Effect of topical nicotinamide 4% gel versus topical clindamycin 1% gel for mild to moderate acne treatment: a comparative study

Ahmed Aladl [a], MD; Al-Sadat Mosbeh [a], MD, Ola O. Abou Zeid [b], MD; and Mohamed L. Elsaie [b], MD

a. Department of Dermatology, Venereology and Andrology, Al-Azhar University, Egypt

b. Department of Dermatology, Medical Research and Clinical Studies Institute; National Research Centre, Egypt.

Corresponding Author

Mohamed L. Elsaie

Egydoc77@yahoo.com (ME)

ORCID ID: 0000-0001-7541-5241

Short title: Nicotinamide for acne

Abstract:

Background Acne vulgaris is a common inflammatory skin disease affecting the pilosebaceous units of the skin in which propionibacterum acnes (P. acne) is one of the primary factors involved in its pathogenesis. **Aim** we aimed to evaluate the effectiveness of topical nicotinamide 4% gel versus topical 1% clindamycin gel for the treatment of mild to moderate acne vulgaris. **Methods** A total of 76 patients suffering from mild to moderate acne vulgaris were randomized to receive either 1% clindamycin gel or 4% nicotinamide gel, which were applied twice daily for a period of 8 weeks. The cases were diagnosed clinically and the degree of acne severity and side effects were assessed. **Results** This study revealed that the improvement of disease severity was better with using topical nicotinamide 4% gel than topical clindamycin 1% gel but with no statistically significant difference between the two groups. No significant side effects were

reported among both groups. **Conclusion** Topical nicotinamide 4% preparation may be a good adjuvant to the 1% clindamycin gel treatment regimens

Key words:

Acne vulgaris , clindamycin, propionibacterum acnes.

Introduction

Acne vulgaris, disease is an extremely common chronic inflammatory disease of pilosebaceous follicle typically manifest during adolescence, though it can occur in all ages. While the pathogenesis of acne vulgaris is complex, the basic physiology is widely accepted, as, blocked sebaceous follicles combined with excess sebum production.[2] Increasing in inflammatory cytokines and free fatty acids caused by Proliferation of Propionobacterium acnes (P. acnes), then leads to further irritation. Studies suggest genetic, neuroendocrine, and dietary factors may also contribute to the multifactorial process of acne vulgaris pathogenesis.[4]

Acne may be inflammatory (papular or pustular acne) or noninflammatory, either in the form of an open or closed comedo. Nodulocystic acne is a more severe form of acne that is characterized by nodules or cysts, and this form of acne especially has a propensity to cause scarring.[5] Pityrosporum folliculitis, also known as fungal acne, is caused by infection of hair follicles with Malassezia furfur or other forms of Malassezia. Pityrosporum folliculitis may appear clinically similar to acne vulgaris but is treated with antifungal agents and is often exacerbated if traditional acne treatments are used.[6]

Topical or oral treatments may be administrated for the Treatments of acne vulgaris by targeting one or more of the steps in pathogenesis. Three topical antibiotics are approved by the United

States of America Food and Drug Administration (FDA) to treat acne: clindamycin, erythromycin, minocycline.[7]

Topical antibiotics are considered first-line treatment for acne.[8] Nicotinamide provides potent anti-inflammatory properties without the risk of bacterial resistance and systemic side effects and represents a potential treatment modality for acne vulgaris. Nicotinamide also known as Niacinamide is a form of vitamin B3, which is an essential water-soluble nutrient present in a variety of foods.[9-14] Moreover nicotinamide decreases the in vitro secretion of interleukin-8, a cytokine secreted by keratinocytes in response to pathogens (including P. acnes), thereby exerting an anti-inflammatory effect through inhibition of leukocyte chemotaxis.[15-16]

The purpose of the study was to compare topical nicotinamide 4% gel to topical clindamycin1% gel in order to determine the effectiveness and side effects of each in treating mild to moderate inflammatory acne vulgaris.

Patients and Methods

The study followed the Helsinki declaration principles and ethical approval was obtained from the institutional review board of faculty of medicine (Al-Azhar University). Written informed consent was obtained from every patient or their guardians before recruitment. Patients were included if they have mild to moderate acne vulgaris. All patients should have inflammatory papular and pustular facial lesions with no improvement to conventional treatments. We exclude Patients with comedones, macules and severe nodulocystic acne, pregnant women, lactating mothers, patients who were unable to follow up according to the study protocol, who were allergic to nicotinamide or clindamycin and chemical peels, within 2 weeks prior to the study.

