IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 12 Ver. XIV (Dec. 2017), PP 12-22
www.iosrjournals.org

Comparative Study of Efficacy And Safety of Clindamycin 1% Gel And Nadifloxacin 1% Cream In Patients With Mild To Moderate Acne Vulgaris

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Abstract
Objective: *Acne vulgaris is a disorder of the pilosebaceous unit commonly affecting the adolescents. Infection with Propionibacterium acnes, a gram positive bacterium is one of the causative factors of acne. Hence antibiotics both systemic and topical are used in the treatment of acne vulgaris. Recent studies have shown the gradual worldwide increase in the prevalence of antibiotic resistant P.acnes strains. Nadifloxacin is a newer flouroquinolone with anti propionibacterium acnes activity and also anti inflammatory activity. This randomized, controlled, single blinded study was done to compare the efficacy and safety of nadifloxacin 1% gel against clindamycin 1% cream in mild to moderate cases of acne vulgaris.*
Material And Methods:*This study was done in 100 patients with mild to moderate acne vulgaris who were randomized into two groups. There were 50 patients in each group. The medications were applied topically for 8 weeks. They were assessed during the period of medication application at 4 and 8 weeks and then followed up at 12 weeks and 16 weeks. The parameters used for assessment were the changes in the inflammatory, non-inflammatory and total lesions, Cardiff Acne Disability Index (CADI) and Investigator Global Assessment (IGA) scores from baseline to the end of the study. Patients were also evaluated for the safety and tolerability of the drugs.*
Results:*The reduction in the mean number of inflammatory, non-inflammatory and total lesions and CADI were significant from the baseline at all time intervals ($p<0.05$). Between the groups there was no statistical difference in these parameters ($p>0.05$). The percentage reduction in the total number of lesions was also significant within the groups and insignificant between the groups. Similar results were found with IGA scores. Both the groups showed high safety and tolerability.*
Conclusion: *This study has shown that topical nadifloxacin 1% cream is non-inferior to topical clindamycin 1% gel in the treatment of mild to moderate acne vulgaris. Nadifloxacin is a promising drug for the treatment of acne vulgaris.*
Keywords: *Acne vulgaris, clindamycin, nadifloxacin, topical treatment, randomized study.*

Date of Submission:19-12-2017 Date of acceptance: 03-01-2018

I. Introduction

Acne vulgaris is a self limiting disorder of the pilosebaceous unit that is seen primarily in adolescents. Most cases present with a pleomorphic array of lesions consisting of comedones, papules, pustules and nodules with varying extent and severity. Acne mostly heralds the onset of puberty [(1)]. It is the most common skin disease of adolescents and young adults with reported prevalence being nearly 80% [(2)].Acne is common enough to be called a physiological process but is better regarded as a disease due to its inflammatory component and the disfigurement it produces on the face which is socially and psychologically the most important body region [(3)]. The economic and psychosocial impact of acne is undeniable often creating self consciousness and social isolation in those affected [(4)]Acne vulgaris occurs in all races worldwide, affecting 90% of people sometime or the other in their life [(3)]. Recent insights into the pathogenesis of acne have aided significantly in further defining the subtypes of acne and establishing effective treatment regimens [(4)]. The general prevalence of acne vulgaris is about 80% - 90%. The incidence of acne usually peaks during the middle to the late teenage period affecting more than 85% and then steadily decreases. Sometimes it may persist through the third decade or even later, particularly in women [(5)]. The prevalence of acne in a study by Lucky et al was found to be 78% in girls aged 9-10 yrs [(9)]. The prevalence of acne is more among Americans compared to the Japanese. Cystic acne is more commonly seen in whites [(3)]. The prevalence data from India in a study conducted at Varanasi shows 50.6% of boys and 38.13% of girls being affected by acne vulgaris in the 12-17 yrs

age group. Also the prevalence was found to be less among the rural population [(10)]. A study among adults shows a prevalence of 54% in women and 40% of women in the age group of above 30 yrs [(2)]. Persons with increased risk of development of acne are those with XYY chromosomal genotype, polycystic ovarian disease, hyperandrogenism, hypercorticism and precocious puberty [(4)].Excessive sebum production, hypercornification of the pilosebaceous duct, abnormality of the microbial flora especially colonization of the ducts with Propionibacterium acnes and inflammation are the four major factors involved in the pathogenesis of acne vulgaris[(5)]. As such there is no ideal treatment for acne vulgaris and various studies are going on to find out a suitable and effective therapy for this disease. Since inflammation due to Propionibacterium acnes has been considered as a major causative factor for this disease, antibiotics both topical and systemic have been tried successfully through various studies.Of the topical antibiotics, the recently developed nadifloxacin, a flouroquinolone has not undergone many studies. In view of the development of antibiotic resistance, the need for the development of new topical antibiotics against the conventional antibiotics becomes a necessity. Comparative studies of nadifloxacin and clindamycin are not much available.This study was conducted to evaluate the efficacy and safety of nadifloxacin in comparison to clindamycin in cases of mild to moderate acne vulgaris and to find out whether nadifloxacin is superior or non-inferior to clindamycin.

II. Materials And Methods

Ethical Consideration:

The study was commenced after getting approval from the Institutional Ethical Committee (Ethical Committee number:166/G.S/IEC 2012 dated 22-3-2012). Written informed consent was obtained in the vernacular language from every patient before enrollment.

