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Evaluation of Topical Spironolactone 5% Gel Versus Eflornithine 13.9 % Cream in Treatment of Idiopathic Hirsutism: A Clinical Trial

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ABSTRACT

Background: Hirsutism is defined as excessive growth of terminal hair (THs) in androgen-dependent regions. It is essential to consider a woman's menopausal status when evaluating the cause of hirsutism. Topical eflornithine has been shown to improve hair reduction. Spironolactone acts by competing for androgen receptors in hair follicles.

Objectives: The current study aimed to evaluate the efficacy of topical spironolactone 5% gel versus those of topical eflornithine 13.9% cream in the management of idiopathic hirsutism. **Patients and methods:** This randomized controlled trial included 58 patients with idiopathic hirsutism who were divided into two groups, Group 1 included 29 hirsute females treated with topical spironolactone gel 5% applied twice daily for 6 months and Group 2 included 29 hirsute females treated with topical eflornithine 13.9% cream applied twice daily for 6 months. Patients underwent scoring according to the Ferriman-Gallwey (F-G) scale for hirsutism before the start of treatment, during follow-up and at the end of the study. **Results**: Regarding F-G score before treatment, the mean scores were comparable between both groups (Group 1: 11.52, Group 2: 10.59), while after treatment, the mean scores significantly decreased in both groups (Group 1: 7.48, Group 2: 7.62). In addition, group 1 showed a significantly lower score after treatment compared with group 2. Group 1 had a higher mean percent improvement in the Ferriman-Gallwey scores and higher satisfaction scores compared to Group 2. **Conclusion**: It could be concluded that both topical spironolactone 5% gel and eflornithine 13.9% cream are effective options for managing idiopathic hirsutism and show a significant decrease in Ferriman-Gallwey scores after treatment, with group 1 reporting higher satisfaction scores and higher mean percent improvement.

Keyword: Topical Spironolactone, Eflornithine, Idiopathic Hirsutism.

INTRODUCTION

Hirsutism is characterized by as excessive TH growth in body regions dependent on androgens in females [1]. It could be caused by increased androgen formation or higher skin sensitivity [2].

It is essential to consider menopausal status when evaluating the cause of hirsutism. Regarding premenopausal females, polycystic ovary syndrome (PCOS) is the most common cause of hyperandrogenemia in hirsutism. The remaining reasons of hyperandrogenemia are uncommon, representing 0.2% of patients. Of note, fifty percent of mild hirsutism and eighty percent of moderate hirsutism are accompanied by hyperandrogenemia [3]. With regard to idiopathic hirsutism patients, androgen values are normal and hirsutism develops as a result of raised skin sensitivity to 5 α-reductase activity and improved transformation of testosterone to more active form [4].

Rare causes comprise congenital adrenal hyperplasia (CAH), Cushing syndrome, acromegaly, certain drugs (such as danazol, metoclopramide, methyldopa, valproic acid), hypertrichosis with minoxidil, diazoxide, steroids, cyclosporine and phenytoin [4]. Non-pharmacologic options are available for hair reduction, such as Waxing, plucking, shaving, and threading could help somewhat at a domestic degree, but don't offer a conclusive effect, and occasionally cause irritation. Electrolysis and laser hair therapy are also available. Systemic agents comprise anti-androgen (spironolactone, Cyproterone acetate (CPA), flutamide), 5-αreductase inhibitors (such as finasteride), gonadotrophin releasing hormone analogues and insulin sensitizer [5].

Although there is little data to support long-term eflornithine use, there may be benefit over the first six months. It has been approved as a treatment option for facial hair [6]. It suppresses the enzyme ornithine decarboxylase. It could be used topically every 12 hours; carefully rub it into the skin. There are different approaches to hair removal, which include shaving and waxing, that could be utilized with local eflornithine. It has to be avoided in pregnant and lactating females and cases under the age of nineteen [5].

