

A randomized, double-blind comparison of nadifloxacin 1% cream alone and with benzoyl peroxide 5% lotion in the treatment of mild to moderate facial acne vulgaris

Hafif-orta şiddetli akne vulgaris yüz tutulumu tedavisinde nadifloksasinin tek başına ve benzoil peroksit ile birlikte kullanımının karşılaştırılması

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ABSTRACT

Objective: To compare the efficacy of nadifloxacin alone and with benzoyl peroxide in the treatment of mild to moderate facial acne vulgaris.

Patients and Methods: This double-blind, randomized study was conducted in a total of 93 acne patients, with at least 10 inflammatory lesions, but no more than 3 nodules or cysts on the face. All patients were instructed to apply nadifloxacin 1% cream twice daily and randomized to apply either benzoyl peroxide 5% lotion or its vehicle once daily for 8 weeks.

Results: The mean percent reduction in inflammatory lesions were 22.08% in the nadifloxacin group (n=46) and 53.5% in the nadifloxacin+benzoyl peroxide group (n=47). Five (10.9%) patients in the nadifloxacin group and 18 (38.3%) patients in the nadifloxacin+benzoyl peroxide group achieved a 50% and greater reduction in the inflammatory lesion count.

Conclusion: Both treatment regimens were statistically effective, but a significantly greater reduction of the inflammatory lesions was seen in the nadifloxacin+benzoyl peroxide group. The number of patients who achieved a 50% and greater reduction in inflammatory lesion count was significantly higher in the nadifloxacin+benzoyl peroxide group. Both treatment regimens were well tolerated with mild side effects.

Key words: Acne, Nadifloxacin, Benzoyl peroxide

ÖZET

Amaç: Hafif-orta şiddetli akne vulgaris tedavisinde nadifloksasin kremin tek başına veya benzoil peroksit ile birlikte kullanımının etkinliğini karşılaştırma.

Hastalar ve Yöntem: Çift kör, randomize çalışma, toplam 93 hasta 2 grup olarak ya nadifloksasin kremi ya benzoil peroksit losyonun baz formu ya da benzoil peroksit ile birlikte 8 hafta süre ile kullandı.

Bulgular: İnflamatuar lezyonlar tek başına nadifloksasin kullanan grupta(n=46) %22, 08, nadifloksasin+benzoil peroksit kullanan grupta(n=47) %53,5 oranında azaldı. Tek başına nadifloksasin kullanan grupta beş (%10,9), nadifloksasin+benzoil peroksit kullanan grupta 18(%38,3) hastada inflamatuar lezyonlarda %50 ve üzeri azalma görüldü.

Sonuç: Her iki tedavi de istatistiksel olarak etkili bulundu ancak nadifloksasin+benzoil peroksit grubunda belirgin olarak inflamatuar lezyonlarda azalma görüldü. Her iki tedavi de hafif yan etkiler ile çok iyi tolere edildi.

Anahtar kelimeler: Akne, Nadifloksasin, Benzoil peroksit

Introduction

Topical agents are the first-line therapy in the management of mild to moderate acne. Retinoic acids, benzoyl peroxide, and topical antibiotics are the most frequently used topical agents. As *Propionibacterium acnes* resistance to common antibiotics has significantly increased over the past 30 years, due to their widespread use in acne treatment, new treatment strategies have been developed to combine topical antibiotics with anti-inflammatory and comedolytic agents, to minimize the development of *P.acnes* resistance [1-5]. Benzoyl peroxide; with its antibacterial, sebostatic and comedolytic effects, suppresses *P.acnes* by oxidative mechanism. There is still no evidence that microorganisms become resistant to benzoyl peroxide, despite its widespread use in the last 5 decades.

Nadifloxacin, a new fluoroquinolone antibiotic, has been developed for topical administration. It is effective against Gram-positive, Gram-negative and anaerobic bacteria, including *P.acnes* [6]. Since 1995, it has been licensed as

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acne medication in many countries, including Japan, Spain, Germany, Mexico, Bulgaria, Korea and Turkey. Clinical studies comparing the efficacy of nadifloxacin with either placebo or other topical agents have been very limited. So far, there has been no clinical study evaluating the combined use of nadifloxacin with an anti-inflammatory and comedolytic agent such as benzoyl peroxide.

