Dermatology Practical & Conceptual

Comparative Efficacy of Topical N-Acetylcysteine-Doxycycline versus Benzoyl Peroxide-Doxycycline in Moderate Acne Vulgaris: An Add-on Double-Blind Randomized Controlled Trial

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ABSTRACT

Introduction: Acne vulgaris is a prevalent skin disorder, especially among adolescents. While topical retinoid and benzoyl peroxide (BPO) are standard treatments, their side effects often decrease patient adherence.

Objectives: This study aimed to explore the efficacy and safety of topical N-acetylcysteine (NAC) plus doxycycline compared to BPO-doxycycline in moderate acne vulgaris.

Method: In this double-blind randomized clinical trial, 40 patients were allocated into one of two groups: Group A received 100 mg/day doxycycline+5% NAC, while Group B received 100 mg/day doxycycline +5% BPO. Patients were assessed over three months using total lesion count (TLC), Investigator Global Assessment (IGA), Global Acne Grading System (GAGS), and Cardiff Acne Disability Index (CADI). Statistical analysis was performed using STATA 14.2, with $P<0.05$ considered significant.

Results: In comparison with BPO, NAC treatment led to a significantly greater improvement in CADI scores (MD=-3.60, 95% CI: -4.26 – -2.95, *P*<0.001), GAGS scores (MD = -9.76, 95% CI: -11.84 – -7.68, *P*<0.001), TLC (MD = -4.29, 95% CI: -6.38 – -2.19, *P*=0.002), inflammatory lesion count (MD = -2.93, 95% CI: -5.18– -0.68, *P*=0.003), and IGA scores (MD = -0.85, 95% CI: -1.12 – -0.58, *P*<0.001). Repeated mixed measures ANOVA further confirmed significant between-group differences in GAGS scores at the second and third months of patients' follow-up. Only one patient reported mild scaling with receiving NAC.

Conclusion: Topical NAC combined with doxycycline was significantly more effective than BPO-doxycycline in acne treatment, with minimal adverse effects. These results indicate that NAC may serve as an acceptable alternative for the treatment of moderate acne vulgaris.

Introduction

Acne is a prevalent inflammation of the pilosebaceous unit that affects around 85% of adolescents [1]. After 25 years of age, acne lesions persist in 3% of males and 12% of females. Only 1% of males and 5% of females with acne experience lesions up to the age of 40 [2]. Several factors contribute to acne, including excess sebum production, often influenced by hormones like androgens, increased keratinization of hair follicles leading to the formation of comedones, proliferation of Propionibacterium acnes bacteria on the skin surface, and elevated levels of inflammatory mediators that trigger the development of inflammatory acne lesions [3,4].

Research shows that inflammatory mediators, such as Toll-like receptor 2 (TLR-2), play a significant role in the development of acne. Propionibacterium acnes releases these mediators through TLR-2, leading to the formation of inflammatory acne lesions. Interleukins (ILs) such as IL1, IL6, IL8, IL12, IL17, and IL22 are key players in the development of acne lesions [3,5].

Acne lesions typically occur in more sebaceous areas such as the face, neck, chest, and back. In the beginning stages, comedones form when the infundibulum of the follicle is blocked. As the condition progresses, inflammatory mediators lead to the development of inflammatory papulopustular lesions, and in severe cases, nodulocystic lesions can form, potentially causing scarring [2,6]. Acne and its side effects, in particular acne scar, can greatly impact a person's quality of life, leading to psychological issues like anxiety and depression. Thus, it is necessary to treat acne before the appearance of the side effects [7,8]

There are various treatments for acne vulgaris, including topical retinoid compounds, antibiotics, comedolytics, isotretinoin, hormonal compounds like spironolactone, and oral contraceptives [9,10]

Oral antibiotics are a common acne treatment, especially in cases of papulopustular acne, mild nodulocystic acne, and when local treatments are not effective. These antibiotics work by fighting bacteria, reducing inflammation, and sometimes suppressing the immune system. Tetracyclines and macrolides are commonly prescribed antibiotics for acne. However, while antibiotics are effective, they can also cause side effects such as gastrointestinal issues, drug sensitivity, photosensitivity, and antibiotic resistance [11,12]. Common topical compounds used for treating skin conditions include retinoid and topical benzoyl peroxide. However, these compounds can cause side effects such as redness, dry skin, burning, and itching, leading some patients to stop using them [13].

