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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 refers to the excessive growth of terminal hair in androgen-dependent areas of the female body. When evaluating the underlying cause, a woman's menopausal status should always be considered. Topical eflornithine has been shown to reduce hair growth by inhibiting ornithine decarboxylase, while spironolactone exerts its effect by competitively blocking androgen receptors within hair follicles.

Objective: To compare the efficacy and safety of topical spironolactone 5% gel with topical eflornithine 13.9% cream in the treatment of idiopathic hirsutism.

Patients and Methods: This randomized controlled clinical trial included 58 women with idiopathic hirsutism. Participants were randomly allocated into two equal groups: Group 1 (n = 29) received topical spironolactone 5% gel applied twice daily for six months, while Group 2 (n = 29) received topical eflornithine 13.9% cream with the same regimen. The severity of hirsutism was assessed using the Ferriman–Gallwey (F–G) scoring system at baseline, during follow-up, and at the end of treatment.

Results: Baseline F–G scores were comparable between groups (Group 1: 11.52; Group 2: 10.59). After six months, both groups showed significant reductions in F–G scores (Group 1: 7.48; Group 2: 7.62; *p* < 0.05). The spironolactone group demonstrated a significantly greater mean percentage improvement and higher patient satisfaction compared with the eflornithine group.

Conclusion: Both topical spironolactone 5% gel and eflornithine 13.9% cream are effective in the management of idiopathic hirsutism, achieving a significant reduction in Ferriman–Gallwey scores. Spironolactone 5% gel, however, produced superior clinical improvement and greater patient satisfaction.

Keywords: spironolactone gel, Eflornithine cream, Idiopathic hirsutism, Ferriman–Gallwey score.

INTRODUCTION

Hirsutism is characterized by the excessive growth of terminal hair in androgen-dependent body regions in females [1]. It may result from increased androgen production or heightened skin sensitivity to circulating androgens [2].

When evaluating the etiology of hirsutism, it is essential to consider the woman's menopausal status. In premenopausal women, polycystic ovary syndrome (PCOS) represents the most common cause of hyperandrogenemia. Other causes are rare, accounting for only about 0.2% of cases. Notably, approximately 50% of women with mild hirsutism and 80% of those with moderate hirsutism exhibit elevated androgen levels [3]. In contrast, idiopathic hirsutism (IH) is characterized by normal circulating androgen levels, with excessive hair growth attributed to increased cutaneous 5α-reductase activity and enhanced local conversion of testosterone to its more active form, dihydrotestosterone [4].

Less common etiologies of hirsutism include congenital adrenal hyperplasia (CAH), Cushing's syndrome, acromegaly, and the use of certain medications such as danazol, metoclopramide, methyldopa, valproic acid, minoxidil, diazoxide, corticosteroids, cyclosporine, and phenytoin [4].

Several non-pharmacologic methods are available for hair removal, including waxing, plucking, shaving, and threading. Although these approaches may provide temporary cosmetic relief, they often lead to irritation and are not curative. More advanced methods include electrolysis and laser hair removal. Pharmacologic treatment options encompass systemic antiandrogens such as spironolactone, cyproterone acetate (CPA), and flutamide; 5α-reductase inhibitors like finasteride; gonadotropin-releasing hormone analogues; and insulin sensitizers [5].

Eflornithine hydrochloride cream, approved for the treatment of facial hirsutism, inhibits the enzyme ornithine decarboxylase, thereby reducing hair growth. It is applied topically every 12 hours and may be combined with conventional hair removal methods such as shaving or waxing. However, it should be avoided in pregnant or lactating women and in individuals under 19 years of age [5,6].

Spironolactone is a potassium-sparing diuretic with potent antiandrogenic properties. It suppresses androgen production from both the ovaries and adrenal glands, competitively blocks androgen receptors, and inhibits 5α-reductase activity. Because spironolactone does not suppress ovulation, concurrent contraception is necessary during therapy [7]. Topical spironolactone has been reported to reduce sebum production, interfere with follicular duct cornification, and prevent comedone formation, making it a potentially effective and safe treatment for acne vulgaris [8,9].