Spironolactone is a potassium-sparing diuretic agent. It suppresses androgen formation from ovaries and the adrenal glands, competes for androgen receptors and causes direct inhibition of the 5-alpha-reductase activity. Suppression of androgen doesn't suppress ovulation, as a result efficient contraception is needed, while the patient receives therapy [7]. Studies displayed that topical spironolactone interferes with follicular duct cornification and comedones formation and decreases sebum formation, so it can be one of the effective and safe treatments of acne vulgaris (AV) [8, 9].

The current study aimed to evaluate the efficacy of topical spironolactone 5% gel versus those of topical eflornithine 13.9% cream in the management of idiopathic hirsutism.

PATIENTS AND METHODS

This randomized controlled trial included a total of 58 patients with idiopathic hirsutism, recruited from the Outpatient Clinic of the Dermatology, Andrology, and STDs Department at Mansoura University Hospitals.

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This study was conducted between (mention period e.g., June 2022 and January 2025).

Patients were divided into two groups: **Group** 1 included 29 hirsute females treated with topical spironolactone 5% gel applied twice daily for 6 months, and **Group** 2 included 29 hirsute females treated with topical eflornithine 13.9% cream applied twice daily for 6 months.

Inclusion criteria: Premenopausal women aged 20 to 40 years with a complaint of hirsutism, who had not received hormonal treatment and who have regular menses. **Exclusion criteria:** Patients with polycystic ovary syndrome, CAH, ovarian or adrenal tumors secreting androgens, Cushing syndrome, or patients who had received anabolic steroids, danazol, or oral contraceptive pills.

Every patient was subjected to full history taking including personal history (age, occupation, married or single, menstrual history and obstetric history), history of medical disorders or drug hypersensitivity and to determine the degree of affection, previous medication or intervention. Clinical and laboratory assessments were performed before treatment, including abdominal ultrasound to exclude ovarian, adrenal tumors and polycystic ovary syndrome (PCOS), and measurement of serum FSH, LH, prolactin, free testosterone and dehydroepiandrosterone sulfate to exclude polycystic ovary syndrome (PCOS). In addition, measurement of 24 hours of urinary free cortisol was performed to exclude Cushing syndrome.

Patients underwent scoring prior to the treatment, throughout follow up and after the end of treatment. The F-G score for hirsutism was conducted. Nine body regions were assigned a score between one and four; a total score of fewer than eight was considered as normal. Mild hirsutism was indicated by a score between 8 and 15, while moderate to severe hirsutism was indicated by a score more than 15. Absence of TH was indicated by a score of zero. Nine androgen dependent areas with scores ranging from one (minimal TH growth visible) to four (excessive terminal hair growth visible) for each area assessed. A maximum score of thirty six is possible, but a score of more than or equal to eight denotes hirsutism [10]. Follow up was done every month for 6 months after treatment. All patients were evaluated clinically and photographically monthly for 6 months taking patient satisfaction into consideration and by using Ferriman-Gallwey to evaluate the improvement of the patient score. Photographed images were taken for every participant before and after treatment.

Ethical consideration

This study was ethically approved by the Research Ethics Committee of Mansoura Faculty of Medicine. Written informed consent was obtained from all participants. Code numbers were assigned to every participant. Photographs of the affected area only were taken. The outcomes were used solely for scientific purposes. Participants had the right to withdraw from the study at any time. Patient privacy was respected. The study protocol conformed to the Helsinki Declaration, the ethical standards of the World Medical Association for research involving human subjects.

Statistical Analysis

Results were statistically analyzed by using SPSS (27.0, IBM/SPSS Inc., Chicago, IL). Descriptive statistics comprised estimates for summarizing the continuous data as mean (X) and SD for normally distributed data or median and IQR for skewed data. Frequency with percentage (%) was used for presenting qualitative data. Chi-square ($\chi 2$) test was utilized to compare between at least two groups concerning a single qualitative variable. One-way ANOVA test was utilized for continuous data to assess for significant difference between at least three groups. The Kruskal-Wallis test was used when ANOVA assumptions were violated to compare more than two groups of skewed data. The post hoc test was utilized for multiple comparison adjustment in cases when the ANOVA test result was significant, whereas the Bonferroni post hoc test was utilized in cases when the Kruskal-Wallis test result was significant. P-values < 0.05 are significant.

