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Research Article

Comparative Study between the Efficacy and Safety of Topical Sildenafil Citrate Solution and Topical Minoxidil 5% in the Treatment of Female Pattern Hair Loss

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ABSTRACT

Background: Female Pattern Hair Loss (FPHL) is a non-scarring progressive thinning of hair with gradual decrease in its number, especially in the frontal, central, and parietal scalp. The loss of terminal hairs in affected areas is usually incomplete and the frontal hairline is often spared. It is caused by follicular miniaturization, a process that gradually reduces the proportion of terminal to vellus hair.

Aim of the work: To evaluate the efficacy and safety of topical sildenafil citrate 1% solution in comparison with topical minoxidil 5% foam in the treatment of female pattern hair loss.

Patients and methods: This exploratory pilot study included 30 female patients suffering from female pattern hair loss. Included patients were divided into 2 groups;

Group 1: Received 1% topical sildenafil citrate solution.

Group 2: Received 5% topical minoxidil foam.

Assessment of treatment response was done using trichoscopy.

Results: In group 1 (treated with topical sildenafil 1%): There was a statistically significant increase in the vellus hair count in the frontal region, vertex and temporal side after treatment as compared to before treatment. Also, there was statistically significant increase in the terminal hair count in the frontal region and vertex region after treatment as compared to before treatment. There was no statistically significant difference in the hair thickness in all the regions after treatment, group 2 (treated with topical minoxidil 5%) there was a statistically significant increase in the terminal hair count and hair thickness in the frontal region, vertex and temporal side after treatment as compared to before treatment. Also, there was statistically significant decrease in the vellus hair count, but it was detected only in the frontal region.

Conclusion: Topical sildinafil 1% treatment proves to be a good alternative in the treatment of FPHL, although topical minoxidil 5% is still the first choice in FPHL treatment.

Keywords: FPHL; Topical; Minoxidil; Sildenafil

INTRODUCTION

Female Pattern Hair Loss (FPHL) is a non-scarring progressive thinning of hair with gradual decrease in its number, especially in the frontal, central, and parietal scalp. The loss of terminal hairs in affected areas is usually incomplete and the frontal hairline is often spared. It is caused by follicular miniaturization, a process that gradually reduces the proportion of terminal to vellus hair [1].

Topical minoxidil is a hair growth stimulator that works by shortening the telogen process of the hair follicles, allowing them to reach the anagen phase prematurely. Minoxidil also prolongs the anagen phase by acting on the potassium channels

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of vascular smooth muscles and hair follicles, which increases the microcirculation near the hair follicles [2].

The molecular structure of sildenafil mimics that of cyclic Guanosine Monophosphate (cGMP), this similarity protects cGMP from degradation because sildenafil can bind to the catalytic site to act as a competitive inhibitor of cGMP specific PDE-5, the enzyme that normally catalyzes the breakdown of vasodilatory cGMP [3].

Phosphodiesterase 5 is highly expressed in human Dermal Papilla Cells (hDPCs) and human Hair Follicles (hHFs). Sildenafil enhances proliferation of hDPCs and up-regulates the mRNA expression of Vascular Endothelial Growth Factor (VEGF) and Platelet Derived Growth Factor (PDGF) which are responsible for hair growth. Additionally, sildenafil up-regulates the levels of phosphorylated Extra Cellular Signal Regulated Kinase (ERK) and accelerates anagen induction by stimulating perifollicular vessel formation [4].

MATERIALS AND METHODS

Patients and methods

This is an exploratory pilot study that was conducted at Al-Azhar university hospitals' dermatology, venereology, and andrology department outpatient clinics (Damietta). The study included 30 cases with FPHL grade 1 and 2 Ludwig classification [5]. Patients were randomly assigned into two groups:

Group I: Fifteen patients were subjected topical sildenafil citrate 1% solution (Standard 1 gm sildenafil dissolved in 100 ml ethanol solution to prepare 1% lotion). Twice daily application for 3 months.

Group II: Fifteen patients were subjected to minoxidil foam 5% (Hair back plus foam, mina pharma) once daily for 3 months [6].

All patients were subjected to the following: Full history taking, general examination, dermatological and dermoscopic examination for grading of female pattern hair loss, digital photographs were taken clinical and dermoscopic monthly and three months after treatment assessment by trichoscopy examination was performed with derma light Dl4. Hair loss regions including the vertex, frontal, temporal line and occipital regions were observed. At least 3 images-4 images were taken with a digital camera that was connected to the dermoscope with the same parameters. Degree of improvement was assessed in females according to the degree of improvement changes in Ludwig classifications. Also the degree of improvement was assessed by comparing the trichoscopic photos before and after treatment as regards hair density, number of terminal to vellus hair and hair thickness [7].

Inclusion criteria: The study included 30 adult female patients between 18 years and 45 years with grade 1 or 2 Ludwig classification.