The primary purpose of this study was to compare the efficacies of nadifloxacin alone and with benzoyl peroxide in the treatment of mild to moderate facial acne vulgaris.

Patients and Methods

Study design

Randomized, double-blind, parallel group study, in which the patients were randomly assigned to use either nadifloxacin 1% cream alone or with benzoyl peroxide 5% lotion during an 8-week treatment period. The study was conducted at Marmara University Hospital Dermatology outpatient clinic and approved by the appropriate institutional ethics committee. All patients and also the parents of patients under 18 years old provided written informed consent in order to participate.

The number of patients in the study group was calculated as 45 in each group in order to detect a 30% difference in inflammatory lesions count at 5% significance level with 80% power.

Inclusion and exclusion criteria

Patients aged 14-40 years with mild to moderate acne vulgaris of the face; with at least 10 inflammatory lesions but no more than three nodulocystic lesions were eligible to enroll for the study. A washout period of at least 2 weeks for topical acne therapies, 4 weeks for oral antibiotics and laser or chemical peelings, 3 months for estrogens or birth control pills and 6 months for oral retinoids was allowed. Patients were excluded if they had pure comedonal acne, truncal acne requiring systemic treatments and other facial skin disorders. Women were excluded if they were pregnant or nursing and showed clinical signs of hyperandrogenism.

Treatment protocol

Patients were randomized consecutively in a 1: 1 ratio to apply either nadifloxacin 1% cream (Nadixa 1% cream; Adeka) twice daily and benzoyl peroxide 5% lotion (Aknefug BP5 lotion; Orva) once daily (5 minutes after nadifloxacin) or nadifloxacin 1% cream twice daily and vehicle of benzoyl peroxide once daily for 8 weeks according to a computer generated list. The integrity of the blinding was ensured by packaging the benzoyl peroxide lotion and its vehicle in identical bottles and allocating a different person to dispense the medications. Patients were instructed to wash their faces with tap water and dry and then apply the medications to the

whole face. The same moisturizer (Neutrogena oil free™) was allowed to be used by all, if needed.

Assessment of efficacy and tolerability

Patients were evaluated at weeks 0, 2 and 8 of the treatment period. To assess the efficacy, inflammatory and noninflammatory lesions were counted on the face excluding the nasal region. At the end of the treatment period, the percentage of reductions in inflammatory and noninflammatory lesions was calculated. In addition, global improvement was rated by the patients using a six-points scale (worsening, no improvement, slight improvement, moderate improvement, good improvement, clearance) at the end of the treatment. For the safety measurements, local side effects were classified as erythema, desquamation, pruritus and burning sensation, with each being assessed for the severity using a five point scale (none, very slight, mild, moderate, severe) and for the duration. Patients were also asked for other adverse events.

The primary efficacy variable was the percentage of the reduction in inflammatory lesions and the secondary efficacy variable, was the number of patients who achieved 50% and a greater reduction in inflammatory lesions after the 8 week-treatment period.

Statistical analysis

Analyses for efficacy and safety were performed on week 8. Data for the intent-to-treat (ITT) population included all randomized patients who were supplied with study medications. The “last observation carried forward (LOCF)” methodology was used for the ITT population analysis (lesion counts), to account for missing data or for data from patients who withdrew from the study. The t-test and X² test was performed to compare the groups. The ANCOVA test was performed to analyze the variables that were incomparable. P<0.05 was considered significant.

