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A Comparative Study of a Topical Active Lotion Containing Triethyl Citrate and Ethyl Linoleate and Clindamycin Solution 1% in the Treatment of Mild to Moderate Acne Vulgaris

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Abstract:
Background: *Acne vulgaris is a major clinical problem; despite a vast array of treatment modalities available for acne, there is considerable dissatisfaction in acne treatment among patients and doctors. Rising antibiotic drug resistance consequent to the widespread use of topical antibiotics is causing concern and effective non-antibiotic treatments are needed.*
Objective: *To compare the effectiveness and side effects of topical clidamycin solution 1% versus active lotion containing triethyl citrate and ethyl linoleate (TCEL)in treatment of mild to moderate acne vulgaris.*
Patients and Methods: *This single, blinded, comparative, therapeutic study was done in the Department of Dermatology – Baghdad Teaching Hospital, Baghdad, Iraq; from May 2013- July 2014. Scoring of acne was carried out and the patients were examined every 2 weeks for 10 weeks of treatment. One month after stopping drugs, patients were evaluated for drug complications and disease recurrence.*
Sixty patients fulfilling enrollment criteria were included in this study. Acne was scored according to Global Acne Grading System (GAGS). Patients were divided into2 groups: ***Group A*** *(**30** patients) treated twice daily with TCEL lotion and* ***Group B*** *(**30**patients) treated twice daily with topical clidamycin solution 1%.*
Results*: In* ***Group A****, the GAG score diminished significantly after 4 weeks (P value **0.04**) and continued to decrease till the end of treatment. In* ***Group B****, the GAG score diminished significantly after 6 weeks (P value 0.046) and continued to decrease till the end of treatment. The percent reduction rate of GAG score from baseline visit up to 10 weeks of treatment for* ***Group A*** *were **33.4%**,* ***Group B*** *were **36.4%.** Both topical TCEL lotion and clindamycin solution were statistically an effective therapy for treatment of mild to moderate acne vulgaris.*
Conclusion*: TCEL lotion is non-antibiotic based, more effective, had quicker onset of action than clindamycin solution and observable improvement of both inflammatory and non-inflammatory acne lesions. Its use would reduce the risk of antibiotic resistance developing within the skin flora.*
Key words: *acne vulgaris, inflammatory, TCEL, clindamycin.*

I. Introduction

Acne vulgaris is the most common chronic inflammatory skin disease. It affects all ages but mainly young people at the sensitive period of puberty and can have an adverse effect on their psychological development, which may lead to social phobias, withdrawal from society and clinical depression.[1–3]
Current treatments for acne include: topical antimicrobials, topical and systemic antibiotics and retinoids . All acne treatments have potential side-effects, some of which may be severe. Topical and oral antibiotics generally need to be used for several months to achieve a response, which leads to major problems with patient compliance. In addition to possible side-effects, long-term exposure to antibiotic has exerted enormous selective pressure on the bacterial skin flora of patients with acne, with the emergence of antibiotic resistant propioni bacteria[4–6].

This has emphasized the need to develop new therapeutic options for the treatment of acne which are preferably non-antibiotic.

For this reason this study was arranged to assess the efficacy and tolerability of a topical lotion composed of 1%triethyl citrate and ethyl linoleate (TCEL lotion) as the active agents in the treatment of mild to moderate acne vulgaris in comparison with topical clindamycin solution .

II. Patients and Methods

This single, blinded, comparative, therapeutic study was carried out at the Department of Dermatology– Baghdad Teaching Hospital-Baghdad, Iraq from May 2013 - July 2014. Sixty patients were included in this study.

Full history was taken from each patient including: age, gender, duration of disease and previous treatment. Physical examination was done to evaluate the severity of acne.

Inclusion criteria were mild to moderate acne vulgaris.

Exclusion criteria were severe and nodulocystic acne, coexistence of any other dermatoses involving the face and allergy to medications, plus patients who had used any topical and systemic treatment in the previous two months, pregnant and lactating women.