Due to the potential side effects of these drugs, we decided to explore an alternative treatment with fewer side effects. N-acetyl cysteine (NAC) is a medicinal compound containing thiol that has been shown to act as an antidote to acetaminophen and as a mucolytic. Since NAC is a precursor to the antioxidant glutathione, using this drug can help inhibit the production of oxygen-free radicals and inflammatory cytokines. Studies have also indicated that NAC may have antibacterial and antiproliferative effects [14].

Objectives

Considering the side effects mentioned about the common acne therapies as well as the risk of antibiotic resistance with the use of antibiotics, the antibacterial and anti-inflammatory effect of NAC, and the fewer side effects of this drug compared to acne treatments, we decided to evaluate the adjuvant effect of this drug in patients with acne vulgaris who were receiving doxycycline. In order to reduce the risk of possible complications, we used the topical form of the drug in the form of a 5% gel.

Method

Study Design, Population, Sampling, and Sample Size Calculation

This study was a double-blind parallel randomized clinical trial on patients suffering from moderate acne vulgaris from April 2023 to January 2024. The study protocol was registered

on the Iranian Registry of Clinical Trials (IRCT) website with a trial registration number of IRCT20230921059485N1. In this regard, patients were included in the study based on the consecutive sampling method. The sample size was calculated based on similar previous studies and using Stata software version 14.2 with "sampsi" module. With a type I error of 0.05 (alpha) and a study power of 80 % (p), the sample size was calculated to be 20 patients in each study group.

A total of 40 patients aged 15–35 years with moderate acne vulgaris referred to our Dermatology Clinic were included in the study.

Inclusion and Exclusion Criteria

Patients with moderate acne who visited our Dermatology Clinic were selected for the study. The diagnosis was based on the clinical presentation of the patients. Patients between 15 and 35 years old with clinically diagnosed acne were included in the study. Married females agreed to use birth control methods during treatment (except for oral contraceptive pills, which can be effective in treating acne).

The exclusion criteria included a history of allergy to the medications used in the study, pregnancy, lactation, use of herbal medicines, use of systemic and topical anti-acne medications one month and two weeks before the study, respectively, the use of nitroglycerine and any drugs that interfere with our medications, liver or kidney disease, menstrual cycle disorders, polycystic ovary syndrome, and being under 15 or over 35 years of age.

Randomization and Blinding

The patients were divided into two groups using Random Allocation Software, version 1.0.0. In this regard, the patients were randomly divided into two groups (group A and group B) using block randomization with six blocks of four. Group A and B received NAC and benzoyl peroxide gel, respectively. In addition, dark envelopments were used to conceal the random allocation sequence.

Moreover, this study was designed as a double-blind clinical trial. The patients received the gels in identical containers which were coded by the second executor of the project. The patients received the drugs from the executor monthly. As the study was double-blinded, neither the participants nor the investigators knew which individuals received NAC or benzoyl peroxide.

The Intervention

All the patients in this study received doxycycline capsule manufactured by Hakim Pharmaceutical Company (Tehran, Iran) 100 mg once a day. Twenty patients in group A received N-acetyl cysteine gel 5% once a day. To prepare N-acetyl cysteine gel, we diluted N-acetyl cysteine powder in ethanol and glycerin; the resulting solution was then added to 3% carboxymethyl cellulose gel. To assess the stability of our product, PH and viscosity were measured at room temperature (25° C) at baseline and after three months The pH values were 6.8 and 7.1 at baseline and after three months, respectively, while the viscosity values were 2.5 and 2.7 Pascal-seconds at baseline and after three months, respectively. Upon confirming the stability of the product, we began using it in our study. In group B, patients received 5% benzoyl peroxide gel (Pangel) manufactured by Pars Behrozan Jam Company (Tehran, Iran).