The study included seventy six patients who were divided into two groups. **Group a** included thirty eight patients who applied nicotinamide 4% gel twice daily for 2 months (4 males and 34 females) while **group b** included thirty eight patients who applied clinadamycin monophosphate 1% gel twice daily for 2 months.

The cases were diagnosed clinically and the degree of acne severity was scored at the start of study and at every visit using the global classifications of dermatologists correlated with numbers of inflammatory eruptions (papules plus pustules). The appropriate divisions of inflammatory eruptions of half of the face to decide classifications were: 0-5, "mild"; 6-20, "moderate"; 21-50, "severe"; and more than 50, "very severe".[8]

Treatment efficacy was determined by counting inflammatory lesion (papules and pustules) in the whole face. Macules, comedones and deep inflammatory lesions were not included in the lesion counts. At each visit, the physician assessed the global change from the baseline. Adverse events were recorded throughout the study and their severity and relationship to the treatment was assessed.

Data were checked, entered and analyzed by using **SPSS** (Statistical Package for Social Science) version 15 software computer package. Quantitative data were described in terms of mean±standard deviation (±SD), while qualitative data were expressed as frequencies (number of cases) and relative frequencies (percentages). Comparison of numerical variables between the study groups was done using Mann Whitney U test for independent samples. Correlation between various variables was done using Spearman rank correlation equation. A probability value (p-value) less than 0.05 was considered statistically significant.

Results

In the present study, 76 patients with to moderate inflammatory facial acne were included. They were divided into 2 groups. The mean age of the patients in group A was 18.4±3.9 years and the majority of patients were females (89.5%), and in group B was18.9±3.7 years and the majority of patients were females (89.5%).

There were highly statistical significant difference between disease severity in first and second visit in nicotinamide group ($p < 0.001$) and similarly at the third visit when compared to the second ($p < 0.001$). The clindamycin group demonstrated decreased acne severity when compared at the third visit to either the second or first ($p < 0.001$)

In the second visit, non significant reduction in acne severity in the clindamycing group when compared to the nocotinamide group while in the third visit the improvement of disease severity was better in nicotinamide group than the clindamycin group but with no statistically significant difference between the two groups ($p > 0.05$).

Discussion

The present comparative study demonstrated that patients with inflammatory mild to moderate facial acne lesions had highly statistical significant decrease in acne severity using both studied medications ($p < 0.001$).

In acne lesions, nicotinamide greatly inhibit the activation of transcription factors NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and activator protein 1 (AP-1), through enzyme poly ADP ribose polymerase-1 (PARP-1) inhibition.[9]

Shalita and his colleagues [17] demonstrate that 4% nicotinamide gel is of comparable efficacy to 1% clindamycin gel in the treatment of acne vulgaris. This is because of emergence of resistant microorganisms, which is parallel with our results In contrast to our results, Dos et al.[18], demonstrated no additional benefit of adding clindamycin phosphate 1% in combination with nicotinamide gel 4% over clindamycin phosphate 1% in alone.

In relation to our study, 75 patients with inflammatory acne vulgaris did not show any added advantage of clindamycin phosphate 1% in combination with nicotinamide gel 4% over clindamycin phosphate 1% alone.[19]

In a randomized double blinded, controlled trial, 160 patients with moderate and predominantly inflammatory acne were given 4% nicotinamide gel or 4% erythromycin gel twice daily for 8 weeks. Both the groups reported similar regression of inflammatory lesions but the group treated with 4% nicotinamide gel had significantly greater improvement in seborrhoea scores, which is in line with our results.[20]

Another double blinded, placebo controlled, randomized trial with 130 patients found that a 2% nicotinamide moisturiser significantly reduced sebum excretion rates when compared to a placebo moisturizer, and this is supporting our results.[21]

A randomized, double-blind clinical trial aimed to compare efficacy of the topical 4% nicotinamide and 1% clindamycin gels in 80 patients, with moderate inflammatory facial acne vulgaris showed that the efficacies were comparable. However, nicotinamide is preferred in oily and clindamycin in non-oily skin because of better function and outcome.[22]

Another randomized, controlled clinical trial in relation to our study was performed on sixty female patients with mild or moderate acne vulgaris showed that Five percent nicotinamide gel is

as effective as 2% clindamycin gel for treatment of mild to moderate acne vulgaris. No side effect was observed during the treatment.[23]