Acne was scored according to Global Acne Grading System (GAGS). [59] GAGS is a quantitative scoring system in which the total severity score is derived from summation of six regional sub-scores. Each is derived by multiplying the factor for each region (factor for forehead and each cheek is 2, chin and nose is 1 and chest and upper back is 3) by the most heavily weighted lesion within each region (1 for ≥ one comedone, 2 for ≥ one papule, 3 for ≥ one pustule and 4 for ≥ one nodule). Final score was calculated according to global score as shown in Table -1.

Table- 1: Global Acne Grading System (GAGS).

Global score	Grade	Severity
0	**0**	None
1-18	**1**	Mild
19-30	**2**	Moderate
31-38	**3**	Severe
≥39	**4**	Very severe

Formal consent was taken from each patient before starting the trial of treatment, after full explanation for the nature of the disease, course of treatment, prognosis and complications, the target of the present work regarding the drug, its efficacy, side effects, the method and duration of treatment and follow up as well as the need of pre and post-treatment photographs. Ethical approval was confirmed from Scientific Council of Dermatology and Venereology Iraqi board for Medical Specializations.

Patients with mild to moderate acne vulgaris were divided into two groups:

Group A: Patients were treated with TCEL ® (Active lotion containing triethyl citrate and ethyl linoleate) Produced by: General Topics s.r.l, Salo' Italy. In this group 30 patients were instructed to apply TCEL lotion twice daily for 10 weeks. Clinical evaluation was done every two weeks till the end of the 10^{th} week . Then patients were asked to stop the use of medication to be re-evaluated again after one month without any treatment to show any relapse. The assessment was carried out by (GAGS).

Group B: Patients treated with clindamycin phosphate solution 1% [(Klicoin - T)^{R} Produced by: ALHAYANI Co., Damascus, Syria. In this group 30 patients were treated in the same manner as in **Group A** patients. Side effects were recorded at each visit for both groups.

Quality of life before and at the end of therapy was measured using the Cardiff Acne Disability Index (CADI) [4] Quality of life before and at the end of therapy was measured using the Cardiff Acne Disability Index (CADI) [4] which is a five-item questionnaire. Questions 1 ("As a result of having acne, during the last month have you been aggressive, frustrated, or embarrassed?") and 4 ("How would you describe your feelings about the appearance of your skin over the last month?") measure feelings, questions 2 ("Do you think that having acne during the last month interfered with your daily social life, social events or relationships with members of the opposite sex?") and 3 ("During the last month, have you avoided public changing facilities or wearing swimming costumes because of your acne?") measure social functioning, and question 5 ("Please indicate how bad you think your acne is now") measures perceived severity. Each question contains 4 possible answers with a score of 0~4. The CADI score is calculated by summing the score of each question resulting in a possible maximum score of 15 and a minimum score of 0. We would recommend that if one item is not answered, that item should be scored zero and the score for that completion would be the sum of the scores of the other four items (not adjusted). If more than one item is not scored, the questionnaire cannot be scored and the entire score should be set to "missing". A score of 0~5 translates to mild quality of life impairment, 6~10 indicates moderate impairment, and 11~15 demonstrates severe impairment.

Color photographs for each patient were obtained by using Sony-digital, high sensitivity, 16.1 megapixel camera with fixed illumination and distance.

Statistical analysis of data was carried out using the statistical package of SPSS-20 (Statistical Packages for Social Sciences- version 20). Data were presented in simple measures of frequency, percentage, mean and

standard deviation. Comparison between groups was done by using independent sample t-test. Comparison before and after treatment in each group was done by using paired t-test, comparison of reduction rate of the lesions in both groups was done by using chi- square, and P-value < 0.05 was considered as the level of significance.