Exclusion criteria: Patients who were <18 years and >45 years old, grade 3 FPHL Ludwig classification, who received systemic or topical treatment for FPHL in the last 6 months prior to the start of the study; who were Pregnant or lactating, who had hormonal disturbance like PCOD, who have any autoimmune disease, with known history of hypersensitivity to minoxidil or sildenafil, with other types of hair loss either cicatricial or non cicatricial and patients with anemia, thyroid disease, and vitamin D deficiency were excluded from the study.

Follow up: The follow up was conducted every month during treatment and for 3 months after the completion of treatment.

Ethical approval: The study was approved by an ethics committee of Damietta Faculty of Medicine IRB (00012367), Al-Azhar University, Egypt. An informed consent was obtained from all participants.

Statistical analysis: Data analysis was performed by SPSS software, version 18 (SPSS Inc., PASW statistics for windows version 18. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-normally distributed data and mean ± standard deviation for normally distributed data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level [8].

- *Chi-square*, Fischer exact test, Monte Carlo tests were used to compare qualitative data between groups as appropriate.
- Student t test was used to compare 2 independent groups for normally distributed data.
- Paired t test was used to compare 2 paired readings distributed data.
- The Spearman's rank order correlation is used to determine the strength and direction of a linear relationship between two non-normally distributed continuous variables and/or ordinal variables.

RESULTS

30 cases with FPHL grade 1 and 2 Ludwig classifications. There were no statistically significant difference in the basic data in the two study groups including age, disease duration, % of cases with positive family history and degree of hair loss [9].

There was a statistically significant increase in the terminal hair count and hair thickness in the group treated with topical minoxidil 5% in the frontal region, vertex and temporal side after treatment as compared to before treatment. Also, there was statistically significant decrease in the vellus hair count, but it was detected only in the frontal region [10].

There was a statistically significant increase in the vellus hair count in the group treated with topical sildenafil 1% in the frontal region, vertex and temporal side after treatment as compared to before treatment. Also, there was statistically significant increase in the terminal hair count in the frontal region and vertex region after treatment as compared to before treatment. There was no statistically significant difference in the hair thickness in all the regions after treatment [11].

When comparing the results of the two drugs, minoxidil showed better results compared to sildenafil in terms of higher terminal hair count, thicker hair diameter and decreased number of vellus hair. The effects were more noticed in the frontal region and temporal region and less noticed in the vertex. Furthermore, there was higher degree of patients' satisfaction in the minoxidil group compared to the sildenafil group, but it didn't achieve a statistically significant difference (Tables 1-3) [12].

Table 1: Comparison of treatment response at the frontal region between the 2 groups.

Variable	Topical sildenafil 1%	Topical Minoxidil 5%	Test of significance	p-value
	n=15	n=15		
Vellus hair count	11.33 ± 7.49	-7.53 ± 7.84	6.73	<0.001*
Terminal hair count	15.53 ± 8.18	26.87 ± 11.79	3.06	0.005*
Hair thickness (mm)	0.001 ± 0.002	0.01 ± 0.004	5.93	<0.001*

Note: Z: Mann Whitney test; P value ≤ 0.05 is significant.

Table 2: Comparison of treatment response at the vertex between the 2 groups.

Variables	Topical sildenafil 1%	Topical Minoxidil 5%	Test of significance	p-value
	n=15	n=15		
Vellus hair count	1.40 ± 2.2	1.53 ± 2.9	0.138	0.892
Terminal hair count	7.2 ± 11.1	13.60 ± 5.68	1.99	0.057
Hair thickness (mm)	0.002 ± 0.004	0.009 ± 0.007	3.41	0.002*

Note: Using mann whitney test P value ≤ 0.05 is significant.

Table 3: Comparison of treatment response at the temporal side between the 2 groups.

Variables	Mean ± SD		Test value	p-value
	Group 1 (Sildenafil citrate solution 1 %) n=15	Group 2 (Minoxidil foam 5%) n=15		
Vellous Hair (VH)	3.80 ± 5.40	-6.07 ± 10.91	3.14	0.004*
Terminal Hair (TH)	-1.3 ± 5.84	13.67 ± 6.45	6.67	<0.001*
Hair thickness	-0.002 ± 0.004	0.009 ± 0.010	3.99	<0.001*

Note:aUsing Mann Whitney test P value ≤ 0.05 is significant.

DISCUSSION

Female pattern hair loss is the most common hair loss disorder in women. Initial symptoms may develop during the teenage years. FPHL is a complex polygenic disorder characterized clinically by diffuse hair thinning over the midfrontal scalp and increased hair shedding.

A number of agents have also been used in the treatment of female pattern hair loss including the androgen receptor antagonists spironolactone, cyproterone acetate, and flutamide as well as the 5 a reductase antagonist finasteride and dutasteride. These agents can be used either alone or in combination with topical minoxidil.