A Comparative cross-sectional study to compare the efficacy of topical 5% nicotinamide gel versus 2% clindamycin gel in 372 patients with mild to moderate acne demonstrated that no significant difference in the efficacy of Clindamycin and Nicotinamide in treating mild to moderate acne.[24]

Minimal reported side effects were encountered in the present study. They included heat sensation in the nicotinamide group and burning sensation in both groups. This was in line with reports from others who noted that only a small number of patients in both groups experienced adverse effects, none of which were severe enough to require discontinuing medication. These side effects included minor burning, dryness, erythema, itching, and skin peeling.[18]

The post-inflammatory erythema and pigmentation were seen to be decreased in the nicotinamide group. This was attributable to the fact that nicotinamide inhibits both the UVA-induced proliferation of melanocytes and block the transfer of melanosomes from melanocytes into keratinocytes by inhibiting keratinocyte factors.[9] Accordingly, topical nicotinamide 4% is an efficient and secure treatment for mild to moderate inflammatory acne vulgaris.

The study was limited by the short follow up period as well as the relatively small sample size and failure to use non invasive digiutal assessment tools such as dermoscopy. In conclusion we have demonstrated that nicotinamide 4% is effective and safe medication in the treatment of mild and moderate inflammatory acne vulgaris and is comparable with clindamycin1% in efficacy.

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Figure Legends

Figure (1) A 25-year-old female patient presented with acne [left: prior to treatment, B: after treatment with nicotinamide

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Table (1): Clinical data of the studied groups:

		Group A (Nicotinamide)		**Group B (Clindamycin)**	
		Cases n= 38		Cases n= 38	
		Mean	SD	Mean	SD
Age (years)		18.4	±3.9	18.9	±3.7
First visit	pustules	4.4	±4.7	6.7	±7.3
	papules	12.0	±6.3	12.4	±7.4
	sum	16.4	±8.9	19.1	±11.9
Second visit	pustules	2	±2.3	1.4	±2
	papules	5.2	±4.4	2.8	±4.3
	sum	7.2	±5.6	6.2	±5.8
Third visit	pustules	0.6	±1	0.7	±1
	papules	2.3	±2.5	1.3	±1.5
	sum	2.9	±3.1	2	±2.3
Sex (ratio)		M/F	4/34	M/F	4/34
Degree (N. and %)	Mild	N.	%	N.	%
		8	21.1%	13	34.2%
	Moderate	30	78.9%	25	65.8%
Side effects	No side effects	35	92.1%	34	89.5%
	Burning sensation	2	5.3%	3	7.9%
	Heat sensation	1	2.6%	0	0%
	Exacerbation	0	0%	1	2.6%

N= number SD= standard deviation M= male F= female

Table (2): The clinical response of both groups:

Clinical response	Nicotinamide group		Clindamycin group	
	2nd visit (No. & %)	**3rd visit (No. & %)**	**2nd visit (No. & %)**	**3rd visit (No. & %)**
Excellent	0 (0.0%)	8(22.2)	2 (5.3)	11(33.3)
Good	6 (15.8%)	22 (61.1)	13 (34.2)	16 (48.5)
Moderate	21(55.3)	5 (13.9)	16 (42.1)	6 (18.2)
Mild	11(28.9)	1 (2.8)	6 (15.8)	0 (0.0)
Worse	0 (0.0)	0 (0.0)	1 (2.6)	0(0.0)
Total	38(100.0)	36 (100.0)	38 (100.0)	33(100.0)

Table (3): The relation between duration of acne and its degree in nicotinamide group:

Duration of acne	Degree		Total (No. &%)	X^2	P.value
	Mild (No. &%)	Moderate (No. &%)			
< 3 years	3(37.5)	14(46.7)	17(44.7)	0.573	>0.05 (N.S)
3-5 years	2 (25)	6(20.0)	8(21.1)		
6-8 years	3(37.5)	9(30.0)	12(31.6)		
9-12 years	0 (0.0)	1 (3.3)	1 (2.6)		
Total	8(21.0)	30(79.0)	38(100.0)		

X^2=chi –square test. P- Value less than 0.05 is significant N.S =non significant.