Regarding the use of topical compounds, the patients were instructed to apply it on their entire face for half an hour at night and then wash it off with water. If there was no redness, the patients were instructed to gradually increase the duration of use and leave it on their face until morning. Patients were advised to use an oil-free sunscreen with an SPF of at least 50 when going out.

It should be noted that oral doxycycline is an established treatment for acne [12]. The rationale for prescribing it to both groups was based on ethical considerations, ensuring that participants were not deprived of a proven effective therapy. In addition, benzoyl peroxide is a common adjuvant treatment for acne, but it has some side effects, like itching and dry skin [6]. Therefore, we decided to use NAC as an adjuvant therapy and compare its efficacy and side effects with benzoyl peroxide, which is an established treatment for acne.

Data Collection and Outcomes Measures

The treatment lasted for three months, with patients being evaluated on a monthly basis. To determine the severity of acne, the total number of lesions according to their type (comedone, papule, pustule, and nodule) as well as the GAGS (Global Acne Grading System) and IGA (Investigator Global Assessment) scores were measured at the beginning of the study by the investigator (PM).

The scoring method of the GAGS scoring system is illustrated in Table 1. According to this system, scores of 1–18, 19–30, 31–38, and above 38 are considered mild, moderate,

Table 1. GAGS scoring system.

Anatomical area	Score	Type of Lesion	Score
Chin	1	No lesion	0
Nose	1	Comedone	1
Forehead	2	Papule	2
Right cheek	2	Postule	3
Left cheek	2	Nodule	4
Chest and back	3		

The score of each area: the lesion type score (0-4) × the anatomic area factor (1-3).

The global score is the sum of local scores.

Table 2. IGA scoring system.

Type of lesions	Grade
Clear skin with no lesion	0
Almost clear with rare non-inflammatory lesions	1
Mild, some non-inflammatory lesions with no more than a few inflammatory lesions, but no nodular lesions	2
Moderate, up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion	3
Severe, up to many non-inflammatory and inflammatory lesions, but no more than a few nodular lesions	4
Many non-inflammatory and inflammatory lesions and more than a few nodular lesions	5

severe, and very severe, respectively [15]. The IGA scoring method is also shown in Table 2 [16].

In order to evaluate the effect of acne on quality of life, the CADI (Cardiff Acne Disability Index) questionnaire was completed by the patient. The Persian version of this questionnaire was obtained from the online site of Cardiff after receiving permission from the author [17].

The efficacy of the treatment was assessed by total lesion count (TLC) and GAGS score monthly as well as by the IGA and CADI scores at the beginning and end of the study.

In order to evaluate the effect of the treatment, photographs were taken using visioface 1000D manufactured by CK Electronics, Germany at the beginning and end of the study.

Ethical Statements

The study protocol was approved by the local Research Ethics Committee (Ethics Code: IR.SUMS.MED.REC.1402.389). All patients signed a written informed consent form to participate in the study and allow the publication of their photos in the journal. In addition, the patients were free to withdraw from the study at any time during the study.

Statistical Analysis

The quantitative variables are described using mean and standard deviation. ANOVA/ ANCOVA was applied for comparison of these variables. In addition, chi-square test was used to compare the qualitative variables. Moreover, the adjustment for the baseline pretreatment score (calculated based on one-way ANOVA / ANCOVA model) was also applied. In addition, mean difference (MD) and standardized mean difference, including Cohen's d, with 95% confidence interval (95% CI), were estimated to explain the effect size of the interventions, which defined the interpretation interval as negligible (0–0.19), poor (0.20–0.49), moderate (0.5–0.79), or strong (0.8–1) [18]. For variables measured repeatedly over time, a mixed design repeated measures ANOVA (RM-ANOVA) was performed to assess the interaction between intervention and time. Post hoc analyses with Bonferroni correction were applied when appropriate. The results were analyzed using the STATA 14.2, and a p-value of <0.05 was considered statistically significant.