RESULTS

Table **(1)** shows that there were 29 patients in Group 1 (topical spironolactone 5% gel) and 29 patients in Group 2 (topical eflornithine cream 13.9%). The mean age in Group 1 was 28.62 years with a standard deviation of 5.67, while in Group 2, it was 27.93 years with a standard deviation of 5.81. The difference in age between both groups wasn't significant ($p > 0.05$). The distribution of marital status also did not vary significantly between the groups ($p > 0.05$).

Among the patients in Group 1, 21 (72.4%) had a regular menstrual history, while in Group 2, 23 (79.3%) had a regular menstrual history. The difference in the distribution of menstrual history between both groups was insignificant ($p > 0.05$). In Group 1, out of 21 patients, 15 (71.4%) had a history of cesarean section (CS), and in Group 2, out of 19 patients, 12 (63.2%) had a history of CS. The difference in obstetric history between both groups wasn't significant ($p > 0.05$).

The distribution of occupations did not differ significantly between Group 1 and Group 2. In Group 1, 9 (31.0%) were medical staff, 9 (31.0%) were workers, and 11 (37.9%) were officers. In Group 2, 10 (34.5%) were medical staff, 10 (34.5%) were workers, and 9 (31.0%) were officers ($p > 0.05$).

Regarding site of disease, in Group 1, 24 patients (82.8%) had hirsutism in the beard area, 21 patients (72.4%) had hirsutism in the moustache area, and 5 patients (17.2%) had hirsutism in the abdomen area. In Group 2, 27 patients (93.1%) had hirsutism in the beard area, 19 patients (65.5%) had hirsutism in the moustache area, and 2 patients (6.9%) had hirsutism in the abdomen area. The difference in the distribution of hirsutism sites between both groups wasn’t significant.

Table (1): Comparison between topical spironolactone 5% gel vs. topical eflornithine cream 13.9% regarding demographic data, menstrual history, obstetric history, occupations and site of disease

	Group 1 N = 29		Group 2 N = 29		Test	P
Age (years)						
Mean±SD.	28.62 ± 5.67		27.93 ± 5.81		t= 0.458	0.649
Median	28.0		27.0			
Minimum – Maximum	20.0 – 37.0		20.0 – 39.0			
Marital status	**No.**	**%**	**No.**	**%**		
Single	8	27.6	10	34.5	X^2= 0.322	0.570
Married	21	72.4	19	65.5		
Menstrual history Regular Irregular	 21 8	 72.4 27.6	 23 6	 79.3 20.7	X^2= 0.377	0.539
Obstetric history CS NVD	 15 6	 71.4 28.6	 12 7	 63.2 36.8	X^2= 0.311	0.577
Occupation Medical staff Worker(factory) Housewife	 9 9 11	 31.0 31.0 37.9	 10 10 9	 34.5 34.5 31.0	X^2= 0.305	0.858
Site of disease						
Beard No Yes	 5 24	 17.2 82.8	 2 27	 6.9 93.1	X^2= 1.462	FE 0.423
Moustache No Yes	 21 8	 72.4 27.6	 19 10	 65.5 34.5	X^2= 0.322	0.570
Abdomen No Yes	 24 5	 82.8 17.2	 27 2	 93.1 6.9	X^2= 1.462	FE 0.423

t: Student t test. X^2: Chi–Square test.

Table **(2)** shows that the onset of the disease with most cases experiencing a gradual onset (Group 1: 79.3%, Group 2: 89.7%). The mean duration of the disease was similar in both groups (Group 1: 2.38 years, Group 2: 2.31 years). Both onset and duration had no significant differences among both groups.

