplementation with *Serenoa repens*, pumpkin seed extracts and cysteine increases the clinical efficacy of topical minoxidil 5% lotion in the treatment of AGA in both men and women in comparison with topical treatment alone.

Keywords: Androgenic Alopecia; Minoxidil; Alpha-reductase inhibition.

Introduction and Study Background

Topical Minoxidil (TM) is an effective treatment of androgenic alopecia (AGA) in men and women, and it is considered the treatment of choice by all national and international guidelines on AGA treatments [1,2]. The mechanisms of action of TM are not yet fully elucidated and include vasodilation, which enhances blood flow to hair follicles, stimulation of signal transduction pathways that promote cellular proliferation and survival, and increase of growth factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), which play essential roles in hair follicle development and regeneration [3]. The combination of these mechanisms collectively contributes to the efficacy of minoxidil in treating AGA, inducing increase of hair number and size and prolonging hair growth, although individual responses to treatment can vary significantly [4]. In fact, a satisfactory clinical response is obtained in 50-55% of the patients [5]. Minoxidil does not act through the hormonal pathway involved in AGA, where progressive miniaturization of hair bulb is caused by dihydrotestosterone (DHT) [6]. This pathway is targeted by finasteride, the other drug approved for the treatment of male AGA [7]. Finasteride acts by inhibition of type II 5-alpha-reductase isoenzyme, which converts testosterone DHT [8]. The mechanisms of actions of minoxidil and finasteride are therefore complementary and synergistic [9]. Several trials have demonstrated that the combination treatment can increase the efficacy in AGA subjects [10]. However, combination therapy is reserved for severe cases of AGA, in order to potentiate the effect of a single drug. Inhibition of 5-alfa reductase can be achieved using nonpharmacological oral supplements including plant extracts, such as *Serenoa repens* and pumpkin seed that represent an interesting coadjutant treatment for minoxidil-treated AGA patients [11,12].

Study Aim

We performed a randomised 6-month prospective assessor-blinded superiority trial comparing the association of topical 5% minoxidil lotion (ML) (twice daily) with oral supplementation product in capsule formulation (AGA-P: *Serenoa repens* extract 320 mg, pumpkin seed extract 320 mg, cysteine 425 mg; one capsule/daily: Cantabria Labs Spain) (Group A) with topical 5% ML alone (Group B).

Subjects and Methods

All patients included in this trial were male or women, aged 18 years or older, with a confirmed clinical diagnosis of AA (Norwood grades III-V or Ludwig grade I2-II2) [13]. A total of 50 subjects with AGA (40 men and 10 women, mean age 36 age) were randomised to Group A (N = 25) and Group B (N = 25). The randomization list was generated by a dedicated computer

program. Both products were commercially available (***Cantabria Labs Difa Cooper, Caronno Pertusella, Italy***). Treatment duration was 6 months. Main inclusion criteria were men and women with AGA. The primary outcome was the Global photographic assessment score [14] (GPAS) using a 7-point scale (from -3: severe worsening of AGA to +3: great improvement of AGA) evaluated by an investigator unaware of group allocation. GPAS was performed after 12 and 24 weeks of treatments. Secondary endpoints were a 5-point (from 0 to 4) clinical global clinical efficacy evaluation score (GCES) and tolerability. Tolerability was assessed reporting spontaneous side effects and using a 5-point investigator-based questionnaire. Finally, a 10-item global patient satisfaction questionnaire (PSQ) was performed at week 24 (from 0 to 30). The trial was conducted according to Good Clinical Practice Guidelines and Helsinki Declaration [15]. All subjects provided a signed informed consent.

Statistical Analysis

A total of 50 participants were enrolled and randomized in a 1:1 allocation ratio. The sample size calculation was performed considering the data of which reported a reduction and a hypothesis to find an additional effect in SGAS reduction of 25% from the combination of the In&Out strategy. With an effect size (Choen's d value) of 0.75, an alpha value of 0.05, and a power of 85%, a total of at least 54 subjects should be enrolled. The sample size was calculated using G*Power statistical software version 3.1.9.4 (G*Power, Heinrich Heine University, Kiel, Germany). Statistical analyses were conducted using GraphPad statistical software version 5.0 (GraphPad Software Inc., La Jolla, CA, USA). A non-parametric unpaired test was used to compare the different groups, while the ANOVA test was applied to compare data at baseline and after 12 and 24 weeks. Data are expressed as mean and standard deviation (SD). Statistical analysis of the primary endpoint was performed on the Intention-to-treat (ITT) principle using the Last Observation Carried Forward Method. A p-value < 0.05 was considered significant.