Results

Demographic Data and Patient Information before Treatment in Both Groups

In the present study, 55 patients were examined, but 46 patients were enrolled, with 23 participants in each study group. At the end of the study, 40 patients, including 20 patients in the NAC group and 20 patients in the benzoyl peroxide group, completed the study and were analyzed, as shown in the CONSORT diagram of the study (Figure 1). Demographic variables including sex and age were approximately similar in both groups (Table 3).

Outcomes Measures

GAGS Score

The GAGS scores before the intervention in the benzoyl peroxide and NAC groups were 23.50±6.04 and 23.65±7.42, respectively, which was not considerably different. After treatment, the GAGS score decreased over time, and this reduction was significantly greater in the NAC group compared with the benzoyl peroxide group in both crude and baseline-adjusted analyses at the second and third months of follow-up (P<0.001), with a strong effect size (Cohen's d>0.80) (Table 4). Moreover, RM-ANOVA demonstrated significant differences in GAGS scores between the study groups at the second and third months of follow-up, as shown in Table 5 and Figure 2.

CADI Score

In both groups, the CADI scores before the intervention did not show a statistically significant difference. Both the benzoyl peroxide and NAC groups demonstrated a reduction in the CADI score over time. At the third month of follow-up, the reduction in CADI score was significantly greater in the NAC group than in the benzoyl peroxide group, both in crude and baseline-adjusted analyses (P<0.001), with a strong effect size (Cohen's d>0.80) (Table 6).

CONSORT
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CONSORT 2010 Flow Diagram