Study Design:

Randomized, controlled, comparative, single blinded, single centre, prospective, parallel group study.

Study Centre:

Department of Dermatology, Tirunelveli Medical College hospital, Tirunelveli.

Study Period:

From March 2012 to September 2013 (18 months)

Inclusion Criteria

1. Age group > 12 yrs and <35 yrs
2. Both genders
3. Patients with inflammatory and non-inflammatory papules, open and closed comedones (mild and moderate grades of acne) with few pustules present over the face.

Exclusion Criteria

1. Age less than 12 yrs and more than 35 yrs
2. Severe grade of acne
3. Subjects on any other medication or cosmetics.
4. Subjects using other anti-acne medications in the last 30 days before study.
5. Patients with h/o allergy to topical antibiotics

Sample Size:

Sample size 100 (50 in each group)

III. Treatment Protocol And Follow Up

Patients with acne in the age group of 12-35 yrs in the skin OP were screened. Demographic data such as age and sex were recorded. The number of lesions at the baseline was counted. The study participants were randomly assigned into 2 groups each having 50 subjects. Participants of one group received clindamycin 1% gel topically and the other group received nadifloxacin 1% cream topically as treatment for mild to moderate acne vulgaris. Total duration of drug administration of the topical preparation for both the groups was 8 wks. The patients were instructed to apply the medications topically twice daily after washing and wiping the face with a clean cloth. It was also insisted that the medications should remain in the face for a period of 4 hrs. Patients were reviewed at the end of 4 wks and 8wks. During every visit total number of lesions was measured. The mean change in the reduction of lesions and the percentage of reduction in the number of lesions were calculated. Other parameters like CADI (Cardiff Acne Disability Index) scoring and IGA (Investigator Global Assessment) scoring were also assessed. CADI is a set of 5 questions. It was given to the patients and they were asked to tick one of the multiple answers framed according to the severity of the lesions. IGA is a six point scale marked by the investigator during the patient's visits. The grades on the IGA scale are

0 - Completely clear
1 - Almost clear
2 - Mildly severe
3 - Moderately severe

4 - Severe
5 - Very severe

Percentage of the patients showing a minimum of 2 scale improvement in the IGA score was measured. Photographs were taken for evidence. The patients were assessed at 12 weeks and 16 weeks. During the follow up visits all the parameters were assessed.

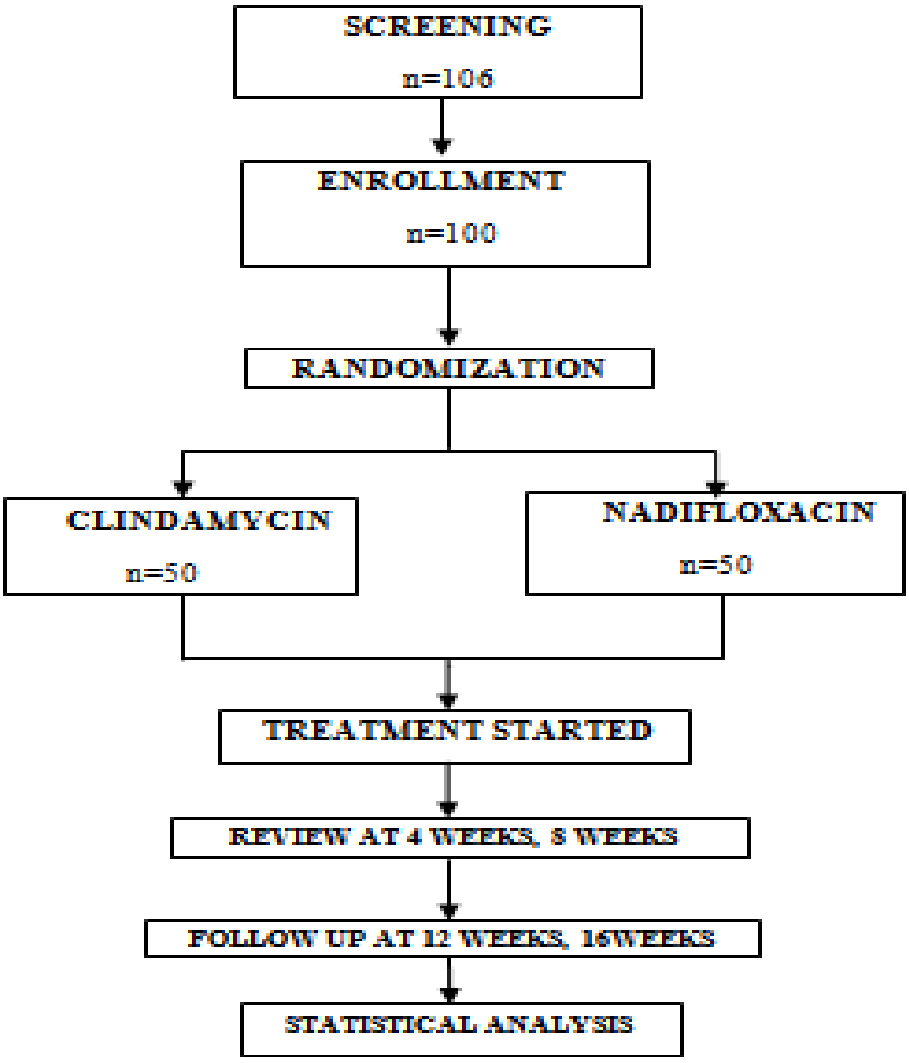
Primary Outcome:

Reduction in the total number of lesions (both inflammatory and non-inflammatory) from the baseline to the end of the study was measured as the primary outcome.