Table (4): The relation between duration of acne and its degree in Clindamycin group:

Duration of acne	Degree		Total	X^2	P.value
	Mild (No. &%)	Moderate (No. &%)	(No. &%)		
< 3 years	7(53.8)	12(48.0)	19(50.0)	1.114	>0.05 (N.S)
3-5 years	5(38.5)	9(36.0)	14(36.8)		
6-8 years	1 (7.7)	2(8.0)	3(7.9)		
9-12 years	0(0.0%)	2 (8.0)	2 (5.3)		
Total	13(34.2%)	25(65.8%)	38(100%)		

X^2=chi –square test P- value less than 0.05 is significant N.S =non significant.

Table (5): Comparison between severity of disease (sum of papules and pustules) in Nicotinamide and Clindamycin groups in first visit, second visit and third visit: .

Sum of papules & pustules in 1st visit	**X±SD**	**Range**	**t –test**	**P. value**
Nicotinamide group	16.4±8.9	5-40	1.124	>0.05 (N.S)
Clindamycin group	19.1±11.9	4-40		
Sum of papules and pustules in 2nd visit	**X±SD**	**Range**	**t –test**	**P. value**
Nicotinamide group	7.2±5.6	1-24	0.763	>0.05 (N.S)
Clindamycin group	6.2±5.8	0-24		
Sum of papules and pustules in 3rd visit	**X±SD**	**Range**	**t –test**	**P. value**
Nicotinamide group	1.73±3	0-14	0.85	>0.05 (N.S)
Clindamycin group	2.3±2	0-7		

P- value less than 0.05 is significant N.S =non significant. SD= standard deviation T: independent sample T test.

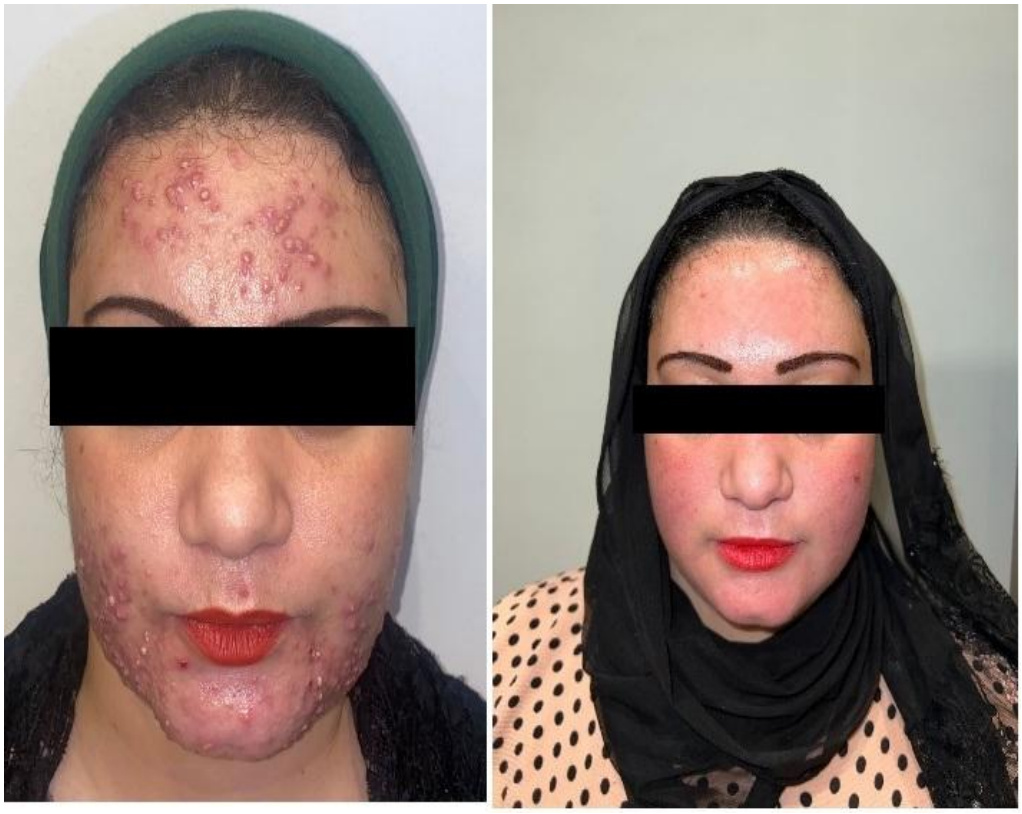

Figure (1) A 25-year-old female patient presented with acne [left: prior to treatment, B: after treatment with nicotinamide