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Original article

Efficacy of Topical ketoconazole 2% cream in the treatment of Acne Vulgaris: A clinical controlled study

Mohamed Hamed Khater, Amany Essam Elsayed Setto*, Al Shimaa Mohamed Ibrahim
Department of Dermatology, Venerology & Andrology, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:**
Amany Essam Elsayed Setto

Email:
amanysetto395@gmail.com

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ABSTRACT

Background: Cutibacterium (*C. acnes*) lipase activity can be reduced by topical antifungal cream called ketoconazole (KTZ). Additionally, it contains anti-inflammatory and anti-androgenic properties. The aim of this study was to evaluate the efficacy of topical ketoconazole 2% cream versus placebo in the treatment of mild and moderate acne vulgaris. **Patients & Methods:** 40 patients presented by mild and moderate acne were instructed to apply ketoconazole 2 % cream to the right half of the face and placebo to the left half of the face twice daily for 8 weeks **Results:** The mean percent reduction of inflammatory lesions (papules and pustules) and Total lesions count from baseline was significantly higher in ketoconazole than placebo. There was a statistically significant decrease in acne severity assessed by IGA score in both sides. The success rate of ketoconazole was significantly higher than placebo. In ketoconazole side, 17.5% of patients considered clear versus12.5%in control side and 52.5% almost clear versus 35% in control side. There was a statistically significant negative relationship between the therapeutic response and number of pustules in each side. **Conclusion:** Topical ketoconazole 2% can be an effective and safe treatment option for mild and moderate acne vulgaris.

Keywords: Acne, Ketoconazole 2%, Placebo

INTRODUCTION

Acne is a frequent skin disorder that affects pilosebaceous units. Some of the factors linked to the pathophysiology of acne include follicular hyperkeratinization, colonization by Cutibacterium acnes (*C. acnes*), abnormal sebum production, and a neutrophilic and lymphocytic inflammatory response **[1]**.

Numerous hormones that regulate the activity of the sebaceous glands impact the etiology of acne. They include insulin, progesterone, growth hormone, estrogens, androgens, as well as insulin-like growth factor-1 (IGF-1) **[2].**

Several studies have demonstrated that girls with acne have greater androgen levels. Anti-androgen treatments are an effective way to regulate the pathophysiology of acne, which is primarily caused by androgen stimulating sebum production and follicular hyperkeratinization **[3].**

For acne, various therapeutic modalities are employed. Their four distinct methods of action include reducing inflammation, regulating hormones, eliminating C. acnes, and returning follicular keratinization and sebum production to normal **[4]**.

Dermatologists are worried about the development of bacterial resistance and the long-term use of antibiotics for acne. Cream containing topical ketoconazole (KTZ) can lower C's lipase activity. Reduced levels of free fatty acids in sebum and a reduction of comedone production

are the outcomes of acne. It also contains anti-androgenic and anti-inflammatory properties. It has been demonstrated that Malassezia has a role in the etiology of *C.acnes*, hence it is a helpful treatment for the condition. Furthermore, the in vitro study showed that KTZ inhibited the growth of C. and was effective against isolates that were resistant to antibiotics *C.acnes* **[5, 6]**. This study was conducted to evaluate the efficacy and safety of topical 2% ketoconazole cream versus placebo in the treatment of mild and moderate acne vulgaris.

PATIENTS AND METHODS

This split face controlled study was conducted in the Out-patient Clinic of Dermatology, Venereology and Andrology Department at Zagazig University Hospitals during the period from March 2022 to March 2023. Written consent was taken from each patient before involvement in the study .this study was approved by Zagazig University Institutional Review Board (IRB#9422).

This study included 40 adult patients of both sexes with mild and moderate Acne vulgaris according to IGA score. Exclusion criteria included pregnancy, lactation, patients with history of acne treatment within last 3 months, and patients with systemic diseases or hepatic disorders.

All patients were subjected to proper dermatological examination for characteristics of the acne lesions including types (comedones, papules and pustules), number and distribution at the start of the study and at each follow-up visit.

Materials:

The materials used in the present study were Ketoconazole 2 % was supplied in the form of cream under the name of wellofung (Health well Egypt for pharmaceuticals) and Placebo was prepared in the faculty of Pharmacy Zagazig University. It is composed of stearic acid which was melted on a water bath until it reached a temperature of 80°C in a porcelain dish. In a separate beaker, potassium hydroxide (KOH) was dissolved in water (emulsifying agent) and glycerin was added to the solution, which was then heated to 80°C. The contents from that beaker were gradually added to the stearic acid solution while both were maintained at 80°C, and the mixture was continuously stirred for 5 minutes within the water bath. Subsequently, the mixture was removed from the water bath while the triturating process was continued. Finally, the resulting cream was transferred to a suitable container and stored adequately until used.