Secondary Outcomes

Reduction in the Cardiff Acne Disability Index (CADI) and Validated IGA (Investigator global assessment) were the secondary outcomes measured. .

Patient Dispositio Consort Diagram



IV. Statistical Analysis

1. The baseline characteristics of both the groups were matched by unpaired student‘t’ test and Pearson’s chi-square test.
2. The efficacy of the two drugs were compared analyzed by unpaired‘t’ test in different intervals.
3. Within group analysis was done by paired ‘t’ test.
4. Percentages were also calculated for reduction in the total lesions and IGA improvement assessment.

The above statistical analysis was done in S.P.S.S. (Statistical Package for the Social Sciences) (version-17.0)The p values of less than 0.05 ($p<0.05$) were considered significant.

V. Results

In the period from March 2012 to August 2013, 106 new cases of mild to moderate acne vulgaris attending the Dermatology Department OP with the eligibility criteria were screened and 100 were included in the study. The included patients were randomly assigned through a computer generated table into 2 groups receiving either clindamycin 1% gel or nadifloxacin 1% cream. All the patients completed the study and the results were analyzed.

Table.1 Mean Age

GROUP	MEAN+ S.D	't'	d.f	'p' value
Clindamycin	19.4+ 4.763	0.7896	98	0.43*
Nadifloxacin	20.12+ 4.345			(p>0.05)

*** p value statistically insignificant**

Table.1: shows the mean age distribution in both the clindamycin and the nadifloxacin group.

The insignificant p value indicates that the 2 groups were comparable with regard to mean age distribution.

Figure.1 Age Distribution

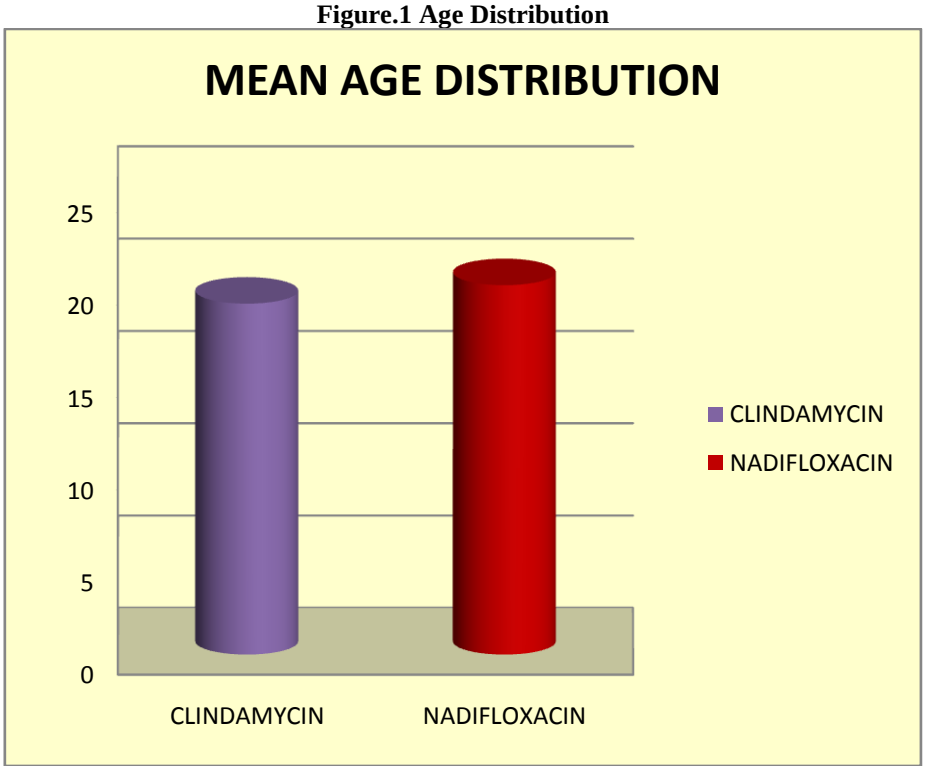


Figure.1: shows the diagrammatic representation of the mean age distribution of the nadifloxacin group compared to the clindamycin group.

The mean age in the clindamycin group (19.4) was similar to the nadifloxacin group (20.12).

Table .2sex Distribution

GROUP	SEX		χ^2	d.f	P VALUE
	MALE	FEMALE			
CLINDAMYCIN	23	27	0.40	1	0.84*
NADIFLOXACIN	24	26			

***p (>0.05) value insignificant**

Table.2: shows the sex distribution in both the groups. The p value indicates that the two groups had equal number of males and females.