III. Results

***Demographic data:**

Patients in **Group A,** their mean age ± SD was 20.33±3.85 years, 21 were females and 9 were males with female to male ratio 2.3:1; **Group B**, their mean age ± SD was 19.97±3.47 years, 17 were females and 13 were males with female to male ratio 1.3:1.

The mean ± SD of duration of acne in patients within **Group A** was 11.1±5.58 weeks, and the mean ± SD for those in **Group B** was 10.70±5.09 weeks. Both groups were statistically matched regarding age, gender and duration of the disease **.**

***GAG Score**

In **Group A** (**TCEL lotion**), the GAG score diminished after 2 weeks of treatment from 24.03±5.07 to 22.10±5.28 but this reduction was not statistically significant (P value **0.15**). At the fourth week the GAG score was **19.53±5.35** which was statistically significant when compared to baseline (P value **0.04**). The GAG score continued to decrease till it became 18.23±6.03 at sixth week, 17.47±6.73 at 8^{th} week and 16.00±6.13 at 10^{th} week (P value 0.016, 0.001, 0.0001 respectively) (**Table-1**)(Figur-1).

In **Group B** (**Clindamycin solution**), the GAG score diminished after 2 weeks of treatment from 22.33±7.28 to 21.07±7.17 but this reduction was not statistically significant (P value 0.33). At the fourth week the GAG score was 18.73±6.78 which was statistically not significant when compared to baseline (P value **0.71**). The GAG score continued to decrease till it became 17.30±6.79 at sixth week, 16.37±7.22 at 8^{th} week and 14.20±6.72 at 10^{th} week and in all these three visits where statistically significant when compared to baseline (P value 0.046, 0.012, 0.001 respectively) (**Table-1**) (Figur-2).

***Percent reduction**

The percent reduction rate of GAG score from baseline visit up to 10 weeks of treatment for **Group A** were **33.4%**, **Group B** were **36.4%** (**Table-2**).

IV. Patient satisfaction:

Subjective improvement of acne was measured by using Cardiff Acne Disability Index (CADI); quality of life of patients in all groups showed less impairment at end of treatment in comparison with that at the starting of therapy (p value < 0.014 for **Group A**, 0.049 for **Group B**. When comparing all groups, patients treated with TCEL had lower CADI than other groups

Relapse rate:

After one month of follow up, there was no significant relapse in all groups as the GAG score did not increased significantly. In Group A it was 16.00±6.13 at the end of the 10 week of treatment and became 16.27±5.84 after 4 weeks following stopping of treatment. In Group B it was 14.20±6.72 and became 14.43±6.66 after stopping treatment. (p value= 0.43 in **Group A**, and 0.83 in **Group B**) which is not significant.

Side effects:

The assessment of local side effects for **Group A** showed burning in 10(33.3%) patients, flare-up in 2(6%), dry skin in 9 (30%), pruritus in 12 (40%) and erythema in 6 (20%) patients. All these symptoms disappeared after 8 weeks from starting treatment. The assessment of local side effects for **Group B** showed burning in 8 (26.7%) of patients, erythema 4 (13.3%), scaling 8 (26.7%), dry skin 6 (20%) and pruritus 6 (20%). All these symptoms disappeared after 8 weeks from starting treatment. For patients in all groups, the side effects did not necessitate stopping the treatment **.**

Table-1: Global Acne Grading System for patients in Group A (TCEL lotion), Group B (Clindamycin solution) at each visit (2 weeks interval).

	GAG Score (Mean ± SD)	
	Group A	**Group B**
Baseline	24.03±5.07	22.33±7.28
After 2 weeks	22.10±5.28	21.07±7.17
	*P=0.15	*P=0.33
After 4 weeks	19.53±5.35	18.73±6.78
	***P=0.04**	*P=0.71
After 6 weeks	18.23±6.03	17.30±6.79
	***P=0.016**	***P=0.046**
After 8 weeks	17.47±6.73	16.37±7.22
	***P=0.001**	***P=0.012**
After 10 weeks	16.00±6.13	14.20±6.72
	***P=0.0001**	***P=0.001**

***Statistically different from the 1st visit within the same group (paired t test).**

Table-2: Showing percent reduction rate for Group A (TCEL lotion), Group B (Clindamycin solution) at each visit (2 weeks interval).