Accordingly, the present study aimed to evaluate the comparative efficacy of topical spironolactone 5% gel versus topical eflornithine 13.9% cream in the

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management of idiopathic hirsutism.

PATIENTS AND METHODS

This randomized controlled clinical trial included 58 female patients diagnosed with idiopathic hirsutism. Participants were recruited from the Outpatient Clinic of the Dermatology, Andrology, and STDs Department, Mansoura University Hospitals. The study was conducted between June 2022 and January 2025).

Study Design and Grouping

Patients were randomly assigned into two equal groups:

Group 1:29 hirsute females treated with topical spironolactone 5% gel, applied twice daily for six months. Group 2: 29 hirsute females treated with topical eflornithine 13.9% cream, applied twice daily for six months.

Inclusion and Exclusion Criteria

Inclusion criteria: Premenopausal women aged 20–40 years with idiopathic hirsutism, regular menstrual cycles, and no history of hormonal treatment.

Exclusion criteria: Patients diagnosed with polycystic ovary syndrome (PCOS), congenital adrenal hyperplasia (CAH), Cushing's syndrome, or androgen-secreting ovarian or adrenal tumors. Patients who had received anabolic steroids, danazol, or oral contraceptives were also excluded.

Clinical and Laboratory Evaluation

All participants underwent a comprehensive medical evaluation, including:

History taking: age, occupation, marital status, menstrual and obstetric history, medical disorders, drug hypersensitivity, and previous therapies.

Clinical and laboratory assessments: abdominal ultrasonography to exclude ovarian or adrenal pathology and PCOS; serum measurements of FSH, LH, prolactin, free testosterone, and dehydroepiandrosterone sulfate (DHEA-S); and a 24-hour urinary free cortisol test to exclude Cushing's syndrome.

Assessment of Hirsutism

The severity of hirsutism was evaluated using the Ferriman–Gallwey (F–G) scoring system. Nine androgen- dependent body areas were each scored from 0 (no terminal hair) to 4 (excessive terminal hair), with a maximum total score of 36.

- Normal: <8
- Mild hirsutism: 8–15
- Moderate to severe hirsutism: >15
- Scoring was performed at baseline, monthly during treatment, and after six months. Clinical photographs were taken before and after treatment to objectively document improvement. Patient satisfaction was also recorded at each follow-up visit.

Preparation of Topical Spironolactone 5% Gel:

- Purpose: Treatment of idiopathic hirsutism (facial or body). Route of administration: Topical (external use only).
- Strength: 5% w/w.
- Batch size:100 g.

This extemporaneous formulation was prepared using commercial spironolactone tablets (e.g., Aldactone®)) according to pharmaceutical compounding principles adapted from dermatologic practice.

Table (1): Formulation Components

Ingredient	Quantity (for 100 g)	Function
Spironolactone (from tablets, 100 mg each)	5 g (from 5 tablets)	Antiandrogen (active drug)
Propylene Glycol	10 mL	Solubilizer, humectant
Carbopol 940	1 g	Gelling agent
Triethanolamine (TEA)	q.s. (approx. 1 mL)	pH adjuster, neutralizer
Purified Water	q.s. to 100 g	Vehicle

Preparation Procedure:

Preparation was carried out in a clean compounding area with appropriate personal protective equipment (gloves, mask, gown) and calibrated instruments in the following steps:

- Drug pulverization: Crush 5 spironolactone 100 mg tablets into fine powder and pass through a 100-mesh sieve to remove coarse excipients.
- Gel base preparation: Disperse 1 g Carbopol 940 in approximately 50 mL purified water with gentle stirring; allow to hydrate for at least one hour.
- Drug dispersion: Mix the sieved spironolactone powder with 10 mL propylene glycol to form a uniform suspension.
- Incorporation: Slowly add the drug suspension to the hydrated Carbopol base with continuous stirring until homogeneous.
- pH adjustment: Add triethanolamine dropwise to raise the pH to 6.0–7.0, initiating gel formation.
- Final adjustment: Make up the total weight to 100 g with purified water and mix thoroughly to ensure uniform consistency.

Packaging and Storage:

- Container: Amber plastic or aluminum tubes with tight-seal caps.
- Label: Topical Spironolactone 5% Gel – For External Use Only. Avoid contact with eyes and mucous membranes.
- Storage: Store at 15–25°C. Use within 30 days unless stability testing supports a longer shelf life.

