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Original Article

Evaluation of the Efficacy and Safety of Topical Sildenafil Citrate Solution in the Treatment of Female Pattern Hair Loss

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ABSTRACT

Introduction: Female pattern hair loss [FPHL] is a type of hair thinning that occurs in females, categorized by a steady drop in the number of hairs, specifically in the central, frontal & parietal regions of the scalp. It does not cause scarring. Female pattern hair loss, also known as female androgenetic alopecia, is a prevalent kind of hair loss in women that becomes more common as they get older. The reason for the condition is still unknown, although there are several factors that have been recognized to affect it.

Aim of the study: To assess the effectiveness as well as security of a 1.0% solution of topical sildenafil citrate in treating female pattern hair loss.

Patients and methods: This Randomized controlled trial done on 40 cases classified as FPHL grades 1 also 2 based on Ludwig classification. Cases were randomly separated into two groups; Group1: Twenty persons treated with topical sildenafil citrate one percent solution. Group II: Twenty patients treated with vehicle for sildenafil citrate solution. Derm Lite Dl4 was utilized for a Tracheoscopy examination.

Results: Group 1, which received topical sildenafil 1.0%, experienced a substantial statistical increase in the number of vellus hairs in the frontal region, vertex, & temporal side during treatment, equated to earlier treatment. Moreover, there was a significant rise in the number of terminal hairs in the frontal & vertex regions after the therapy, as equated to before the treatment. There was no discernible variation in hair thickness across all regions following the therapy, as demonstrated by statistical analysis. In Group II [treated with vehicle for sildenafil citrate solution]: There was a statistically rise in vellus hair count & decrease in terminal hair count & hair thickness following treatment compared to prior to treatment in frontal, vertex and temporal area.

Conclusion: Topical use of sildenafil 1.0% showed to be a promising therapeutic alternative for FPHL. Larger studies on different concentrations of topical sildenafil, and its combined use with other standard therapies of FPHL such as minoxidil and finasteride are highly recommended.

Keywords: Female Pattern Hair Loss; Topical; Sildenafil.

INTRODUCTION

Female pattern hair loss is a non-scarring progressive hair thinning with a gradual decrease in hair count, particularly in the frontal, central, as well as parietal areas of the scalp. In most cases, the hairline is often unaffected and the affected areas only experience partial terminal hair loss. It is caused by follicular miniaturization, a gradual reduction in the ratio of terminal to vellus hair [1].

Approximately 55.0% of females over the age of 70 suffer from female pattern hair loss, which affects 6.0-12.0% of women in their twenties and thirties [2].

Dermoscopy can help in diagnosis of FPHL, particularly when the condition is in its early stages. Important trichoscopic features include a heterogeneity in hair shaft thickness in excess of 20.0%, vellus hair, a preponderance of hair follicles with single hairs, a brown depressed halo at the follicular opening, yellow dots, wavy hair, as well as honeycomb pigmentation. Peripolar sign is also visible [3].

Chemically, sildenafil citrate is a synthetic compound. When it comes to the phosphodiesterase-5 enzyme, sildenafil has a molecular structure that is extremely similar to its competitor, the cyclic guanosine monophosphate molecule. Through competitive inhibition, sildenafil stops the enzyme phosphodiesterase-5 from breaking down cyclic guanosine monophosphate [4].

Sildenafil is a potent vasodilator, sildenafil also increases the mRNA expression of vascular-endothelial growth factor [VEGF] & platelet derived growth factor [PDGF] in human dermal papilla cells [hDPCs], in which key components perform an essential part in promoting hair growth. Additionally, sildenafil increases extracellular signal-regulated kinase [ERK] phosphorylation. Another effect of sildenafil is that it has a role in angiogenesis, so it could affect perifollicular angiogenesis around hair follicles & increase hair growth rate [5].

PATIENTS AND METHODS

This double-blind placebo controlled randomized trial was conducted at the Outpatient Clinics of the Dermatology, Venereology, and Andrology Department at Al-Azhar University Hospitals in Damietta. The study included 40 cases between 18 and 45 years classified as FPHL grades 1 and 2 based on Ludwig classification.