Results

Demographic features

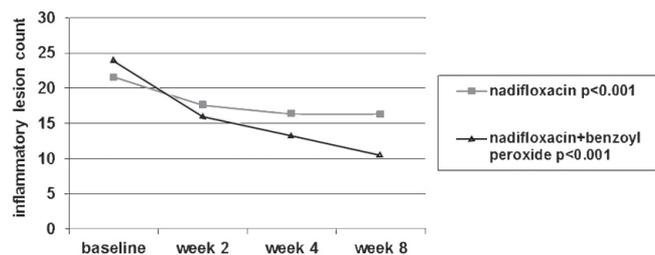
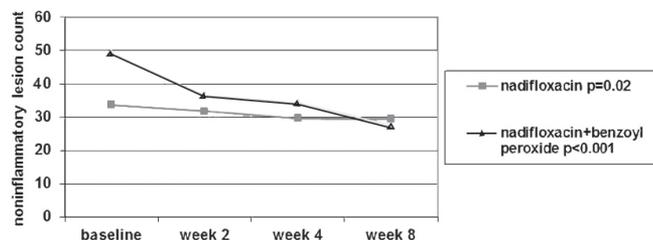
A total of 93 patients; 46 (30 females, 16 males) in the nadifloxacin group, and 47 (27 females, 20 males) in the nadifloxacin+benzoyl peroxide group were involved in the study. Fourteen patients were dropped due to follow-up failure (3 patients), noncompliance (10 patients), and side effects (1 patient). A total of 79 patients completed the 8 week-treatment. The baseline characteristics of the patients are summarized in Table I. The treatment groups were comparable in respect to the demographic characteristics and baseline number of inflammatory lesions, but not in respect to the noninflammatory lesions. The mean number of noninflammatory lesions were higher in the nadifloxacin+benzoyl peroxide group.

Table I. The baseline characteristics of the patients.

	Nadifloxacin (n=46)	Nadifloxacin+ Benzoyl peroxide (n=47)
Age (mean) (min-max)	19.67 (14-29)	19.06 (14-29)
Sex		
F (n) (%)	30 (65.2%)	27 (57.4%)
M (n) (%)	16 (34.8%)	20 (42.6%)
Duration of acne (mean-month)	52.96	55.23
Inflammatory lesion count (mean) (min-max)	21.52 (10-50)	23.98(10-53) p=0.192
Noninflammatory lesion count (mean) (min-max)	33.67 (5-150)	49.11(4-162) p=0.032
Total lesion count (mean) (min-max)	55.13 (17-179)	73.38(19-190) p=0.022

Efficacy evaluation

The number of inflammatory and noninflammatory lesions was significantly reduced at the end of the treatment period in both treatment groups. The mean percent reduction in inflammatory and noninflammatory lesions was 22.08% and 7.6% in the nadifloxacin group, and 53.5% and 34.8% in the nadifloxacin+benzoyl peroxide group respectively (Figure 1,2). The reduction rates for inflammatory and noninflammatory lesions were significantly superior for nadifloxacin+benzoyl peroxide comparing to nadifloxacin alone (all, $P < .001$). Five patients (10.9%) in the nadifloxacin group and 18 patients (38.3%) in the nadifloxacin+benzoyl peroxide group achieved 50% and greater reduction in inflammatory lesions count. There was a statistically significant difference in favor of the nadifloxacin+benzoyl peroxide group ($P = .002$). Global improvement was rated by 89 patients, a significantly greater number of patients using nadifloxacin+benzoyl peroxide reported “good” or “moderate” improvement compared to patients using nadifloxacin alone (68% vs 24%; $P < .001$). None of the patients in the nadifloxacin+benzoyl peroxide group but four patients in the nadifloxacin group reported “worsening”. None of the patients in the study groups defined “clearance”.

**Figure 1.** Reduction of inflammatory lesion count in the treatment groups.**Figure 2.** Reduction of noninflammatory lesion count in the treatment groups.

Safety evaluation

The number of patients experiencing at least one adverse event was significantly higher in the nadifloxacin+benzoyl peroxide group with 61.7% vs 37% ($P = .002$). One patient in the nadifloxacin+benzoyl peroxide group withdrew because of “severe” burning sensation. Four patients had to use moisturizer for “moderate” desquamation and erythema in the nadifloxacin+benzoyl peroxide group. The other side effects were “very slight” or “mild”. In general, all were observed at the initial treatment phase and resolved with time.