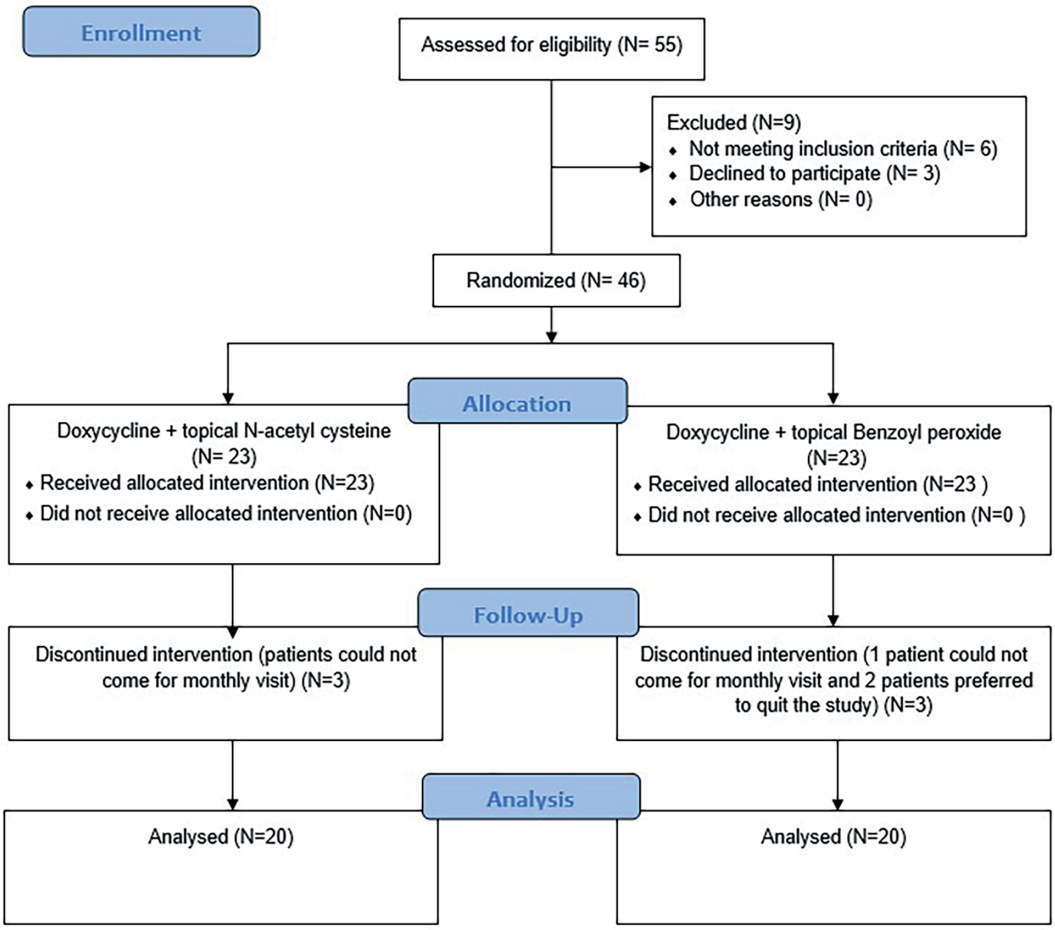

Figure 1. Consort diagram.

Table 3. Demographic characteristics of the participants in the study.

Demographic characteristics	Doxycycline + NAC (N=20)	Doxycycline + Benzoyl peroxide (N=20)	p-value
Age (Mean± SD)	21.95± 6.54	20.7±5.06	0.503
Sex (N, %)	Female: 11 (55%) Male: 9 (45%)	Female: 13 (65%) Male: 7 (35%)	0.519
Baseline CADI score	7.7±1.46	8.25± 1.65	0.271
Baseline GAGS score	23.65± 7.42	23.5± 6.04	0.94
Baseline total lesions count	24.45± 14.15	24.25± 12.69	0.962
Baseline inflammatory lesions count	13.9± 8.89	18.8± 11.57	0.141
Baseline non-inflammatory lesions count	10.05± 10.22	5.45± 7.38	0.111
Baseline IGA score	3.2± 0.62	3.1±0.55	0.592

Table 4. Efficacy of combination of doxycycline and topical N-acetyl cysteine versus doxycycline and topical benzoyl peroxide in the treatment of acne: evaluation of the study outcomes (GAGS) pre- and post-intervention according to different models.

Outcome	Model	Time	Group A (N=20) *	Group B (N=20) **	Mean Difference (95% CI)	Cohen's d (95% CI)	Partial Eta^2	P- value***	Adjusted R^2
GAGS	Crude	Pretreatment	23.65±7.42	23.5±6.04	0.15 (-4.18 to 4.49)				
		After 1 month	17.45±5.92	20.15±5.92	-2.7 (-6.49 to 1.09)	-0.46 (-1.18 to 0.08)	0.05	0.158	0.027
		After 2 months	13.6±5.42	20.5±5.42	-6.9 (-10.37 to -3.43)	-1.27 (-1.95 to -0.58)	0.30	<0.001	0.280
		After 3 months	9.05±4.20	18.75±4.20	-9.7 (-12.39 to -7.02)	-2.31 (-3.11 to -1.50)	0.58	<0.001	0.574
	Adjusted[a]	Pretreatment	23.65± 7.42	23.5±6.04	0.15 (-4.18 to 4.49)				
		After 1 month	17.42±5.34	20.18±5.34	-2.76 (-6.18 to -0.66)	-0.51 (-1.14 to 0.12)	0.07	0.11	0.208
		After 2 months	13.56±4.29	20.54±4.29	-6.98 (-9.73to -4.23)	-1.63 (-2.34 to -0.90)	0.42	<0.001	0.550
		After 3 months	9.02±3.24	18.78±3.24	-9.76 (-11.84 to -7.68)	-3.01 (-3.92 to -2.09)	0.71	<0.001	0.75