Most patients in both groups had mild hirsutism (Group 1: 75.9%, Group 2: 86.2%), while moderate hirsutism was found in 24.1% and 13.8% of Group 1 and II respectively.

Table (2): Comparison between both groups regarding onset, duration, grading of the disease

	Group 1 **N = 29**		**Group 2** **N = 29**		**Test**	**P**
	No.	**%**	**No.**	**%**		
Onset						
Gradual	23	79.3	26	89.7	X^2= 1.184	FE 0.470
Sudden	6	20.7	3	10.3		
Duration (years)						
Mean ± SD.	2.38 ± 0.94		2.31 ± 0.85		U= 408.5	0.843
Median	2.0		2.0			
Min. – Max.	1.0 – 4.0		1.0 – 4.0			
Grading Mild Moderate	 22 7	 75.9 24.1	 25 4	 86.2 13.8	X^2= 1.010	0.315

Min.: Minimum, Max.: Maximum, U: Mann Whitney. X^2: Chi–Square test, FE: Fisher Exact.

Regarding Ferriman-Gallwey score, table (3) shows that (before treatment), the mean scores were comparable between both groups (Group 1: 11.52, Group 2: 10.59), while Ferriman-Gallwey score (after treatment), the mean scores significantly decreased in both groups after treatment (Group 1: 7.48, Group 2: 7.62). The difference was statistically significant in the favor of group 1. In addition, Group 1 showed a significantly lower score after treatment when compared to group 2 (p=0.035).

The comparison between topical spironolactone 5% gel (Group 1) and topical eflornithine cream 13.9% (Group 2) shows that Group 1 had a higher mean percent improvement of the F-G score (35.03%) compared to Group 2 (27.35%). The difference between both groups was significant ($p < 0.001$).

Group 1 reported higher satisfaction scores (mean: 7.66) compared to Group 2 (mean: 6.86). The difference was significant (p=0.002).

Table (3): Comparison between both groups regarding Ferriman-Gallwey score

Ferriman-Gallwey score	**Group 1** **N = 29**	**Group 2** **N = 29**	**Test**	**P1**
Before treatment				
Mean ± SD.	11.52 ± 3.78	10.59 ± 2.69	U1= 398.5	0.716
Median	10.0	10.0		
Min. – Max.	8.0 – 19.0	8.0 – 18.0		
After treatment				
Mean ± SD.	7.48 ± 2.60	7.62 ± 1.72	U1= 290.5*	0.035*
Median	6.0	7.0		
Min. – Max.	5.0 – 13.0	6.0 – 13.0		
t2	7.751*	7.629*		
p2	<0.001*	<0.001*		
% Improvement Mean ± SD. Median Min. – Max.	 35.03 ± 6.35 33.33 25.0 – 50.0	 27.35 ± 6.86 30.0 12.50 – 44.44	 U= 169.5*	<0.001*
Satisfaction Mean ± SD. Median Min. – Max.	 7.66 ± 0.94 8.0 6.0 – 10.0	 6.86 ± 0.95 7.0 5.0 – 9.0	 t= 3.196*	0.002*

Min.: Minimum, Max.: Maximum, t1: Student t test, U: Mann Whiteny test. t2: Paired t test. p1: Comparing the two groups, p2: Comparing before and after treatment. *: Significant when p value <0.05

Table (4) reveals the relationship between the percent improvement of the F-G score and various parameters among patients with idiopathic hirsutism. Among the parameters examined, only satisfaction displayed a significant positive correlation ($r = 0.600$, $p < 0.001$), denoting that greater satisfaction levels were accompanied by greater improvement in the hirsutism score. The other parameters, including age, duration of the condition, F-G score before and after treatment, did not show significant correlations with the percent improvement.

Table **(5)** presents the correlation between the percent improvement of the F-G score and different parameters for Group 1 and Group 2. Among the parameters, only satisfaction displayed a significant positive correlation in both groups ($p < 0.001$). The other parameters, including age, duration of the condition, F-G score before and after treatment, did not show significant correlations with the percent improvement in either group ($p > 0.05$).