Results

The study flow is reported in the Figure 1. The trial was conducted from February 2023 to September 2024 in a third-level University Hair Clinic (Ambulatorio di Tricologia, Ospedale Sant'Orsola, Bologna, Italy). All subjects concluded the trial except 4 (1 in group A and 3 in group B). In comparison with baseline the GPAS, mean (SD), in group A was 1.4(0.8) after 12 weeks and 2.3(0.4) after 24 weeks of treatment. In group B, GPAS was 1.0 (0.7) and 1.8 (0.5), respectively. The GPAS score in Group A was statistically higher ($p=0.0016$) in comparison with group B at week 24 with an absolute difference of 0.5 points (Figure 2). At week 12 a better result in favour of combination treatments was observed ($p = 0.08$). At week 24, the GEC score was higher in group A (3.4) in comparison with group B (3.1), but this difference was not statistically significant. Both regimens were well tolerated. Two subjects (1 in group A and 2 in group B) reported mild scalp dermatitis. The 10-item satisfaction questionnaire (from 0 to 30) average score was 22 in Group A and 20 in Group B (NS). Figure 3 shows the pictures of scalp of four subjects (2 in the Group A and 2 in the group B) at baseline and after 12 and 24 weeks of treatment.

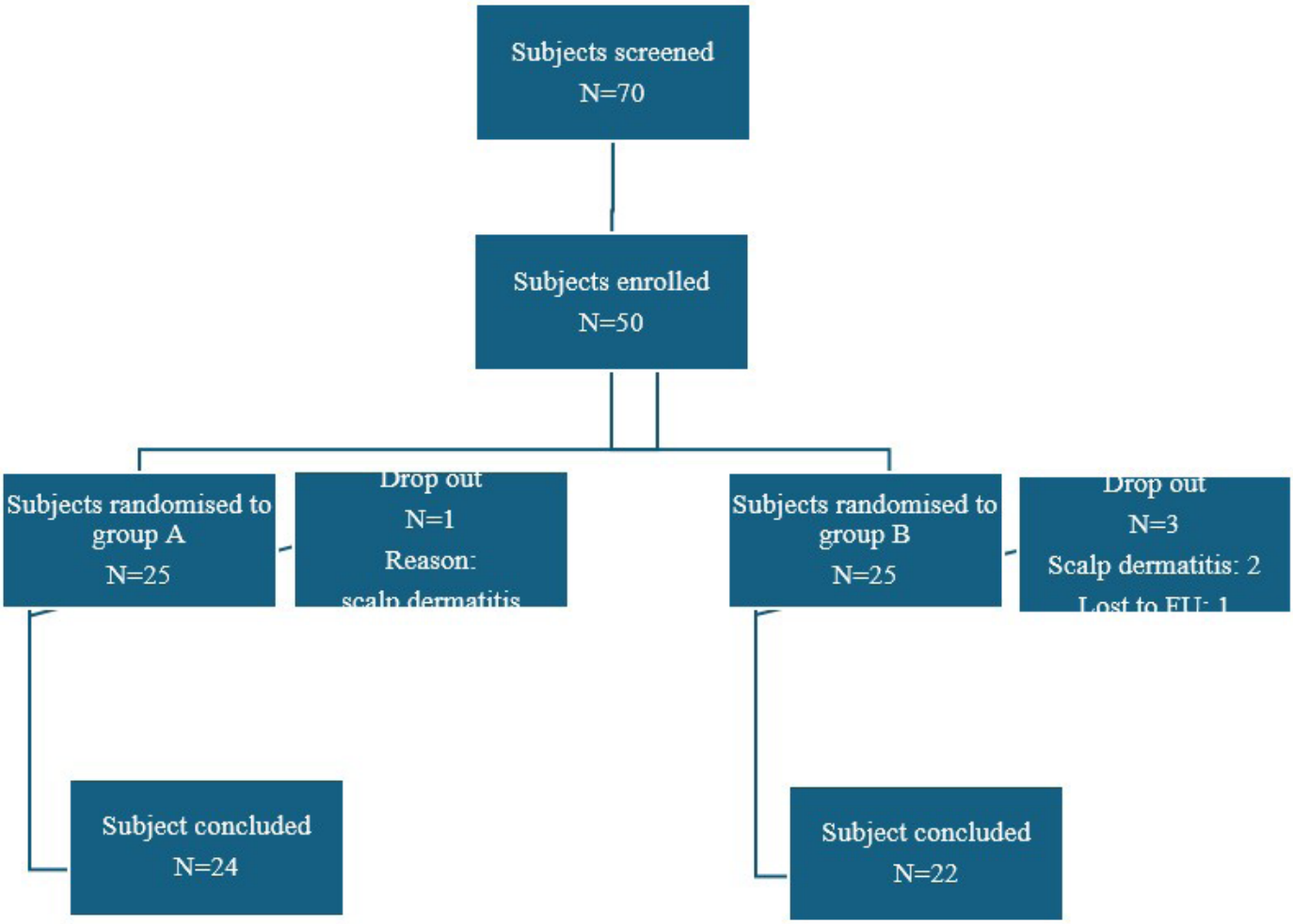

Figure 1: Study Flow.