Methods:

All patients were instructed to apply ketoconazole 2 % cream to the right half of the face and placebo to the left half of the face twice daily for 8 weeks.

Assessment of Clinical response and follow up:

Photographs were taken at each treatment session and at follow up 1month after the end of treatment. Total lesions count (TLC) and Investigator Global Assessment (IGA) score **[7]** were calculated for each patient on the right and the left face before and after the course of treatment.

Statistical Analysis:

Version 26 of the SPSS (Statistical Package for the Social Sciences) program was used to analyze the data. When comparing categorical variables, the chi square test and, when necessary, the Fisher exact test were used to characterize the variables according to their absolute frequencies. The independents sample t test (for normally distributed data) and the Mann Whitney test (for non-normally distributed data) were used to compare quantitative data between two groups. In the case of qualitative and non-normally distributed data, the Wilcoxon signed rank test was employed to compare changes in a single variable over two time periods within the same group. The level statistical significance was set at $P<0.05$. Highly significant difference was present if $p\leq0.001$.

RESULTS

This study included 40 patients with age range from 13 to 26 years with mean age 18.83 years ±2.85. Female represented 82.5% of them. The duration of acne in our patients ranged from 3 to 15 months with mean 8.42 months. Positive family history was reported in 47.5% of patients.

According to severity, 67.5% had mild disease and 32.5% had moderate disease (Table 1).

After treatment, there was a statistically significant decrease in total lesion counts in both sides. TLC significantly decreased in ketoconazole side more than control side (P<0,001) (Table 2).

The mean percent reduction of inflammatory lesions (papules and pustules) and T.L.C from baseline was significantly higher in ktz than placebo (Table 3).

Assessment of acne severity at the end of treatment according to IGA scores:

After treatment there was a statistically significant decrease in acne severity assessed by IGA score in both sides. The improvement of acne was significantly higher in treatment side than control side. In ketoconazole side, 17.5% of patients considered clear (versus12.5%in control side) and 52.5% almost clear (versus 35%in control side) (Table 5). The success rate of ketoconazole was significantly higher than placebo (70% versus 47.5%) **(**Table 4**).**

There was a statistically significant negative relationship between the therapeutic response and number of pustules in each side. The relationship between the therapeutic response and the number of papules, comedones and T.L.C wasn't statistically significant.

Adverse effects: All side effects were mild and well tolerated. Redness was reported in (45% within Ketoconazole group versus 7.5% within control group), peeling (12.5% within Ketoconazole group versus 0% within control group) and dryness (15% within Ketoconazole group versus 0% within control group) as shown in table 5.

Case Presentation:

Figure ligands: Female patient presented by mild acne vulgaris showing excellent therapeutic response. Rt side treated by ketoconazole and Lt side treated by placebo) (A ,C before treatment), (B,D after treatment) **figure (1)**.

Figure (2): male patient presented by moderate Acne vulgaris showing excellenttherapeutic response. (Rt side treated by ketoconazole and Lt side treated by placebo) (A ,C before treatment), (B,D after treatment).

Table (1): Distribution of studied patients according to demographic data:

	N=40	**%**
Gender:		
Female **Male**	33 7	82.5% 17.5%
	Mean ± SD	**Range**
Age (year)	18.83 ± 2.85	13 – 26
Occupation:		
Housewife **Student**	5 35	12.5% 87.5%
Disease severity:		
Mild **Moderate**	27 13	67.5% 32.5%
Family history:		
Negative **Positive**	21 19	52.5% 47.5%
	Mean ± SD	**Range**
Disease duration (month)	8.42 ± 3.4	3 – 15

Table (2): Number of acne lesions among studied patients before and after treatment