Table (4): Correlation between percent improvement of Ferriman Gallwey score and different parameters among patients with idiopathic hirsutism

	% Improvement of Ferriman-Gallwey score	
	Correlation Coefficient	**P**
Age	0.188	0.157
Duration	0.146	0.275
Ferriman Gallwey score before treatment	0.213	0.109
Ferriman Gallwey score after treatment	-0.168	0.208
Satisfaction	0.600	<0.001*

r: Spearman's rho. *: Significant when p value <0.05.

Table (5): Correlation between percent improvement of Ferriman Gallwey score and different parameters

	% Improvement of Ferriman Gallwey score			
	Group 1 N=29		**Group 2 N=29**	
	Correlation Coefficient	**p**	**Correlation Coefficient**	**p**
Age	0.145	0.453	0.218	0.256
Duration	0.015	0.937	0.285	0.134
Ferriman Gallwey score before treatment	-0.001	0.996	0.293	0.135
Ferriman Gallwey score after treatment	-0.285	0.134	-0.030	0.877
Satisfaction	0.750	<0.001*	0.646	<0.001*

r: Spearman's rho.

DISCUSSION

Hirsutism is a frequent problem that affects about 10% of premenopausal females. It is described as excessive THs growth in a male pattern [4]. Idiopathic hirsutism is defined as hirsutism accompanied by normal androgen level, normal ovarian structure and ovulatory functions [11].

Although the pathophysiology of idiopathic hirsutism (IH) is not totally identified, it is thought to be secondary to impaired adrenal steroid hormone formation, exaggerated activity of 5 α-reductase enzyme, and increased androgen receptor sensitivity [12]. Management of hirsutism is typically resistant, and from medical treatment to laser hair reduction, the treatment of hirsutism and its evaluation are the most challenging [13].

In cases with moderate hirsutism, it is suggested to use an OCP and, if no improvement has arisen following six months to add in an anti-androgen. A combined therapy of COCP and anti-androgen might be more effective [14].

In addition, eflornithine was demonstrated to decrease facial hair growth and was approved as a topical treatment of hirsutism. It causes permanent suppression of ornithine decarboxylase responsible for the conversion of ornithine to putrescine, critical for hair follicle growth [15]. Spironolactone reveals dose-dependent competitive suppression of the androgen receptor and suppression of five alpha-reductase enzyme activity [16].

No previous studies had compared the two drugs in the treatment of hirsutism , and there was also a lack of the studies on the efficiency of the two drugs in the management of hirsutism. The current study included 58 patients with hirsutism who were randomly assigned into two groups: Group 1 (topical spironolactone 5%) and Group 2 (topical eflornithine 13.9% cream).

In general, the F-G scale is utilized for clinical or laboratory evaluation of hirsutism [10], although changes in race significantly interfere with characteristics of TH growth and presentation of IH and it isn't clear still whether racially specialized cut off values are important for the diagnosis of hirsutism [17].

In the current study, regarding the Ferriman Gallwey score (before treatment), the mean scores were comparable between both groups (Group 1: 11.52, Group 2: 10.59), while Ferriman Gallwey score (after treatment), the mean scores significantly decreased in both groups after treatment (Group 1: 7.48, Group 2: 7.62). The difference was significant. In addition, Group 1 showed a significantly lower score after treatment when compared to group 2 (p = 0.035). The degree of improvement and the degree of patient satisfaction were significantly higher in Group 1.

Regarding the previous studies assessed the value of spironolactone in the treatment of hirsutism, another study comparing spironolactone 100 mg/d to the controls showed a higher decrease in F-G score with spironolactone. The effect of spironolactone is known to be dose dependent, despite the lack of thorough dose-response studies [18].

Spironolactone is broadly utilized as a diuretic and anti-androgen in several clinical conditions. Androgens have a role in the pathogenesis of a lot of skin disorders, such as AV, and hirsutism. These diseases could be accompanied by hyperandrogenism, even though the majority of cases progress without systemic androgenic changes. Antiandrogens are a reasonable modality in this sitting, and spironolactone is a safe cheap substitute.