Exclusion Criteria: Individuals aged less than 18 and more than 45 years old, with grade 3 FPHL according to the Ludwig classification, as well as those who had received either systemic or topical treatment for Female pattern hair loss within the six months preceding the commencement of the trial; Pregnant or lactating individuals, those who experienced hormonal imbalances for example PCO, individuals with a known history of hypersensitivity to sildenafil, individuals with other forms of hair loss [either cicatricial or non-cicatricial], individuals with autoimmune diseases & individuals with thyroid disease, anemia & Vitamin D deficiency were not included in the study.

Ethical approval: Ethical review by the Al-Azhar University, Egypt's Damietta Faculty of Medicine IRB [00012367] gave the go-ahead for the research. Every single case was covered by informed consent.

Patients were alienated randomly into 2 groups:

- Group I: Twenty cases were subjected to solution of one percent sildenafil citrate for topical application to make 1.0% solution [standard 1gm sildenafil dissolved in 100 ml ethanol solution to prepare 1.0% lotion]. It was applicated twice daily for three months.

- Group II: Twenty patients treated with vehicle for sildenafil citrate solution twice daily for three months.

All patients were subjected to full history taking, general, dermatological and Dermoscopy examination for grading og FPHL. DermLite DL4 was utilized for a Trichoscopy examination and evaluation of hair loss in the vertex [Twenty-four centimeters from nose tip], frontal [18 cm from the tip of the nose], temporal area, and occipital regions. A digital camera connected to a DermLite DL4 Dermoscope was used to capture at least three to four images with the same parameters. After each treatment, patients had monthly follow-up photos as well as Dermoscopy images.

The degree of improvement was assessed in females according to the degree of improvement changes in Ludwig classification. Additionally, the amount of progress was evaluated by comparing the pre- and post-treatment Trichoscopy images in terms of hair density, the ratio of terminal to vellus hair, in addition hair thickness.

Analysis of both terminal besides vellus hair count and mean hair thickness was done by ImageJ® freeware [http://imagej.nih.gov/ij]. The mean hair thickness was calculated in every case by adding hair thickness of 10 hair and dividing the total by 10 in frontal, vertex and temporal area before and after treatment.

Follow up: Both during and for three months following treatment, patients were seen for follow-up appointments once a month.

Statistical analysis: Version 18 of SPSS [SPSS Inc., PASW statistics for Windows] was employed to analyze the statistics. Chicago, Illinois: SPSS, Inc. Quantitative data was represented by percentages & numbers. For quantitative data that did not follow a normal distribution, the median [highest and lowest values] and the mean were used for description. Data that was previously considered normally distributed and then subjected to the Kolmogorov-Smirnov test for normality the outcomes were considered statistically significant at the 0.05 level. Fischer exact test, Chi-Square, in addition to Monte Carlo tests were functioned to equate qualitative data amongst groups as appropriate. A paired t test was functioned to compare 2 paired readings of distributed data. A student t test was utilized to compare two independent groups of normally distributed information. Two ordinal or continuous variables that do not follow a normal distribution can have their linear relationship's direction as well as strength assessed using the Spearman rank-order correlation.

RESULTS

Forty cases were included in the study, all with Ludwig classifications of FPHL grade 1 or 2. When comparing the two groups based on demographic variables such age, illness duration, family history positivity, and hair loss severity, no statistically distinctions were detected [Tables 1 and 2]. In the control group treated with [vehicle for sildenafil citrate solution], a significant rise in vellus hair count in addition to a decrease in hair thickness & terminal hair count following treatment compared to prior to treatment in frontal, vertex and temporal area [Tables 3-5].