Quality Control:

- Visual inspection for homogeneity, absence of lumps, and phase separation. pH range: 6.0–7.0.
- Optional microbial limit testing if stored beyond 30 days.

Patient Counseling:

Patients were instructed to apply the gel once or twice daily to clean, dry skin for at least 8–12 weeks for noticeable improvement. Hands were to be washed after application, and treatment discontinued if irritation, rash, or allergic reaction occurred.

Ethical Considerations: The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Mansoura University (MS.20.12.1327, 21-03-2021). The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Mansoura University (Approval No. MS.20.12.1327; dated March 21, 2021). Oral informed consent was obtained from all participants prior enrollment, and each participant was assigned a unique identification code to ensure confidentiality. Participants were informed of their right to withdraw from the study at any time without affecting their standard of care. All research procedures adhered to the principles of the Declaration of Helsinki and complied with the ethical standards of the World Medical Association for research involving human subjects.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Chicago, IL, USA). Descriptive statistics were expressed as mean ± standard deviation (SD)for normally distributed continuous variables or as median (interquartile range, IQR) for skewed data. Categorical variables were presented as frequencies and percentages (%).

The Chi-square (χ^2) test was applied to compare categorical variables between groups. For continuous variables, the one-way ANOVA test was used when normal distribution and homogeneity of variance assumptions were met. When these assumptions were violated, the Kruskal–Wallis test was applied as a non-parametric alternative. Post hoc multiple comparisons were performed using the Bonferroni correction following ANOVA or the Bonferroni-adjusted Mann–Whitney test following Kruskal–Wallis, as appropriate. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 58 women were enrolled and evenly distributed into two groups:

Group 1:29 patients treated with topical spironolactone 5% gel. Group 2:29 patients treated with topical eflornithine 13.9% cream.

The mean age was 28.62 ± 5.67 years in Group 1 and 27.93 ± 5.81 years in Group 2, with no significant difference between groups ($p > 0.05$). Similarly, the distribution of marital status did not differ significantly ($p > 0.05$).

Regarding menstrual history, 21 patients (72.4%) in Group 1 and 23 patients (79.3%) in Group 2 reported regular menstrual cycles, with no significant difference between groups ($p> 0.05$).

In terms of obstetric history, 15 of 21 married women (71.4%) in Group 1 and 12 of 19 (63.2%) in Group 2 had a history of cesarean section (CS), showing no significant variation ($p > 0.05$).

Occupational distribution was also comparable between groups. In Group 1, 9 patients (31.0%) were medical staff, 9 (31.0%) were workers, and 11 (37.9%) were officers, while in Group 2, 10 (34.5%) were medical staff, 10 (34.5%) were workers, and 9 (31.0%) were officers ($p> 0.05$).

With respect to site of hirsutism, the beard area was the most frequently affected region, followed by the moustache and abdomen. In Group 1, beard involvement was observed in 24 patients (82.8%), moustache in 21 (72.4%), and abdomen in 5 (17.2%). In Group 2, beard involvement occurred in 27 patients (93.1%), moustache in 19 (65.5%), and abdomen in 2 (6.9%). None of these differences were statistically significant ($p> 0.05$), (Table 2).

Table (2): Comparison between topical spironolactone 5% gel and topical eflornithine 13.9% cream with respect to demographic characteristics, menstrual and obstetric history, occupation, and site of hirsutism.

		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			
		No.	**%**	**No.**	**%**		
Marital status	Single	8	27.6	10	34.5	X^2= 0.322	0.570
	Married	21	72.4	19	65.5		
Menstrual history	Regular	21	72.4	23	79.3	X^2= 0.377	0.539
	Irregular	8	27.6	6	20.7		
Obstetric history	CS	15	71.4	12	63.2	X^2= 0.311	0.577
	NVD	6	28.6	7	36.8		
Occupation	Medical staff	9	31.0	10	34.5	X^2= 0.305	0.858
	Worker(factory)	9	31.0	10	34.5		
	Housewife	11	37.9	9	31.0		
Site of disease							
Beard	No	5	17.2	2	6.9	X^2= 1.462	FE 0.423
	Yes	**24**	82.8	27	93.1		
Moustache	No	21	72.4	19	65.5	X^2= 0.322	0.570
	Yes	8	27.6	10	34.5		
Abdomen	No	24	82.8	27	93.1	X^2= 1.462	FE 0.423
	Yes	**5**	17.2	2	6.9		