Discussion

In this study, we observed the superior efficacy of nadifloxacin 1% cream+benzoyl peroxide 5% lotion compared to nadifloxacin 1% cream+vehicle of benzoyl peroxide in the treatment of mild to moderate facial acne vulgaris. The mean percentage of reduction in inflammatory lesion was 22.08% and 53.5% in the nadifloxacin and combination group respectively. Combinations of topical antibiotics and benzoyl peroxide or retinoids are the current standard regimens for the treatment of mild to moderate acne vulgaris [1,2]. Since they targeted multiple pathogenetic factors, greater and faster efficacy were provided by these combinations. Development of antibiotic-resistant *P. acnes* can also be prevented by these combined topical treatments. At present, to our knowledge, there has been no published study evaluating the combination of nadifloxacin, a new topical antibiotic, with benzoyl peroxide and comparing it to nadifloxacin alone.

Nadifloxacin, a new broad spectrum antibiotic was licensed as acne medication in Turkey in 2008. A double-blind, vehicle-controlled study showed nadifloxacin cream to be superior as clinically and bacteriologically to vehicle [7]. A recent split face, double-blind vehicle controlled with clinical and histological evaluation in 37 Korean patients, supported the previous data [8]. Plewig et al. noted similar efficacy in reducing inflammatory lesion count with both nadifloxacin 1% cream (66.7%) and erythromycin 2% cream (64.7%) and superior efficacy of nadifloxacin in reducing *P. acnes* in 474 participants [9]. A recently published Turkish data verified the similar clinical efficacies of nadifloxacin 1% cream and erythromycin 4% gel [10]. In a study by Bojar et al, erythromycin-resistant *P. acnes* were isolated from 27.9% of erythromycin treated subjects, whereas no nadifloxacin-

resistant *P. acnes* were isolated from nadifloxacin treated subjects after a 12 week-treatment [11]. An in-vitro study from Germany showed that *P. acnes* has not developed resistance to nadifloxacin during the last two years of use in their country [12].

In this study, it has been shown that inflammatory and noninflammatory lesions were reduced in a ratio of 22.08% and 7.6% in the nadifloxacin group, 53.5% and 34.8% in the nadifloxacin+benzoyl peroxide group respectively. The efficacy of nadifloxacin cream in our study was lower than in the previous studies. The efficacy of topical antibiotics such as erythromycin and clindamycin has been documented in a range of 35-70%. The efficacy of benzoyl peroxide alone 36-60% when combined with erythromycin or clindamycin was 54-75% in well designed studies in the literature [13-19]. The efficacy of vehicle has also been found to be 5-35% in these studies. In the light of these data, nadifloxacin in our study can be assumed to have similar efficacy with vehicles. The question was if nadifloxacin had any additive effect to the results of our nadifloxacin+benzoyl peroxide group. A four-armed study with an additional two treatment groups (benzoyl peroxide and vehicle alone) would be more suitable to answer this question. Unfortunately, we could not add these groups to the study because of technical problems.

The treatment duration was lower in our study compared to a previous study (8 vs 12 weeks respectively) [9]. Topical antibiotics are generally recommended for 8 weeks with the limitation of maximum 12 weeks by the authors [1,2,20]. We observed maximum improvement with all treatment regimens at week 2. There was no additional statistically significant improvement after 2 weeks of nadifloxacin use. We also provided the subject number as has been mentioned in the study design. We believe that treatment duration and the number of subjects were sufficient to show the difference in efficacies in our study.

Although nadifloxacin is still superior to other antibiotics in the rate of resistant pathogens, this fact might be due to its very recent availability among the other acne medications in the market [21]. Judging from the perspective of effectiveness, resistance and cost; the currently recommended therapy for mild to moderate acne is to use topical retinoids, benzoyl peroxide and/or antibiotics together [1,2,20].

In conclusion; although nadifloxacin has lower efficacy when used alone, it might have an additive effect in combination treatment of mild to moderate acne. Well designed, comparative studies and cost-effectivity analysis are still needed to include nadifloxacin as a specific agent.

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