After treatment, there was a statistically rise in the number of vellus hairs in the frontal region, vertex, and temporal side of the group that had been treated with topical sildenafil one percent. This was compared to the number of vellus hairs that were present before treatment. Additionally, the terminal hair count in the vertex & frontal areas increased significantly after treatment as opposed to before. Statistical analysis revealed no significant change in hair thickness across all areas following treatment. After the administration of sildenafil, none of the participants or those in the control group reported experiencing any specific adverse effects. This information pertains to the safety of the treatment. Individuals in the sildenafil treated group [Group1] reported more satisfaction overall in comparison to those in the control group [Group2] [Figures 1 and 2]. No side effects were reported in study groups [Data not tabulated].

Table [1]: comparison of demographic and family history between the studied groups

Variable	Group 1 [Sildenafil citrate solution 1.0%] N = 20	Group 2 [control group] N = 20	Test of significance
Age [years] Mean ± SD	36.67 ± 8.67	32.93 ± 7.17	T = 1.29 P = 0.209
Negative Family history Positive Family history	2 [10.0%] 18 [90.0%]	2 [10.0%] 18 [90.0%]	FET = 0.0 P = 1.0

T: Student t test, FET: Fischer exact test.

Table [2] Duration and degree of disease among studied groups

Variable	Group 1 [Sildenafil citrate solution 1.0%] N = 20	Group 2 [control] N = 20	Test of significance
Duration [years]	8 [1-15]	0.5 [1-15]	Z = 1.60 P = 0.108
Degree 1 Degree 2	10 [50.0%] 10 [50.0%]	10 [50.0%] 10 [50.0%]	FET = 0.186 P = 0.666

Z: Mann Whitney U test, FET: Fischer exact test.

Table [3]: Comparative analysis of response to treatment in the frontal region among both groups.

Variable	Topical Sildenafil 1.0% N = 20	Control group N = 20	Test of significance	P-value
Vellus hair count	12.04 ± 7.49	17.5 ± 6.35	2.49	0.017*
Terminal hair count	16.64 ± 8.18	12.35 ± 6.5	1.84	0.07
Hair thickness [mm]	0.004 ± 0.001	0.0002 ± 0.001	12.02	<0.001*

Table [4]: Evaluation of treatment response at the vertex amongst each of the groups.

Variable	Topical Sildenafil 1.0% N = 20	Control group N = 20	Test of significance	P-value
Vellus hair count	2.40 ± 2.1	4.3 ± 2.8	2.42	0.02*
Terminal hair count	8.1 ± 10.9	5.5 ± 2.1	1.05	0.302
Hair thickness [mm]	0.004 ± 0.001	0.001 ± 0.001	9.48	0.001*

Table [5]: Comparison of the two groups' temporal responses to medical treatment.

Variable	Mean ± SD		Test-value	P-value
	Topical Sildenafil 1.0% N = 20	Control group N = 20		
Villous hair [VH]	4.20 ± 4.1	8.15 ± 3.65	3.22	0.002*
Terminal hair [TH]	1.9 ± 5.71	1.25 ± 6.2	0.345	0.732
Hair thickness	0.005 ± 0.002	0.002 ± 0.003	3.72	0.0006*

Case presentation:

The first was 35 years old female patient with FPHL, grade 2 on Ludwig grading before and after treatment with topical sildenafil citrate 1%solution, patient was completely satisfied [Figure 1a-h].

The second was 30 years old female patient with FPHL, grade 2 on Ludwig grading before and after treatment with vehicle for topical sildenafil citrate 1% solution, patient was not satisfied [Figure 2a-h]