To the best of our knowledge this is the first study to compare the efficacy of topical sildenafil versus topical minoxidil in treatment of FPHL.

The results were in accordance with who included a total of 381 women (18 years-49 years old) with female pattern hair loss applied 5% topical minoxidil solution (n=153), 2% topical minoxidil solution (n=154), or placebo (vehicle for 5% solution; n=74) twice daily. The results of the study showed that after 48 weeks of treatment, the 5% topical minoxidil group demonstrated statistical superiority over the 2% topical minoxidil group and the placebo group in terms of increase terminal hair count, decrease vellus hair count and increase hair growth/scalp coverage.

Blume-Peytavi, et al., conducted a study to compare the efficacy, safety, and acceptability and to show noninferiority of once-daily 5% Minoxidil Topical Foam (MTF) with twice-daily 2% MTS in women with androgenetic alopecia. A total of 113 women with androgenetic alopecia were randomized to 24 weeks of treatment with 5% MTF or 2% MTS. The results showed that after 24 weeks, women randomized to 5% MTF once daily showed noninferior target area hair count and target area hair width and experienced greater, but nonsignificant, improvements in target area hair count, target area hair width, and overall efficacy by global photographic review than those randomized to 2% MTS

used twice daily. 5% MTF was significantly superior to 2% MTS in participants' agreement with "the treatment does not interfere with styling my hair" (P=0.002). Women randomized to 5% MTF experienced significantly lower rates of local intolerance (P=0.046) especially in pruritus and dandruff compared with 2% MTS.

Choi and his colleagues investigated the expression of PDE5 in human Dermal Papilla Cells (hDPCs) and human Hair Follicles (hHFs). The effects of sildenafil on hDPC proliferation were evaluated and the mRNA expression of growth factors and Extracellular Signal Regulated Kinase (ERK) phosphorylation were investigated using real time PCR and western blotting, respectively. Additionally, anagen induction and perifollicular vessel formation were evaluated using an *in vivo* mice model. The authors confirmed high expression of PDE5 in hDPCs and hHFs. Sildenafil enhances proliferation of hDPCs and up-regulates the mRNA expression of Vascular Endothelial Growth Factor (VEGF) and Platelet Derived Growth Factor (PDGF), which are responsible for hair growth. Additionally, sildenafil up-regulates the levels of phosphorylated ERK and accelerates anagen induction by stimulating perifollicular vessel formation after topical application in mice.

Stimulating blood flow in the human bald scalp promotes microcirculation in the surrounding HFs and can lead to promotion of hair growth and hypertrichosis. In addition, PDGF is also well known as a hair growth-promoting factor and is expressed in hDPCs and follicular keratinocytes. Phosphodiesterase inhibitors help to increase cutaneous blood flow and this helps in promoting hair growth. As a support for this principal, showed that cilostazol, a PDE3 inhibitor, promotes hair growth by stimulating hDPC proliferation, enhancing hair shaft elongation and acceleration of anagen induction in C57BL/6 mice.

The results of the current study agreed with a previous study that was conducted in male patients with androgenic alopecia. The study included 30 male patients suffering from androgenic alopecia. Included patients were divided into 2 equal groups based on treatment received; one group received 1% topical sildenafil and the other group received 5% topical minoxidil. Assessment of treatment response was done using trichoscopy. The results showed that sildenafil treated group showed statistically significant increase in VH and TH count at 18 cm point, 24 cm point after treatment compared to before treatment.

While, temporal side showed statistically significant increase in VH only. Minoxidil treated group showed statistically significant increase in TH count, T/V hair ratio and hair thickness at 18 cm point and temporal side after treatment compared to before treatment. VH count was significantly decreased after treatment compared to before treatment at 18 cm point. At 24 cm point, only TH was significantly increased after treatment compared to before treatment.

The authors showed better treatment results in the minoxidil group and higher patients' satisfaction. The degree of difference in treatment response was better noticed in the temporal region followed by the frontal region and at last the vertex.

Despite the reported efficacy of minoxidil, one of its major disadvantages is that the treatment needs to be continued indefinitely. If treatment is stopped, clinical regression occurs within six months. The degree of alopecia will return to the level that would have occurred if there were no treatment.

CONCLUSION

Topical application of sildenafil 1% proved to be beneficial in FPHL patients with minimal side effects while Topical minoxidil proved to be a gold standard in treatment of FPHL with high tolerability and satisfaction in treated patients.

RECOMMENATION

Larger studies are recommended to ascertain the effects of topical sildenafil 1% in FPHL patients, comparison between different concentrations of both topical treatments are recommended to develop comprehensive view of effects and response and combination of topical sildenafil and minoxidil together or with other treatments like finasteride, PRP or lasers are recommended to ensure the best response with either combination.

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