Figure.2

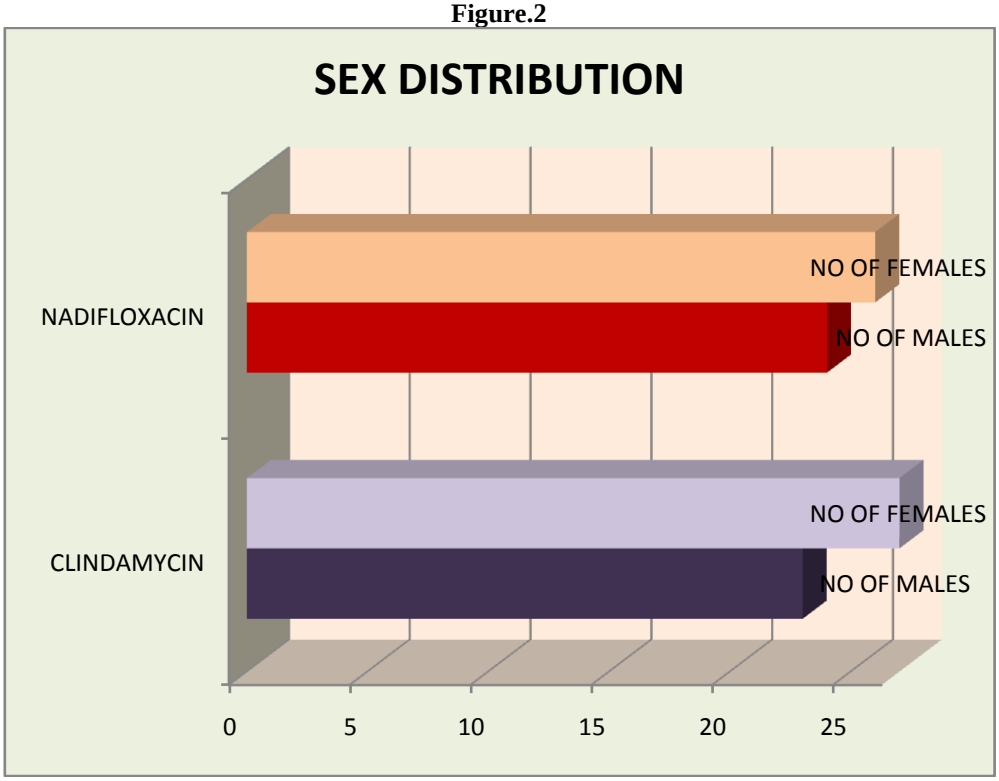


Figure.2: shows the pictorial representation of sex distribution in both the groups. The number of males and females were comparable in both the groups.

Table.3 Baseline Number Of Lesions

variables	Clindamycin	Nadifloxacin	t	d.f	p value
IL	12.08+4.43	12.96+4.58	0.0976	98	0.33*
NIL	9.54+3.05	10.14+ 3.4	0.9269	98	0.36*
TL	21.62+ 6.82	23.10+6.89	0.0789	98	0.28*

***p>0.05-insignificant.**

IL- inflammatory lesions
NIL- non inflammatory lesion
TL- total lesions

The clindamycin and the nadifloxacin groups are equal in their baseline characteristics like age, sex and the mean number of lesions.

The p value is >0.05 for all the variables.

Table.4 Efficacy Of Clindamycin At Various Intervals

	Duration (Mean with S.D)				
	Baseline	**4 wks**	**8 wks**	**12wks**	**16 wks**
IL	12.08+4.43	8.72+3.95*	3.32+2.72*	3.80+3.01*	4.68+3.34*
NIL	9.54+3.05	6.10+2.78*	2.68+2.35*	3.50+2.47*	4.16+2.51*
TL	21.62+6.82	14.62+6.0*	6.00+4.83*	7.30+5.26*	8.78+5.40*
CS	13.32+1.58	9.60+2.45*	3.16+2.55*	3.44+3.92*	3.94+2.88*

*** p value <0.001- significant**

IL- inflammatory lesions
NIL- non inflammatory lesion
TL- total lesions
CS- Cardiff Acne Disability Index scoring

Table.4 shows the mean values of the parameters at various intervals.

1. The mean total number of lesions has decreased from 21.62 of the baseline to 6 at 8 wks and 8.78 at 16 wks.
2. The CADI scoring also has decreased from the baseline of 13.32 to 3.16 at 8 wks and 3.94 at 16 wks.

Compared to the baseline all the parameters are statistically significant.

Table.5 Efficacy Of Nadifloxacin At Various Intervals

Variables	Duration (mean with S.D)				
	Baseline	4 wks	8 wks	12wks	16 wks
IL	12.96+4.58	8.48+3.55*	3.04+2.57*	3.58+2.45*	4.10+2.72*
NIL	10.14+3.40	6.20+2.77*	2.22+1.9*	2.70+2.17*	3.28+2.43*
TL	23.10+6.89	14.68+5.61*	5.26+4.16*	6.28+4.26*	7.36+4.72*
CS	13.36+1.17	10.02+1.96*	3.04+2.06*	3.22+2.36*	3.46+2.53*

p value <0.001- significant

Table.5 shows the mean values of the parameters at various intervals.

1. The mean total number of lesions has decreased from 23.10 of the baseline to 5.26 at 8 wks and 7.36 at 16 wks.
2. The CADI scoring has decreased from the baseline value of 13.36 to 3.04 at 8 wks and 3.46 at 16 wks.

Compared to the baseline all the parameters are statistically significant.