Visits	Group A	Group B
Baseline	**0**	**0**
After 2 weeks	**8%**	**5.6%**
After 4 weeks	**18.7%**	**16.1%**
After 6 weeks	**24.1%**	**22.5%**
After 8 weeks	**27.3%**	**26.7%**
After 10 weeks	**33.4%**	**36.4%**

*Percent réduction = (**X-Y)/X***100, **X** is an initial value, **Y** is a final value

Table-3: The Cardiff Acne Disability Index for groups before and at the end of treatment.

Cardiff Acne Disability Index		CADI Pre-treatment		CADI Post-treatment		*P value
		N	%	N	%	
TCEL lotion	Mild impairment	**0**	**0.0%**	**12**	**40.0%**	**0.014**
	Moderate impairment	**15**	**50.0%**	**18**	**60.0%**	
	Severe impairment	**15**	**50.0%**	**0**	**0.0%**	
Clindamycin solution	Mild impairment	**0**	**0.0%**	**3**	**10.0%**	**0.049**
	Moderate impairment	**9**	**30.0%**	**22**	**73.3%**	
	Severe impairment	**21**	**70.0%**	**5**	**16.7%**	

***Using Mann-Whitney Test for ordinal data.**

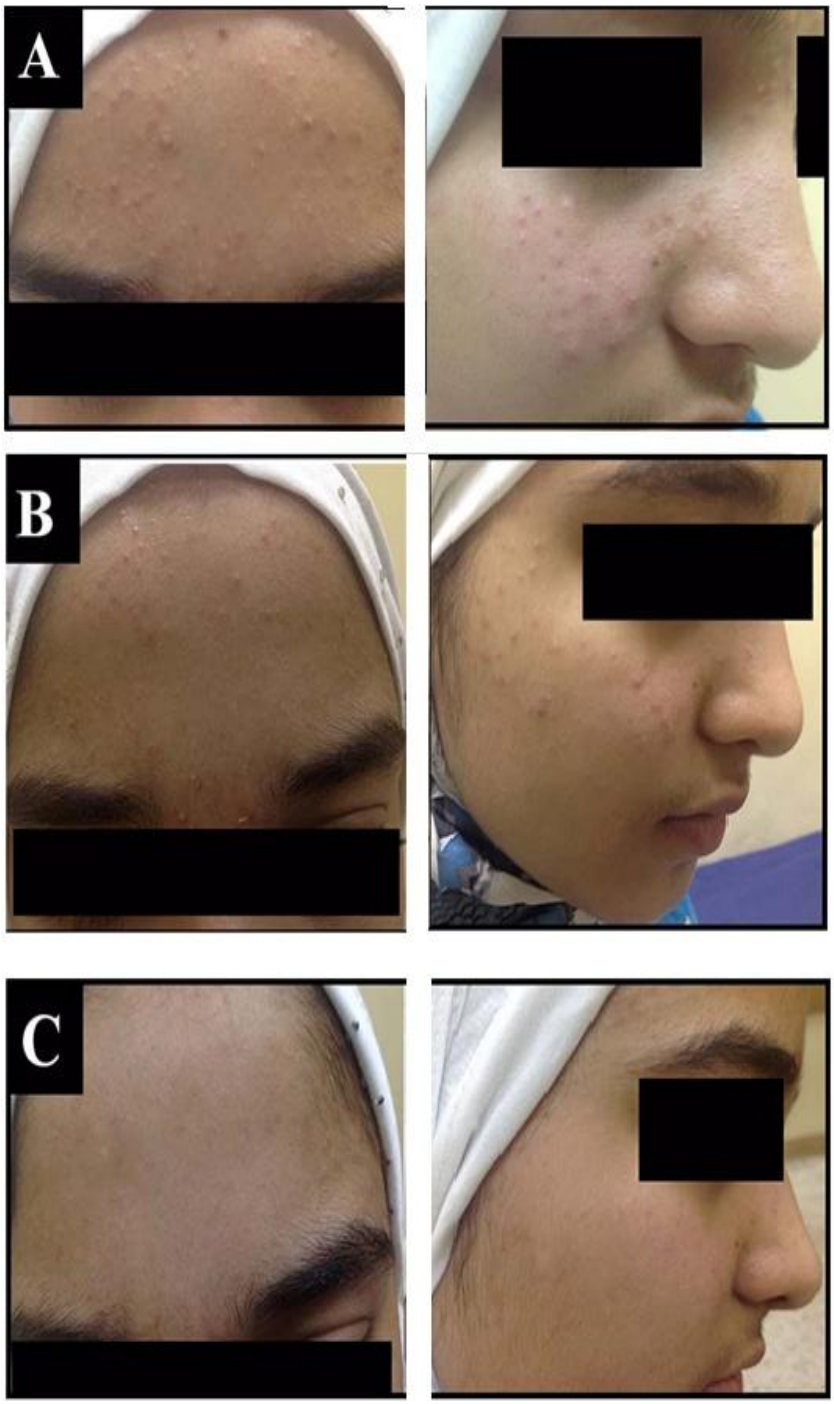

Figure-1: Seventeen years old female with moderate acne vulgaris (**A**) Before treatment, **(B)** after 4 weeks and (**C**) 10 weeks after treatment with topical Aknicare cream.