Another study assessing the outcomes of twenty-six trials with different anti-androgens displayed that spironolactone 100 mg/d improved the score on the F-G scale, as a result displaying it to be superior to finasteride and comparable to oral contraceptive pills (OCPs) [19]. Further studies have reinforced the efficacy of spironolactone alone [20], and combined with OCPs and finasteride [21]. Combined therapy was displayed to be superior to monotherapy [22].

Erunus *et al.* [23] included 40 females with idiopathic hirsutism who were chosen and randomly assigned to receive five mg of finasteride or 100 mg of spironolactone for nine months. According to their results, hirsutism scores diminished significantly in the two groups at the termination of nine months. As for the finasteride and spironolactone groups, the mean percent change in hirsutism scores was 5.91%±7.18% and 20.6%±12.59% at three months, 10.61%±12.18% and 32.57%±15.68% at six months, and 15.15%±15.38%

and 42.36%±12.31% at nine months. The spironolactone group was associated with a significant increase in the response at the termination of nine months. Fifty percent of cases in the spironolactone group developed adverse events such as burning sensation. On the other hand, none of them stopped treatment due to adverse events.

Lumachi and Rondinone [24] conducted their study to compare three various treatments: 100 mg spironolactone, 12.5 mg/day of CPA, and 5 mg/day of finasteride. There was a significant difference twelve months following the termination of therapy in those females receiving spironolactone compared with CPA and finasteride in favor of spironolactone. There was an insignificant difference in complications between the three treatments; two of the cases receiving finasteride displayed loss of libido throughout the initial three to four months, and three of the cases receiving spironolactone developed temporary polyuria and headache, but this resolved with long-term usage.

Another study compared the use of metformin 1000 mg and spironolactone 25mg every day. The F-G score was significantly diminished at six months in the spironolactone group. There was an insignificant difference in the serum testosterone or DHEAS levels. Several adverse events were recorded, in which irregular menstruation was the commonest in the spironolactone group, while diarrhea was the commonest in the metformin group [20].

Regarding eflornithine, in a randomized controlled trial (RCT) assessing the efficacy and safety of local application of eflornithine 13.9% cream the treatment of hirsutism in females, twice-daily application of the cream for 24 weeks significantly reduced hair length and hair mass compared with controls. Based on the clinician's assessment, about 1/3 of eflornithine-managed individuals displayed successful outcomes, and about 58% of the eflornithine-managed individuals displayed better outcomes to some extent compared to controls, regardless of the approach of hair removal [25].

Jackson *et al.* [26] conducted their study based on patients's assessments of success; approximately 2/3 of eflornithine-managed cases recorded a reduction in the general bother after six months, compared with 1/3 of the controls. On the other hand, eight weeks following the end of therapy, the bother levels in the two groups were to some extent similar.

Another study of the combined use of eflornithine cream and laser treatment versus laser only for managing unwanted hair on the upper lip in females was done in 31 evaluable patients. The use of combined therapy displayed better outcomes compared to laser only. Complete hair removal was reached in 93.5% and 67.9% of the combined group and the placebo cream-laser–treated areas, respectively ($P<0.05$) [27].

Eflornithine suppresses hair growth by suppressing the enzyme ornithine decarboxylase, with a subsequent decrease of polyamines, essential building blocks for rapidly dividing tissues, including the hair. Eight weeks are needed for considerable hair reduction [28]. These initial results could be taken as a cornerstone for performing further studies to evaluate the efficacy of the two drugs during the management of hirsutism.

CONCLUSION

It could be concluded that both topical spironolactone 5% gel and eflornithine 13.9% cream are effective options for managing idiopathic hirsutism and show a significant decrease in Ferriman-Gallwey scores after treatment, with group 1 reporting higher satisfaction scores and higher mean percent improvement.

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