Figure.3

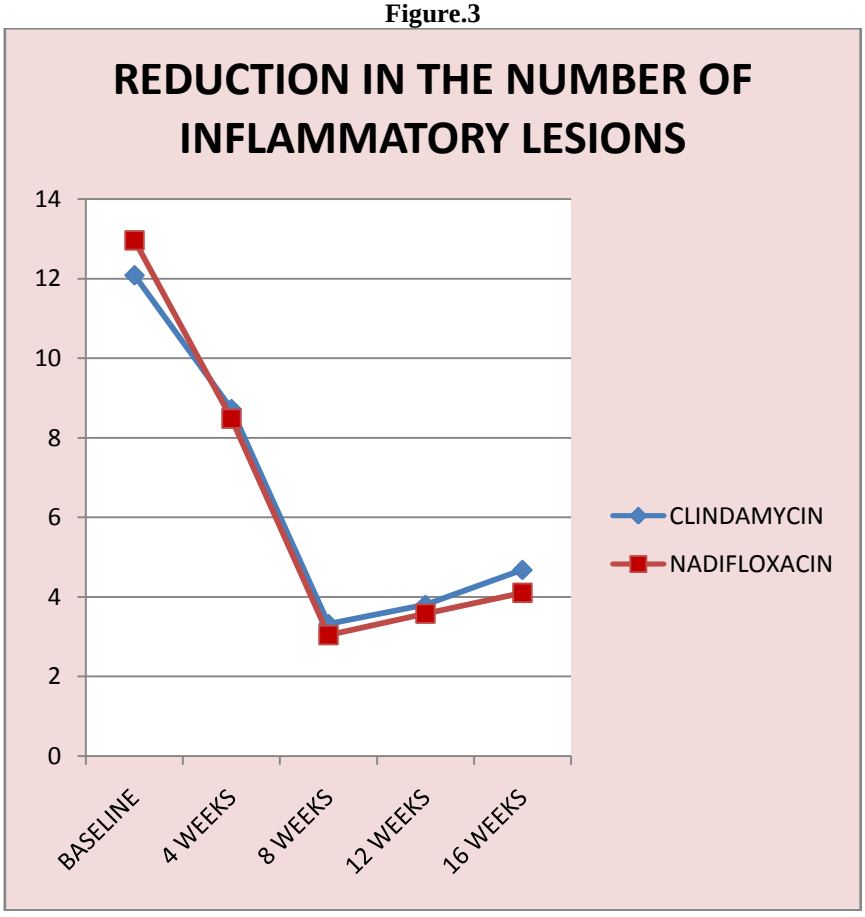


Figure.3: shows the pictorial representation of mean reduction in the number of inflammatory lesions in both the groups.

1. There is a steep fall of the curves from baseline to 8 weeks.
2. This level at 8 weeks is maintained till 16 weeks (post treatment period)

Figure.4

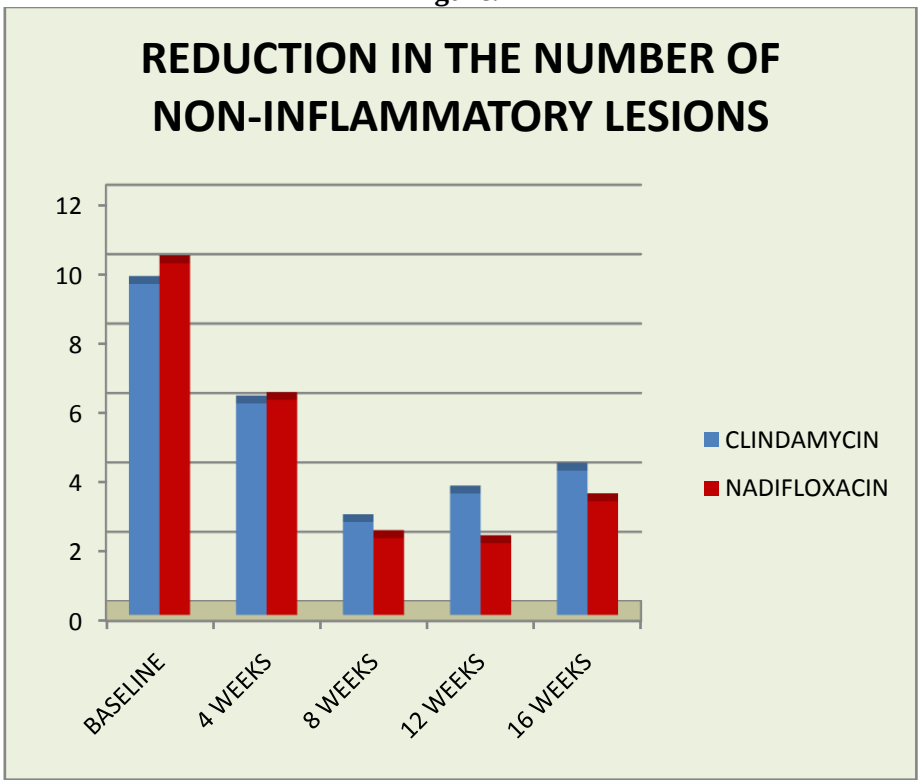


Figure.4: shows the diagrammatic representation of the reduction in the mean number of non-inflammatory lesions in both the study groups.