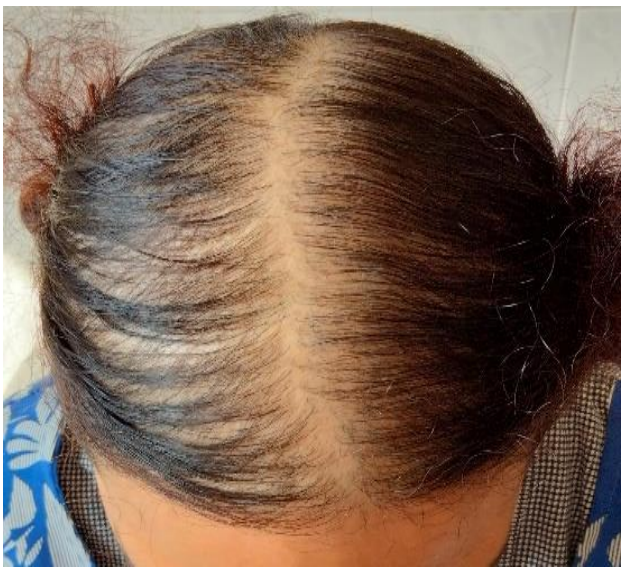

Figure [1a]: Before treatment

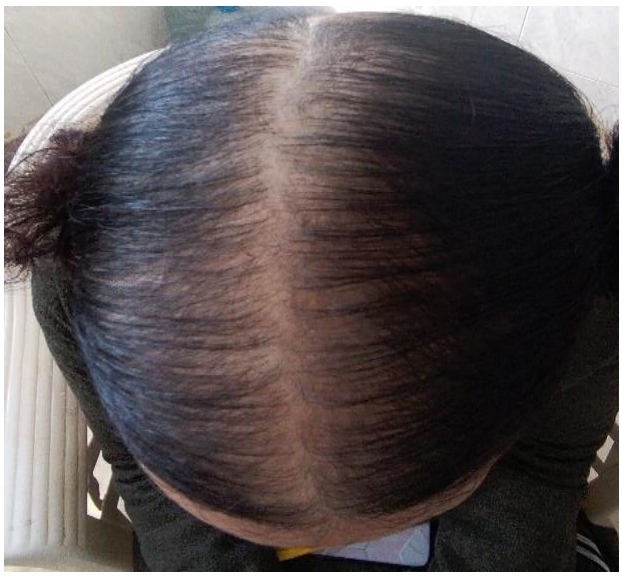

Figure [1b]: After treatment

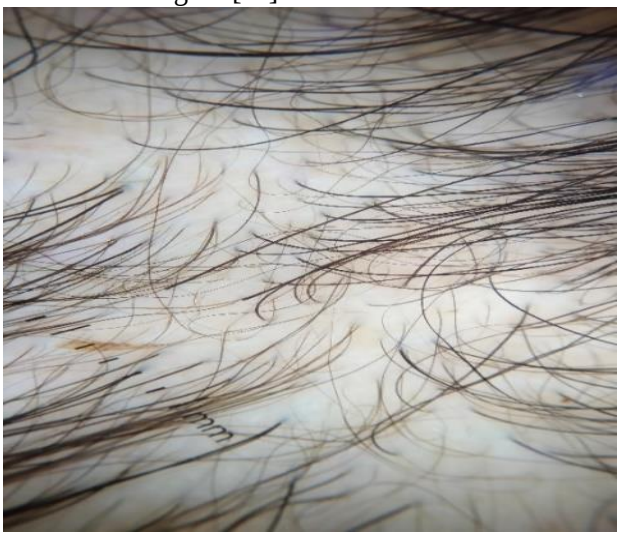

Figure [1C]: Before treatment

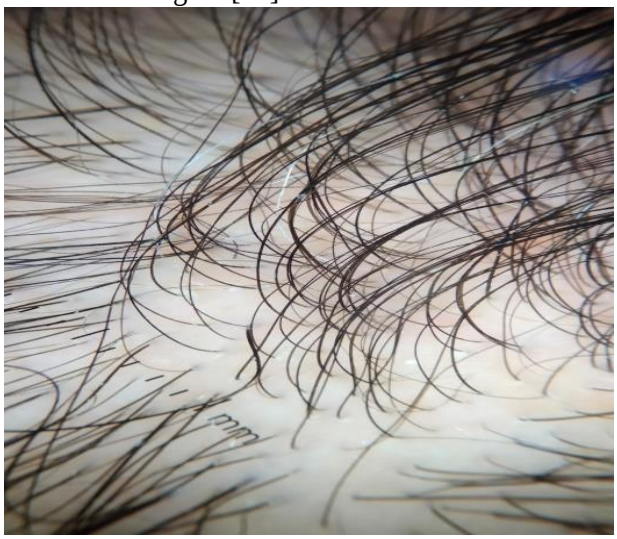

Figure [1D]: After treatment

Trichoscopic assessment at the frontal region

Figure [1e]: Before treatment

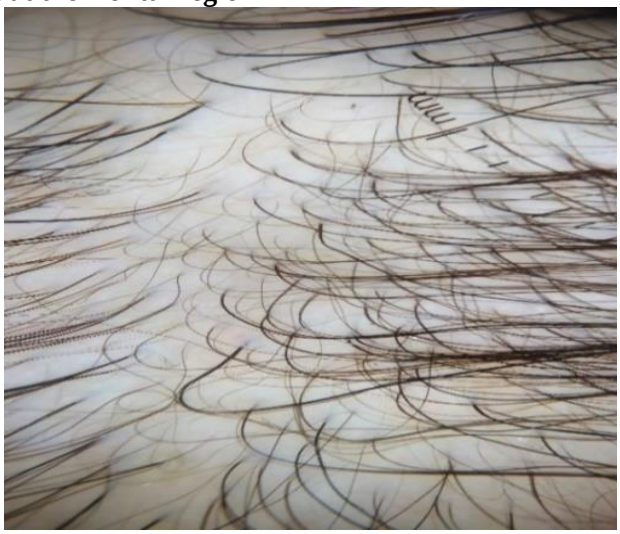

Figure [1f]: After treatment

Trichoscopic assessment at the vertex

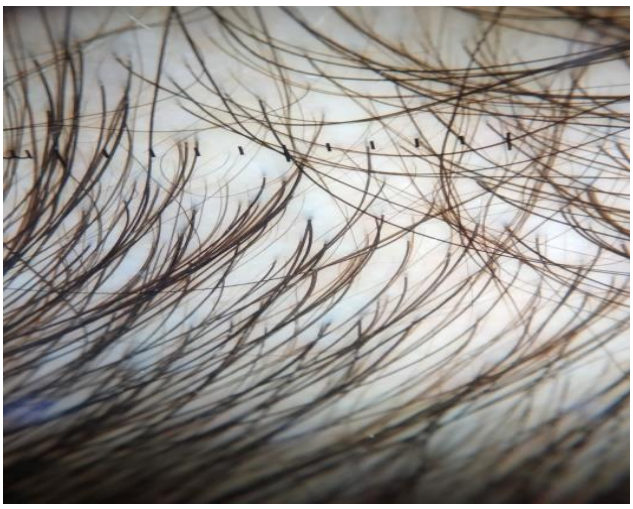