	Ketoconazole (right side) (n=40)	Control (left side) (n=40)	Z	p
	Median (IQR) Range	Median (IQR) Range		
Comedones				
Before:	11(7 – 18) 2 – 40	15(6.25 – 20) 3 – 50	-2.257	0.024*
By the end	7(3 – 10) 0 – 40	9(4 – 13) 0 – 50	-3.912	<0.001**
P(Z)	**<0.001****	**<0.001****		
Papules				
Before:	6.5(4.25 – 8) 2 – 20	4(2 – 6.75) 1 – 14	-4.16	<0.001**
By the end:	3(1.25 – 4) 0 – 8	3(2 – 4) 0 – 6	-0.138	0.890
P(Z)	**<0.001****	**<0.001****		
Pustules				
Before:	5(2.25 – 8) 0 – 12	5(3 – 9.5) 1 – 17	-1.72	0.085
By the end:	0(0 – 1) 0 – 5	0 (0 – 2.75) 0 – 7	-0.142	0.887
P (Z)	**<0.001****	**<0.001****		
Total lesion count				
Before:	21(14 – 29) 7 – 57	26(17 – 39.5) 11 – 65	-3.328	<0.001**
By the end:	9.5(5.25 – 18.75) 2 – 48	12.5(6.25 – 15) 2 – 57	-5.513	<0.001*
P (Z)	**<0.001****	**<0.001****		

Z Wilcoxon signed rank test *p<0.05 is statistically significant

**p≤0.001 is statistically highly significant IQR interquartile range

Table (3): Percent reduction in acne lesions among studied patients by the end of therapy

	Ketoconazole group (n=40)	Control group (n=40)	Wx	p
Comedeones	50% (19.89 – 60%)	35% (16.67 – 53.33%)	-0.672	0.502
Papules	52 (33.3 – 80%)	40% (0 – 65%)	-4.076	<0.001**
Pustules	100% (71.7 – 100%)	57.74% (36.46 – 87.5%)	-3.624	<0.001**
Total lesion count	53.11 (38.27–69.99%)	48.46 (29.47–66.67%)	-2.017	0.044*

*p<0.05 is statistically significant **p≤0.001 is statistically highly significant IQR interquartile range Wx Wilcoxon signed rank test

Table (4): Acne severity among studied patients before and by the end of therapy

Acne severity assessed by IGA	Ketoconazole side (n=40)	Control side (n=40)	χ^2	p
Before:				
Mild **Moderate**	27 (67.5%) 13 (32.5%)	27 (67.5%) 13 (32.5%)	0	>0.999
By the end:				

Clear **Almost clear** **Mild**	7 (17.5%) 21 (52.5%) 12 (30%)	5 (12.5%) 14 (35%) 21 (52.5%)	3.025	0.082
P (Z)	**<0.001****	**<0.001****		
By the end:				
Succeed **Failed**	28 (70%) 12 (30%)	19 (47.5%) 21 (52.5%)	4.177	0.04*

Z Wilcoxon signed rank test χ^2Chi square test

Table (5): Relation between therapeutic response and acne severity

	Ketokonazole (right side)			**Control (left side)**		
	Median (IQR)	**Z**	**p**	**Median(IQR)**	**Z**	**p**
Comedenoes						
Mild **Moderate**	33.3(18.2 – 60) 50(46.67 – 61.25)	-0.713	0.476	35(26.7 – 60) 14.29 (0 – 53.33)	-1.246	0.213
Papules						
Mild **Moderate**	50(33.3 – 100) 73.3(33.04 – 80)	-0.015	0.988	40(0 – 100) 40(8.3 – 54.76)	-0.452	0.651
Pustules						
Mild **Moderate**	100(100 – 100) 66.7(50 – 89.29)	-4.133	<0.001**	75(50 – 100) 37.5(27.5 – 54.17)	-2.943	0.003*
Total count						
Mild **Moderate**	52.38(44 – 70.33) 63.6(26.3 – 72.3)	-0.578	0.563	50(29.41 – 71.43) 45.45(29.6 – 57.7)	-0.824	0.41

*p<0.05 is statistically significant **p≤0.001 is statistically highly significant IQR interquartile range Z Mann Whitney test