Figure.5

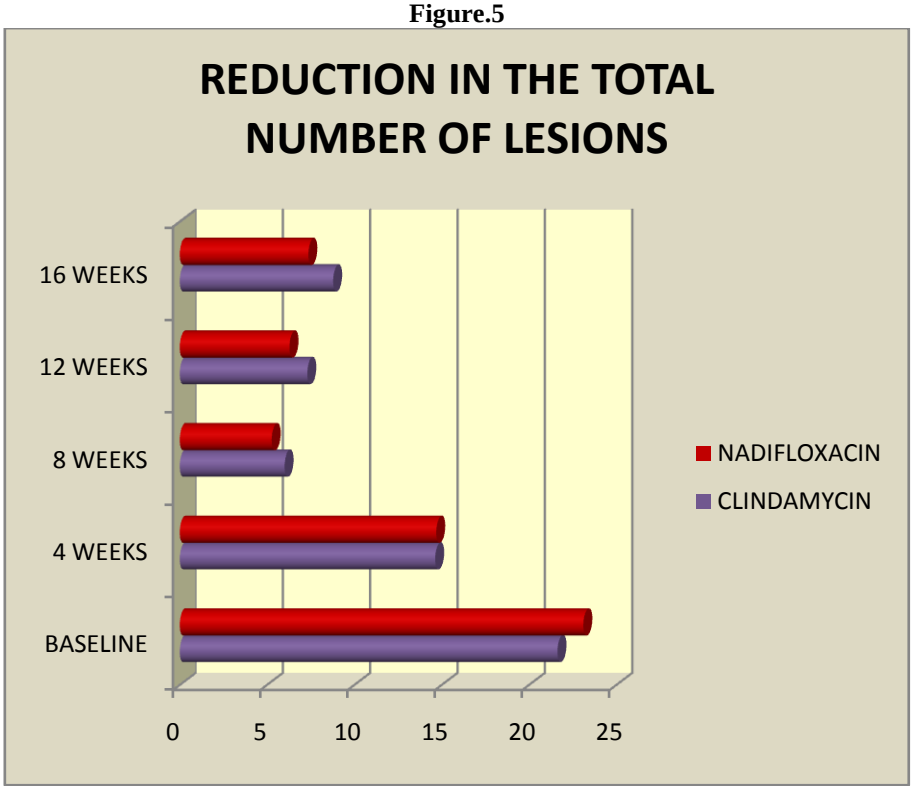
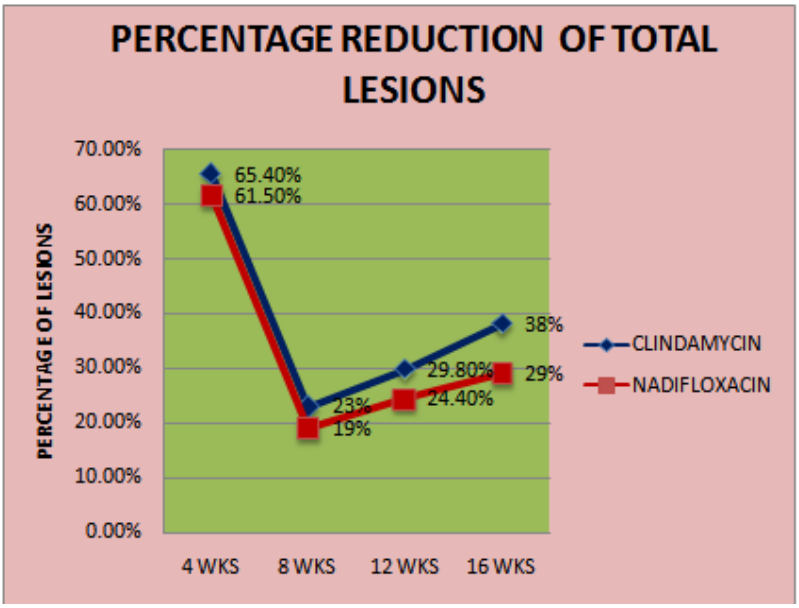


Figure.5: shows the diagrammatic representation of the reduction in the mean of the total number of lesions in both the groups.

FIGURE.6



1. This figure shows the percentage reduction in the total number of lesions of both the groups. It is evident from the picture that both the groups are similar.
2. The baseline is taken as 100%.
3. The reduction in the in the percentage of lesions from the baseline is to 23% at 8 wks and to 38% at the end of 16 wks in the clindamycin group.
4. The percentage of lesions has reduced to 19% at 8 wks and 29% at 16 wks in the nadifloxacin group.

Table.6 Percentage Reduction- Comparison Between Groups

DURATION	CLINDA (%)	NADI (%)	t	d.f	P
4 WKS	34.6	38.5	0.405	98	0.68*
8 WKS	77.0	81.0	0.491	98	0.63*
12 WKS	70.2	75.6	0.607	98	0.55*
16 WKS	61.9	71.0	0.964	98	0.38*

***p value >0.05 – insignificant**

1. The above table shows the difference in the percentage reduction of the total lesions in both the groups.
2. The percentages are statistically similar at the various time periods- 4 wks, 8 wks, 12 wks and 16 wks.