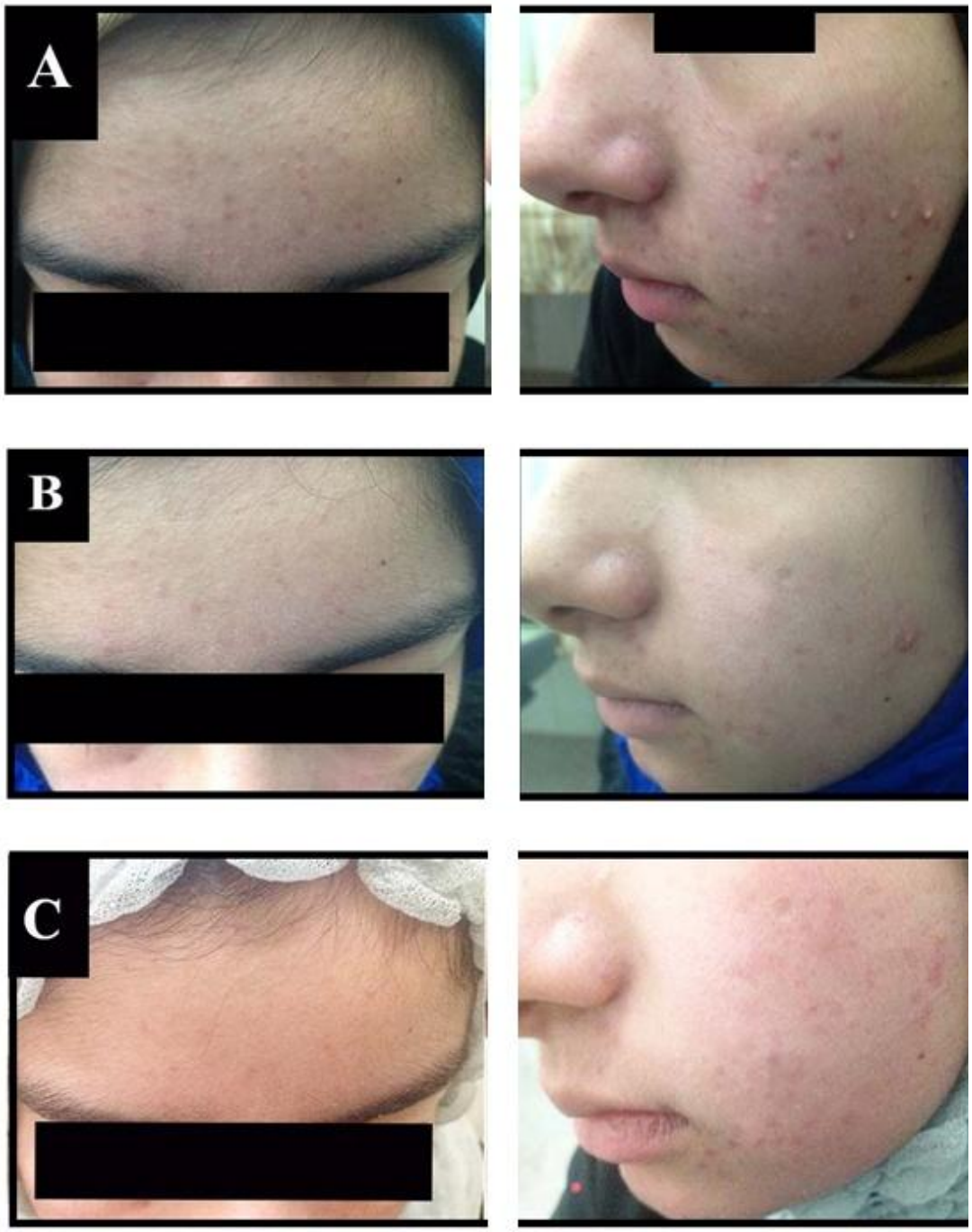

Figure-2: Twenty years old female with moderate acne (**A**) Before treatment, **(B)** after 4 weeks and (**C**) 10 weeks after treatment with topical clindamycin solution 1%.

V. Discussion

Acne vulgaris remains one of the most common diseases afflicting human being and it is the skin disease most commonly treated by physicians. [1, 2] Topical antibiotics are the main stay for mild to moderate inflammatory acne vulgaris. [6]

This study demonstrates that this new lotion containing triethyl citrate which is an ester of citric acid and ethyl linoleate which is an essential fatty acid (TCEL) is an effective and well-tolerated topical agent in the treatment of mild to moderate acne vulgaris. The use of lotion twice daily for 10 weeks was associated with significant improvement in acne severity.

The combination of ethyl linoleate and triethyl citrate can reduce the hyperkeratinization of the pilosebaceous duct, the bacterial colonization of the infundibulum by Propioni bacterium acnes and seborrhoea, targeting the different steps in the pathogenesis of acne. [7, 8, 11-13]

The exact mechanism of action in the treatment of acne is not yet known. The antimicrobial, anti-keratinization, and anti-inflammatory effects have been implicated. The antimicrobial action may be related to inhibition of microbial cellular protein synthesis.

Clindamycin solution also was effective in clearing acne. However TCEL lotion seem to act quicker, the GAG score was significantly reduced in Group A in the 4 week of treatment, while in Group B was significantly reduced from the 6 week of treatment.

Mild side effects appear of both drugs like burning pruritis and dry skin which disappear after 8 weeks of treatment, and there were no significant relapse in both groups after 4 weeks of follow up.

These results are comparable to other studies. As Charakida A et al showed that TCEL lotion had significant reduction of inflammatory acne lesions within 4 weeks of treatment. [(7)] Akamatsu H et al also showed significant reduction in inflammatory lesion count within the same period. [(8)]

Schachner L etal showed that clindamycin solution had significant reduction of inflammatory acne lesions. [(9)] Alirezaï M et al also showed 65% reduction in inflammatory lesion count with both clindamycin 1% water-based gel and solution. [(10)]

So in conclusion ,TCEL seems to be a promising drug in the treatment of acne vulgaris because of its effectiveness, quicker action, minimum side effects and low relapse rate since it is not antibiotic, it doesn't induce bacterial resistance.

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