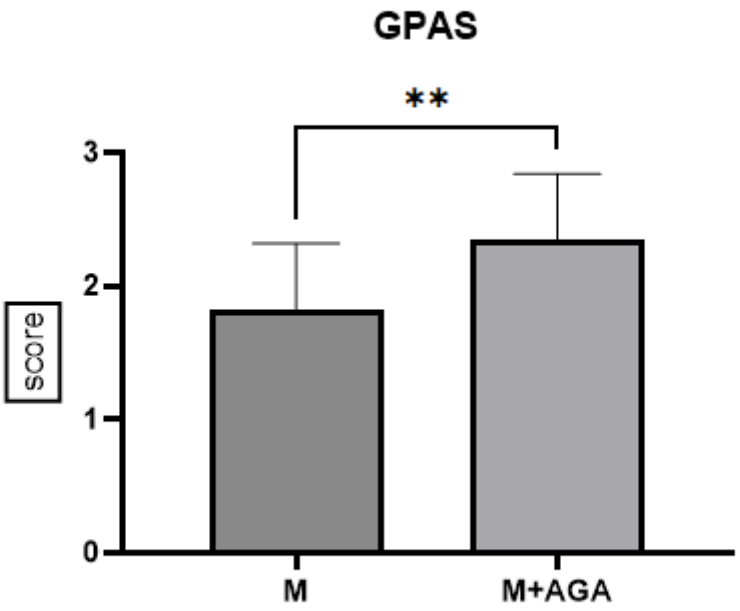

Figure 2: GPAS (Global Photographic assessment Scale) score at week 24 in minoxidil lotion (M) treated group and Minoxidil lotion plus dietary supplementation (M+AGA) group. **p=0.0016, Mann-Whitney Test.

Figure 3: Pictures of 4 subjects (Baseline, week 12 and 24).

Discussion

Androgenic alopecia (AA) is a common form of hair loss characterized by progressive thinning of hair, predominantly affecting men and women across various age groups [16]. Current therapeutic approaches largely focus on pharmacological treatments, with topical minoxidil being a widely used option due to its vasodilatory properties, which enhance blood flow to hair follicles and promote hair growth [17]. Despite its effectiveness, not all patients respond adequately to minoxidil monotherapy, necessitating exploration of combination therapies [18]. Emerging evidence suggests that dietary supplements, particularly those containing herbal extracts and amino acids, can complement existing treatments for AA [19]. This trial examines the efficacy of minoxidil lotion alone versus its combination with a dietary supplement formulated from *Serenoa repens* extract, pumpkin seed extract, and cysteine. The rationale for including these supplements stems from their proposed synergistic mechanisms of action [20]. *Serenoa repens* is known to inhibit the conversion of testosterone to dihydrotestosterone (DHT) [21], a key factor in androgenic alopecia, while pumpkin seed extract is rich in nutrients that may strengthen hair follicles [22]. Cysteine, an amino acid, plays a critical role in keratin production, potentially enhancing hair shaft strength and resilience [23]. Given the multifaceted nature of hair loss, this study aims to elucidate whether the addition of these supplements can enhance the therapeutic effects of minoxidil, providing a more effective treatment option for individuals with androgenic alopecia. By comparing outcomes between the two groups, the trial seeks to determine the potential benefit of a synergistic approach to managing this condition. The oral supplementation evaluated in our study contains *Serenoa Repens* extract (320 mg) pumpkin seed extract (320 mg) and cysteine (425 mg) per capsule. *Serenoa repens* has been shown to inhibit the enzyme 5-alpha-reductase, which converts testosterone to dihydrotestosterone (DHT), a primary contributor to follicle miniaturization in AGA [24]. Reducing DHT levels may slow hair loss and promote hair regrowth. Pumpkin seed extract is rich in phytosterols, pumpkin seed extract may also reduce DHT levels, and its antioxidant properties protect hair follicles from oxidative stress [25]. Additionally, it could play a crucial role in hair growth and repair. Finally, cysteine is an essential amino acid, cysteine is a key component of keratin, the primary protein in hair strands [26]. Cysteine supplementation can strengthen hair structure, promote growth, and enhance overall hair health. Together, these components may provide a multi-faceted approach to managing AGA, targeting hormonal pathways, oxidative stress, and structural integrity of hair, thereby supporting improved hair density and health. The present trial demonstrated that this dietary supplementation increases the clinical efficacy of topical minoxidil treatment in AGA subjects. Some study limitation should be taken into account in evaluating our results. The trial was not a double-blind study. However, we adopted a randomised assessor-blinded trial in order to increase the internal validity of final results. The “In&Out” strategy adopted in our clinical trial represents a forward-thinking approach to androgenic alopecia treatment by harnessing the complementary mechanisms of minoxidil lotion and the *Serenoa repens*/pumpkin seed extracts and cysteine dietary supplementation. By addressing both the symptoms and hormonal causes of hair loss, we have hypothized that this dual-modality regimen could offer a balanced and effective therapeutic solution in AGA treatment approach. The result of the present study supports this view.

Conclusion

The findings from our study indicate that oral supplementation with *Serenoa repens*, pumpkin seed extracts, and cysteine significantly enhances the clinical efficacy of topical minoxidil 5% lotion in the treatment of androgenetic alopecia (AGA) in both male and female patients. This implies that incorporating these dietary supplements may provide a synergistic effect, leading to better outcomes compared to the use of topical treatment alone. By combining these supplements with minoxidil, patients may experience improved hair growth and overall treatment effectiveness, offering a promising multifaceted approach to managing AGA.

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