Figure.6

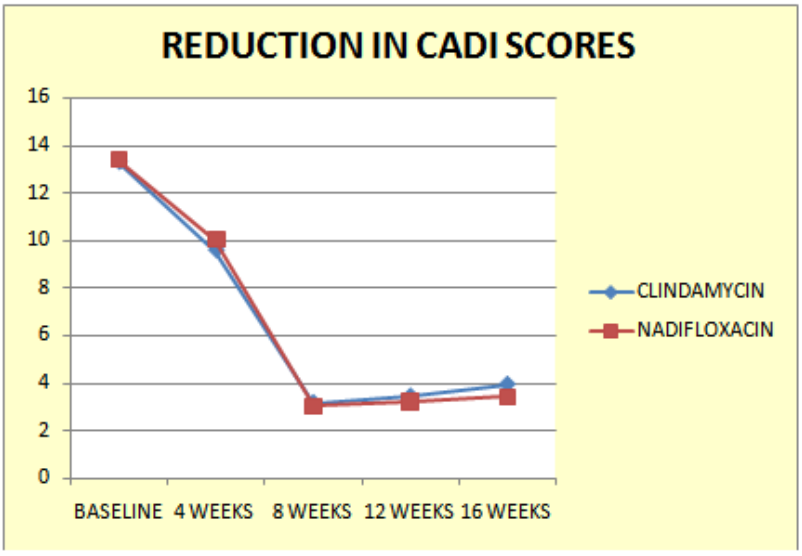


Figure.6: shows the pictorial representation of the reduction in the CADI scoring of both groups.

The two groups have shown dramatic reduction in the CADI (Cardiff Acne Disability Index) scores indicating the psychological improvement in the patients after treatment.

Table.7 Between Groups At 4 Wks And 8 Wks

VARIABLES	DURATION	CLINDA		NADI		t	d.f	p
		Mean	S.D	Mean	S.D			
IL	4 wks	8.72	3.959	8.48	3.553	0.3190	98	0.75*
	8 wks	3.32	2.729	3.04	2.571	0.5281	98	0.59*
NIL	4 wks	6.10	2.772	6.20	2.770	0.1804	98	0.85*
	8 wks	2.68	2.351	2.22	1.898	1.0765	98	0.28*
TL	4 wks	14.62	6.000	14.68	5.611	0.0516	98	0.95*
	8 wks	6.00	4.832	5.26	4.164	0.8203	98	0.41*
CS	4 wks	9.60	2.449	10.02	1.964	0.9460	98	0.34*
	8 wks	3.16	2.558	3.04	2.060	0.2584	98	0.79*

***p value > 0.05 (insignificant)**

Table.7: shows the difference in between the two groups at 4 wks and 8 wks intervals.

1. After 8 wks of therapy both groups have shown similar mean number of total lesions (6 in clindamycin group and 5.26 in nadifloxacin group).
2. The two groups have shown insignificant p values.

Table.8 Between Groups At 12 Wks And 16 Wks:

VARIABLES	DURATION	CLINDA		NADI		t	d.f	p
		Mean	S.D	Mean	S.D			
IL	12 wks	3.80	3.097	3.58	2.459	0.3934	98	0.69*
	16 wks	4.68	3.341	4.10	2.727	0.9510	98	0.34*
NIL	12 wks	3.5	2.476	2.7	2.178	1.7154	98	0.08*
	16 wks	4.16	2.510	3.28	2.433	1.7801	98	0.07*
TL	12 wks	7.30	5.265	6.28	4.262	1.0648	98	0.28*
	16 wks	8.78	5.403	7.36	4.720	1.3996	98	0.16*
CS	12 wks	3.44	2.922	3.22	2.367	0.4137	98	0.68*
	16 wks	3.94	2.881	3.42	2.532	0.9587	98	0.34*

***p value (>0.05) insignificant**

Table.8: shows the difference in between the two groups at 12 wks and16 wks intervals.
The two groups have shown insignificant p values.

Table.9 Improvement In Iga Scores

DURATION	CLINDA (%)	NADI (%)	t	d.f	p
4 WKS	18	22	0.5	98	0.62*
8 WKS	90	90	Values are equal		
12 WKS	86	84	0.280	98	0.78*
16 WKS	88	86	0.297	98	0.76*

***p value >0.05 – insignificant**

1. At 4 wks of therapy the IGA scores are 18% and 22% in the clindamycin and nadifloxacin groups respectively.
2. There is significant improvement in the IGA scores at 8 wks and this has continued till 16 wks.

VI. Discussion

Acne vulgaris is a common disease of the adolescent age group in both the sexes. The prevalence has been found to be as high as 80% through various studies [(2)]. The presence of acne vulgaris is common durind the onset of puberty [(1)]. It also affects the people in other age groups like neonates, infants, mid childhood, preadolescents and post adolescents. The prevalence in these age groups is less compared to adolescence. Even though a milder disease without any life threatening complications, it produces lot of psychological stress with symptoms like depression, irritability, low self esteem, lack of self confidence leading to suicidal ideation and unemployment[(4)]. The four major factors in the pathophysiology of acne vulgaris are increased sebum production, colonization of the follicles by the Propionibacterium acnes bacteria, alteration in the keratinization process and release of inflammatory mediators into the skin. These lead to the formation of comedones, papules, pustules and cysts. Many forms of therapy are available but none has been identified as the most effective, tolerable, cost effective form without any adverse effects. Studies have shown that inhibition of the Propionibacteria acnes infection by the use of topical antibiotics is very effective for the treatment of mild to

moderate acne vulgaris.This study was done to compare the efficacy and safety of clindamycin 1% gel and nadifloxacin 1% cream in mild to moderate acne vulgaris.The basal characteristics like age, sex and the mean number of inflammatory and non-inflammatory lesions were comparable in both the groups with no statistically significant difference between them ($p>0.05$). The mean age of the study participants is 20 falling in the range of 15-25 years. This correlates well with the literature showing the highest prevalence in this age group. The mean age of the patients in our study is also comparable to that in certain other studies [8, 9].