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

Table (3) shows that most cases in both groups experienced a gradual onset of the disease (Group 1: 79.3%; Group 2: 89.7%). The mean duration of the disease was comparable between the two groups (Group 1: 2.38 years; Group 2: 2.31 years), with no statistically significant difference observed.
Regarding disease severity, the majority of patients in both groups had mild hirsutism (Group 1: 75.9%; Group 2: 86.2%), whereas moderate hirsutism was observed in 24.1% of Group 1 and 13.8% of Group 2.

Table (3): Comparison between both groups with respect to disease onset, duration, and severity grading.

	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	22	75.9	25	86.2	X^2= 1.010	0.315
Mild	7	24.1	4	13.8		
Moderate						

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

Regarding the Ferriman–Gallwey (F–G) score, Table (4) shows that before treatment, the mean scores were comparable between both groups (Group 1: 11.52; Group 2: 10.59). After treatment, the mean scores significantly decreased in both groups (Group 1: 7.48; Group 2: 7.62), with a statistically significant difference favoring Group 1 (p = 0.035). When comparing the percentage improvement in the F–G score, Group 1 (topical spironolactone 5% gel) demonstrated a higher mean percent reduction (35.03%) than Group 2 (topical eflornithine 13.9% cream) (27.35%), and this difference was statistically significant (p< 0.001).
Additionally, patient satisfaction scores were significantly higher in Group 1 (mean: 7.66) compared to Group 2 (mean: 6.86) (p= 0.002).

Table (4): Comparison between both groups regarding Ferriman–Gallwey scores before and after treatment.

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 (5) illustrates the relationship between the percentage improvement in the Ferriman–Gallwey (F–G) score and various clinical parameters among patients with idiopathic hirsutism. Among the examined variables, only patient satisfaction showed a significant positive correlation with F–G score improvement (r = 0.600, p< 0.001), indicating that higher satisfaction levels were associated with greater clinical improvement. Other parameters—including age, disease duration, and F–G scores before and after treatment—did not demonstrate significant correlations with the percentage improvement.

Table (5): Correlation between percentage improvement of Ferriman–Gallwey score and different clinical 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 (6) presents the correlation analysis between percentage improvement in the F–G score and various parameters within each treatment group. Similarly, patient satisfaction was the only variable showing a significant positive correlation with F–G score improvement in both groups (*p* < 0.001). No significant correlations were observed between the percent improvement and other factors such as age, disease duration, or baseline and post-treatment F–G scores (p> 0.05).

Table (6): 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 common clinical condition affecting approximately 10% of premenopausal women and is characterized by excessive terminal hair growth in a

male-pattern distribution [4,10]. Idiopathic hirsutism (IH) is defined by the presence of hirsutism despite normal serum androgen levels, normal ovarian morphology, and preserved ovulatory function [11].

Although the exact pathophysiology of IH remains unclear, several mechanisms have been proposed, including altered adrenal steroidogenesis, increased 5α-reductase activity, and enhanced sensitivity of androgen receptors in hair follicles [12]. The management of hirsutism remains challenging, as therapeutic responses are often variable and relapse may occur after discontinuation of treatment [13].

For moderate hirsutism, the use of combined oral contraceptive pills (COCPs) is typically recommended as first-line therapy. If inadequate improvement occurs after six months, an antiandrogen may be added. Combination therapy with COCPs and antiandrogens is generally more effective than monotherapy [14].

Eflornithine cream, approved for the topical treatment of facial hirsutism, acts by irreversibly inhibiting ornithine decarboxylase, an enzyme essential for the conversion of ornithine to putrescine, which is critical for hair follicle cell proliferation [15]. Spironolactone, on the other hand, exerts its antiandrogenic effects by competitively blocking androgen receptors and inhibiting 5α-reductase activity in a dose-dependent manner [16].