Figure [1g]: Before treatment

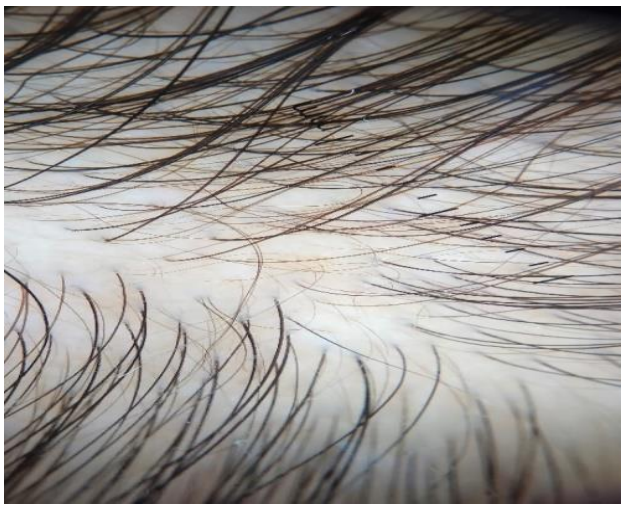

Figure [1h]: After treatment

Trichoscopic assessment at the temporal region

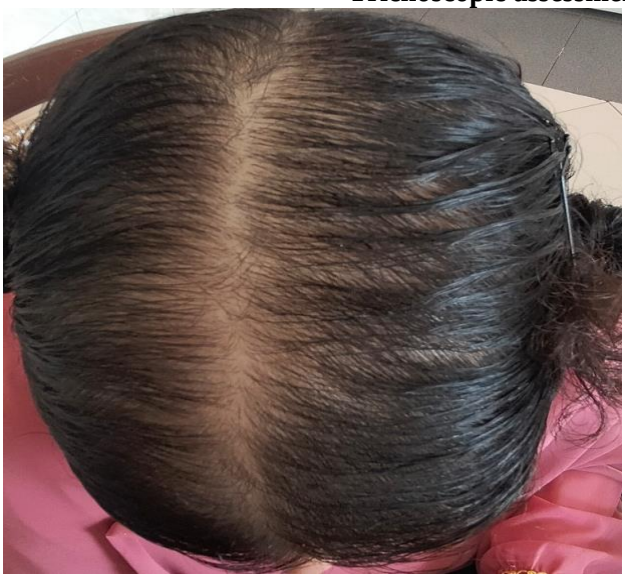

Figure [2a]: Before treatment

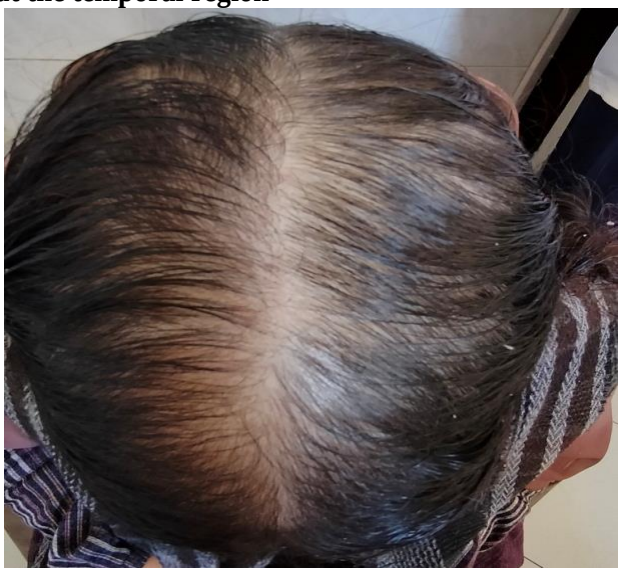

Figure [2b]: After treatment

Figure [2C]: Before treatment

Figure [2D]: After treatment

Trichoscopic assessment at the frontal region

Figure [2e]: Before treatment

Figure [2f]: After treatment

Trichoscopic assessment at the vertex