The prevalence of acne is more among the males due to increased androgen secretion [3]. In our study the number of males and females were almost equal in both the study groups. This correlates with the sex distribution of certain other studies [8, 9]. Baseline value of the mean number of total, inflammatory and non-inflammatory lesions was also equal in both the groups.The clindamycin and the nadifloxacin groups showed significant reduction in the number of inflammatory, non-inflammatory and total lesions ($p<0.001$) at 4 wks of treatment. The mean values of those parameters between the two groups were similar at 4 wks ($p>0.05$). The parameters measured at 8 wks also have shown significant difference in the response to treatment within the groups ($p<0.001$). There was no significant difference between the groups (p values >0.05). This is comparable to the results of the studies done in EU [10] and Choudhury [11] et al in India. The study in EU with nadifloxacin was a non-interventional study. The efficacy of nadifloxacin was rated as very good/good in 82.1% of cases in that study. In the study conducted by Choudhury et al, the efficacy of nadifloxacin was good showing a significant reduction of number of lesions from the baseline (p value <0.0001 at 4 wks and 8 wks). Similar results also were seen in e study conducted in Korea by Choi et al at 4 wks of treatment [12].The CADI scores were also significantly improved within the groups at 4 weeks and 8 wks. The mean baseline value has reduced from 13.36 to 10.02 at 4 wks and 3.04 at 8 wks. There is significant statistical difference when compared to the baseline ($p <0.001$). This shows that the patients have gained confidence and improved social contact after the reduction in the severity of the disease. Between the groups there is no difference statistically ($p >0.05$). Nadifloxacin showed marked improvement in the psychological assessment in the study conducted in EU [10] where the feeling of shameness reduced from 51% in the baseline to 16.9%. A study by Noguchi et al [13] in Japan showed significant satisfaction of the patients after therapy ($p<0.002$).

The topical medications were stopped at 8 weeks. The patients reviewed for first follow up at 12 wks showed continued good response. This is evident by the statistically significant reduction in the mean number of lesions and improvement in the CADI scoring ($p<0.001$). Between the groups there is no statistical difference at 12 weeks in all the parameters ($p>0.05$). Response at 16 weeks was also statistically significant in both the groups compared to the baseline. There was a mild increase in the mean values of all parameters at 16 wks compared to those at 12 wks but with no statistical significance (p- 0.23 for total lesions and p-0.62 for CADI scoring).The percentage reduction of the total lesions showed statistical significance from the baseline. In the clindamycin group they were 34.6, 77, 70.2 and 61.9 at 4, 8, 12 and 16 wks respectively. Nadifloxacin showed reductions of 38.5, 81, 75.6 and 71 percentages during the same time intervals. Both the groups were similar in this percentage reduction at all time periods ($p>0.05$). This is comparable to the study done in EU [10].IGA scoring is assessed by the percentage of patients showing atleast 2 scale improvement. At 8 wks both the groups showed 90% of patients with improved IGA score. At the end of 16 wks this was 88% for the clindamycin and 86% for the nadifloxacin group. The study done in India by Choudhury et al [11] has shown 54% patients showing improvement in IGA score for clindamycin and 73.8% for nadifloxacin at 8 wks of treatment. Regarding the adverse effects none of the patients in either group complained of any side effect and both the drugs were well tolerated. The study in EU has demonstrated the tolerability of nadifloxacin by the patients. It is measured as very good/good in more than 90% of the study patients [10].Topical antibiotics definitely have a role in the treatment of mild to moderate acne vulgaris. Clindamycin is a well known topical antibiotic used for the treatment of acne vulgaris. It is used either alone or in a combination therapy. It has shown good efficacy in the treatment of acne vulgaris in various clinical studies [14-18]. The recent sensitivity studies of Propionibacterium acnes have revealed development of resistance against most of the commonly used antibiotics like cyclines, macrolides like erythromycin and clindamycin. Nadifloxacin is a newer topically used quinolone that has shown excellent efficacy in the in vitro studies against Propionibacterium species [19, 20] and good tolerability [10]. This study has shown that nadifloxacin is as effective as clindamycin in the treatment of mild to moderate acne vulgaris. Topical nadifloxacin 1% cream is non inferior to topical clindamycin 1% gel and is well tolerated. It will be a promising drug for acne vulgaris. In view of the development of antibiotic resistance by Propionibacterium species, nadifloxacin will be a better alternative for the treatment of acne vulgaris. In our study the microbiological examination and sensitivity to the drugs was not assessed. Further studies with more number of patients, long term follow up and microbiological susceptibility testing would provide better scientific evidence regarding the efficacy and safety of nadifloxacin.

VII. Conclusion

1. This study has shown that topical nadifloxacin 1% cream is non-inferior to topical clindamycin 1% gel in the treatment of mild to moderate acne vulgaris.
2. Nadifloxacin is definitely a promising drug for the treatment of acne vulgaris.

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*S.Anbarasi. "Comparative Study of Efficacy And Safety of Clindamycin 1% Gel And Nadifloxacin 1% Cream In Patients With Mild To Moderate Acne Vulgaris." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) , vol. 16, no. 12, 2017, pp. 12–22.