To date, few studies have directly compared these two topical agents for the management of idiopathic hirsutism. The present study aimed to evaluate and compare the clinical efficacy and patient satisfaction of topical spironolactone 5% gel versus topical eflornithine 13.9% cream in 58 female patients with IH.

In this trial, the Ferriman–Gallwey (F–G) scores before treatment was comparable between both groups (Group 1: 11.52; Group 2: 10.59). Following six months of therapy, both groups demonstrated a statistically significant reduction in F–G scores (Group 1: 7.48; Group 2: 7.62; $p = 0.035$). Notably, patients treated with topical spironolactone showed greater improvement and higher satisfaction scores compared with those treated with eflornithine.

The F–G scale remains a widely used and validated method for the assessment of hirsutism [10]. However, it is important to note that racial and ethnic variations may influence terminal hair growth patterns, suggesting that population-specific cutoffs could improve diagnostic precision [17].

Previous studies have demonstrated that systemic spironolactone (typically 100 mg/day) effectively reduces F–G scores in hirsutism, with the response being dose-dependent despite the absence of well-defined dose–response trials [18]. Spironolactone is a well-established diuretic and antiandrogen used for various dermatologic conditions, including acne vulgaris and hirsutism. Even in the absence of overt hyperandrogenemia, androgen-mediated mechanisms are believed to contribute to these disorders, supporting the use of antiandrogens as a safe and cost-effective therapeutic option.

A meta-analysis of 26 clinical trials reported that spironolactone significantly improved F–G scores compared with placebo and was comparable in efficacy to COCPs, while outperforming finasteride [19]. Further research has corroborated its benefit when used alone [20] or in combination with COCPs or finasteride, with combination therapy yielding superior outcomes [21,22].

Erenus *et al*. [23] compared finasteride (5 mg/day) and spironolactone (100 mg/day) in 40 women with IH over nine months. Both groups demonstrated significant reductions in hirsutism scores, with greater improvement observed in the spironolactone group (mean reduction: 42.36% ± 12.31% at nine months). Although mild adverse effects such as transient burning sensations were reported, no participants discontinued treatment.

Similarly, **Lumachi and Rondinone**[24] compared spironolactone (100 mg/day), cyproterone acetate (12.5 mg/day), and finasteride (5 mg/day) and found spironolactone to be the most effective after 12 months, with minimal and reversible adverse effects. Ganie et al. [20] also demonstrated significant F–G score reduction after six months of spironolactone (25 mg/day) compared with metformin (1000 mg/day), although serum testosterone and DHEAS levels remained unchanged.

Regarding eflornithine, a randomized controlled trial evaluating topical eflornithine 13.9% cream showed significant reductions in hair length and mass after 24 weeks of twice-daily application. Clinicians rated approximately one-third of treated patients as having marked improvement and over half as showing moderate improvement compared with placebo [25]. Similarly, **Jackson *et al*. [26]** found that two-thirds of women using eflornithine reported reduced discomfort and cosmetic bother after six months, though this effect diminished within eight weeks of discontinuation.

In another study, the combination of eflornithine cream with laser therapy produced superior results compared to laser treatment alone for upper lip hair removal, achieving complete clearance in 93.5% versus 67.9% of patients, respectively ($p < 0.05$) [27]. The inhibitory effect of eflornithine occurs through the suppression of ornithine decarboxylase and subsequent reduction of polyamine synthesis, which is vital for rapidly proliferating tissues, including hair follicles. Noticeable clinical improvement typically appears after eight weeks of continuous use [28].

Overall, the present study supports that both agents are effective for managing idiopathic hirsutism. However, topical spironolactone 5% gel demonstrated superior clinical efficacy and higher patient satisfaction scores compared with eflornithine 13.9% cream, possibly due to its direct antiandrogenic mechanism at the follicular level.

CONCLUSION

Both topical spironolactone 5% gel and eflornithine 13.9% cream are effective therapeutic options for the management of idiopathic hirsutism, achieving a significant reduction in Ferriman–Gallwey scores after six months of treatment. Nevertheless, topical spironolactone 5% gel provided greater clinical improvement and higher patient satisfaction, suggesting its potential as a superior and well-tolerated alternative for hirsutism management.

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