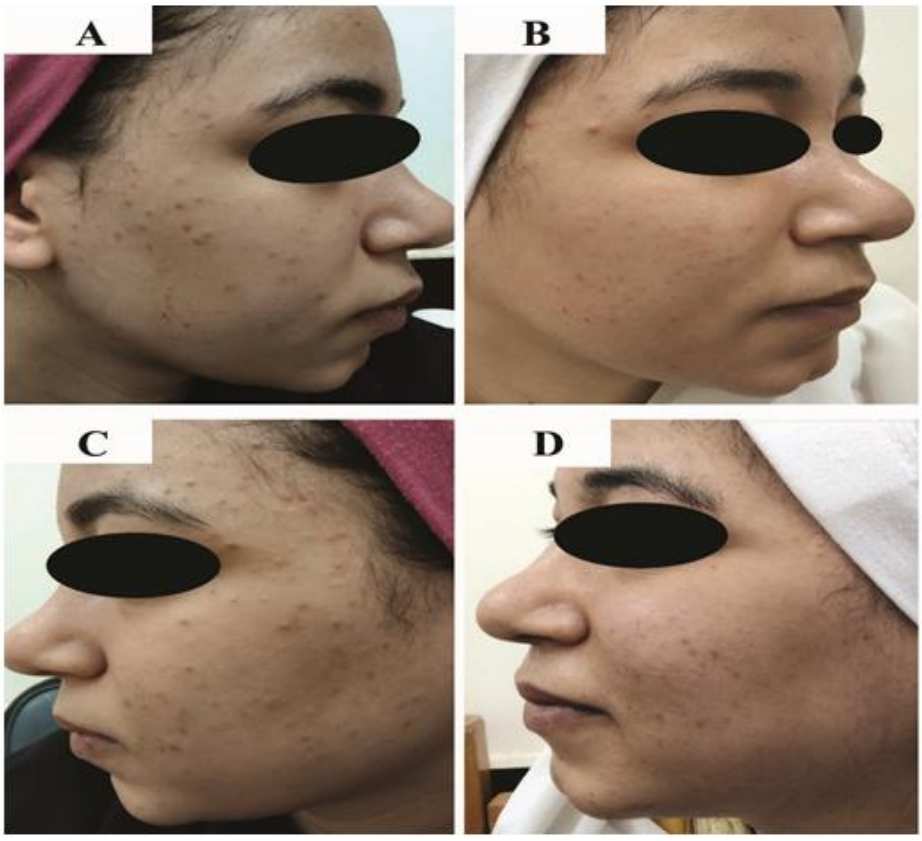

Figure 1: Female patient presented by mild acne vulgaris

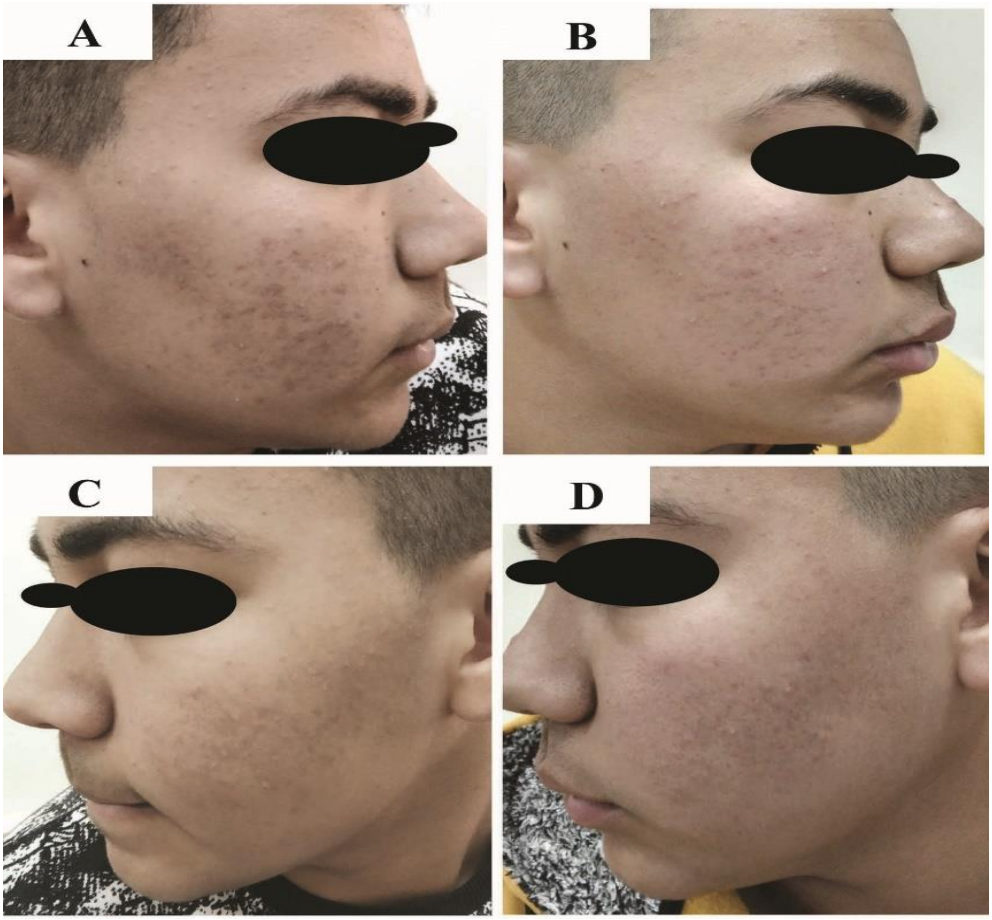

Figure 2: Male patient presented by moderate Acne vulgaris

DISCUSSION

This split face controlled study was conducted to evaluate the efficacy and safety of topical 2% ketoconazole cream versus placebo in the treatment of mild and moderate acne vulgaris. At end of study, there was a high statistically significant decrease in the number of all acne lesions (comedones, papules and pustules) in both sides. The number of comedones and TLC significantly decreased in ketoconazole side more than control side.