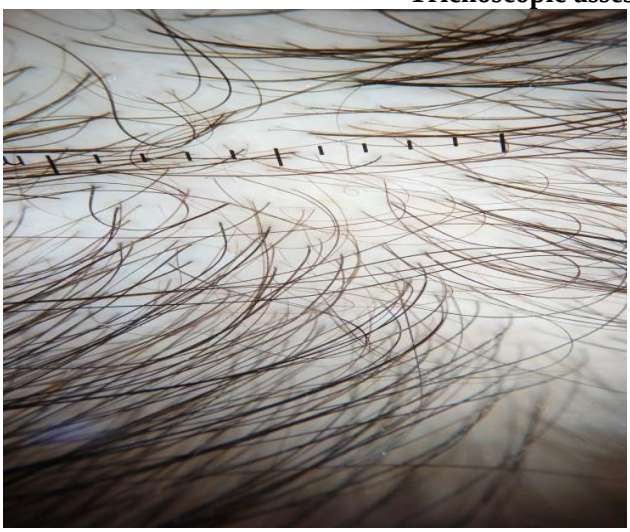

Figure [2g]: Before treatment

Figure [2h]: After treatment

Trichoscopic assessment at the temporal region

DISCUSSION

The central-parietal region of the scalp is the most affected by female-pattern hair loss, which is also termed female androgenetic alopecia. The hair follicles in this area gradually shrink in size and density. Diffuse thinness of hair & elevated hair shedding over the midfrontal scalp are clinical hallmarks of FPHL, a complicated polygenic illness [6].