Assessment of IGA score after treatment revealed improvement of acne more in treatment side than control side. In ketoconazole side, 17.5% of patients considered clear and 52.5% almost clear .The success rate of ketoconazole was 70% versus 47.5% success rate of placebo. In both sides, there was a statistically significant negative relationship between the therapeutic response and number of pustules, however, the relationship between the therapeutic response and number of papules, comedones and TLC wasn`t statistically significant.

The improvement of acne lesions in placebo side may return to extension of the effect of topical ketoconazole to whole face, incompliance of some patients who used ketoconazole on both sides, or due to improvement of psychological condition of patients with treatment.

According to our research, **Chottawornsak et al. [6]** found that adult female patients' acne counts were significantly lower in the KTZ 2% cream group at week 8 when compared to the placebo group. Additionally, KTZ treatment had a success rate that was three times higher than the placebo group (45% versus 14.3%), and comedon counts were decreased more than inflammatory lesions.

Furthermore, **Anwar et al. [8]** found that adult female patients treated with ketoconazole 2% cream for eight weeks experienced a much larger reduction in acne lesions compared to those who received a placebo for a comparable length of

time (46.7% success rate against 13.3% in the control group). Topical KTZ has been proposed as the preferred treatment choice for adult female acne patients by **Chottawornsak et al. [6] and Anwar et al. [8].**

The success rate of KTZ in this investigation was more than that of studies by **Anwar et al. [8]** and **Chottawornsak et al. [6]** (70%, 45%, and 46.7%, respectively). The observed variation in the therapeutic response assessment tools (IGA score in our study versus Adult Female Acne Scoring Tool) between **Chottawornsak et al. [6]** and **Anwar et al. [8]** may be the cause of this, as both studies used ketoconazole exclusively for the treatment of acne in adult female patients, whereas our approach treats acne in both male and female patients across various age groups.

Regarding our results, all side effects were mild and well tolerated by all patients. The common side-effects found in the KTZ group were erythema, dryness and desquamation which spontaneously resolved without discontinuation of the treatment. This came in accordance with **Chottawornsak et al. [8]** who demonstrated absence of serious or major adverse effects after 2% topical KTZ treatment.

Androgens stimulate the sebaceous glands, making them produce more sebum. This excess sebum blocks the sebaceous duct, making a good media for *C.acne* **[9].**

The two oral anti-androgens that are most frequently recommended are spironolactone and contraceptive tablets (cocs). However, systemic exposure to oral anti-androgens increases the risk of potential adverse effects, including as nausea, hyperkalemia, dizziness, breast enlargement, and irregular menstruation **[10]**.

Topical clascoterone and topical spironolactone are types of topical anti androgen that can be used in the treatment of acne vulgaris.

With (95%) IGA success rates, topical clascoterone exhibits a statistically significant decrease in both inflammatory lesion counts (ILCs) and non-inflammatory lesion counts (NILCs) **[11,12] .**

Our study indicates that the side effects of topical clascoterone, including as dryness, scaling, erythema, and irritation, were well tolerated. On the other hand, topical ketoconazole is far less expensive than clascoterone **[11]**.

The antilipase activity and antiandrogenic effect of topical KTZ are proposed mechanisms of action for its anti-acne effects. One of the virulence factors of Candida acnes that promotes follicular hyperkeratosis and inflammation is lipase. KTZ suppresses the production of comedones and lowers the amount of free fatty acid in sebum by inhibiting the lipase activity of *C.acnes* that is both susceptible to and resistant to antibiotics **[13].** KTZ also affect lipase activity of malassezia which has higher lipase activity than *C.acnes*. Refractory acne and other related facial dermatoses, such as seborrheic dermatosis, are linked to malassezia**[6].**

CONCLUSION

These findings suggest that individuals with acne can benefit from topical KTZ, particularly if they are worried about skin irritation from existing topical anti-acne treatments. When used in conjunction with other treatments, this could lead to the best possible acne management.

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