Clinical manifestations of FPHL, a complicated polygenic condition, include increased hair shedding as well as generalized hair thinning over the midfrontal scalp [7].

There are several drugs that have been utilized in the management of female pattern hair loss. These treatments include the 5-a reductase inhibitors finasteride & dutasteride, as well as cyproterone acetate, the androgen receptor blockers' spironolactone and flutamide. In addition to being used on their own, these medicines can also be used with topical minoxidil treatments [8].

In terms of the applications of topical sildenafil in the treatment of hair loss, **Sarifakioglu** and his colleagues assessed the effectiveness of topical sildenafil 1.0% in children with alopecia areata who had not reacted to previous topical treatment. They administered 1.0% sildenafil twice daily for a period of three months. All of the patients participated in the trial and finished it. Two of the patients developed vellus hair, whereas one of the individuals had terminal hair. Both of these hair growth patterns were observed. On the other hand, these results were acknowledged as indications of the disease's natural retreat. [9].

Choi *et al*. examined PDE5 expression in human hair follicles as well as dermal papilla cells. Sildenafil was tested for its impact on growth factor expression, human dermal papilla cell proliferation and extracellular signal-regulated kinase phosphorylation by real-time PCR & western blotting. Using hair development, a live mouse model, & blood vessel formation around hair follicles were examined. They identified strong PDE5 expression in hDPCs & hHFs. Sildenafil increases hDPC proliferation as well as vascular endothelial growth factor along

with platelet-derived growth factor mRNA expression, which promote hair growth. After topical administration in mice, sildenafil increases phosphorylated ERK and perifollicular vascular development, accelerating anagen induction [5].

Enhancing blood circulation in the scalp of individuals with baldness stimulates the flow of blood in the nearby hair follicles, which can result in the stimulation of hair development and excessive hair. Moreover, PDGF is present in follicular keratinocytes and hair DPCs & is widely recognized as a factor that stimulates hair development [10]. Phosphodiesterase inhibitors enhance the circulation of blood in the skin, hence stimulating the development of hair [10].

Choi *et al*. [11] demonstrated that cilostazol, a PDE3 inhibitor, supports hair development in C57BL/6 mice by promoting the proliferation of human dermal papilla cells, boosting the elongation of hair shafts, and speeding the initiation of the anagen phase.

The findings of the present study corroborated the results of a prior trial conducted by **Al-Shabkhon *et al***. The study was performed out on male individuals suffering from androgenic alopecia. The study involved a cohort of thirty male participants who were experiencing androgenic alopecia. The patients included in the study were distributed into 2 equal groups according to the medication they got: one group received a 1.0% topical solution of sildenafil, while the other group received a 5.0% topical solution of minoxidil. Trichoscopy was employed to estimate the usefulness of the treatment. The findings indicated that the group treated with sildenafil exhibited a statistically augmentation in the number of Vellus hair and Terminal hair at the 18 - 24 cm points following the therapy, as compared to the pre-treatment count. The temporal side exhibited a significant rise in VH only. The group treated with minoxidil exhibited a significant augmentation in T/V hair ratio, TH count, also hair thickness at the 18 cm point & on the temporal side following treatment, in comparison to the pre-treatment condition. The VH count shown a notable reduction following management in evaluation to the pre-treatment measurement at the 18 cm location. At the 24 cm mark, only the TH showed a significant rise following therapy compared to before treatment. According to the authors' findings, the minoxidil group exhibited superior treatment outcomes along with greater patient satisfaction. The temporal region had the most significant disparity in treatment response, followed by the frontal region, as well as ultimately the vertex [12].

Conclusion:

In conclusion, Topical use of sildenafil 1.0% showed to be a promising therapeutic alternative for FPHL. Larger studies on different concentrations of topical sildenafil, and its combined use with other standard therapies of FPHL such as minoxidil and finasteride are highly recommended.

Disclosure:

None to be disclosed.

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