*Doxycycline+N-acetylcystein; **Doxycycline+Benzoyl peroxide; ***Significant ($P \leq 0.05$); a: Adjusted for baseline pretreatment score (calculated based on one-way ANOVA / ANCOVA model)

Table 6. Efficacy of combination of doxycycline and topical N-acetyl cysteine versus doxycycline and topical benzoyl peroxide in the treatment of acne: evaluation of the study outcomes (IGA and CADI) pre- and post-intervention according to different models.

Outcome	Model	Time	Group A (N=20)*	Group B (N=20)**	Mean Difference (95% CI)	Cohen's d (95% CI)	Partial Eta^2	P- value***	Adjusted R^2
IGA	Crude	Pretreatment	3.2±0.62	3.1± 0.55	0.1 (-0.27 to 0.47)				
		After 3 months	1.8±.51	2.6±.51	-0.8 (-1.12 to -0.47)	-1.56 (-2.26 to -0.84)	0.39	<0.001	0.374
		Pretreatment	3.2±0.62	3.1± 0.55	0.1 (-0.27 to 0.47)				
		After 3 months	1.77±0.42	2.62±0.42	-0.85 (-1.12 to -0.58)	-2.00 (-2.76 to -1.23)	0.52	<0.001	0.573
CADI	Adjusted[a]	Pretreatment	7.7±1.45	8.25± 1.65	-0.55 (-1.55to 0.45)				
		After 3 months	2.55±1.40	6.5±1.40	-3.95 (-4.84 to -3.06)	-2.84 (-3.71 to -1.94)	0.68	<0.001	0.670
		Pretreatment	7.7±1.45	8.25± 1.65	-0.55 (-1.55to 0.45)				
		After 3 months	2.72±1.02	6.32±1.02	-3.60 (-4.26 to -2.95)	-3.55 (-4.5 to -2.53)	0.77	<0.001	0.82

*Doxycycline+N-acetylcystein; **Doxycycline+Benzoyl peroxide; ***Significant ($P \leq 0.05$); a: Adjusted for baseline pretreatment score (calculated based on one-way ANOVA / ANCOVA model

IGA Score

The initial IGA score in the benzoyl peroxide and NAC groups before the treatment was 3.1± 0.55 and 3.2 ± 0.62, respectively, showing no considerable difference. The IGA scores in both groups decreased at the end of the study, but the reduction in the NAC group was significantly more than the other group (P<0.001), with a strong effect size (Cohen's d>0.80) (Table 6).

Total Lesion Count

TLC before the treatments in the benzoyl peroxide and NAC groups were 24.25±12.69 and 24.45±14.15, respectively, which did not show considerable difference. After the treatment, TLC significantly decreased over time in both groups. However, the reduction in the NAC group was more significant than the benzoyl peroxide group at the end of the third month (*P*=0.002), with strong effect sizes (Cohen's d>0.80) (Table 7). As presented in Table 5 and Figure 2, RM-ANOVA indicated a non-significant interaction between intervention and time regarding patients' TLC.

Inflammatory Lesion Count

Inflammatory lesion count before the treatment in the benzoyl peroxide and NAC groups were 18.8± 11.57 and 13.9± 8.89, respectively, which did not show significant difference. The inflammatory lesion count in both groups decreased at the end of the study, but the reduction in the NAC group was greeater in comparison with other group, with a strong Cohen's d (Table 7).

Non-Inflammatory Lesion Count

Before treatment, the non-inflammatory lesion counts were 5.45±7.38 in the benzoyl peroxide group and 10.05±10.22 in the NAC group, showing no considerable difference between them. The non-inflammatory lesion counts in both groups decreased over time, but the reduction was not significantly different, according to both crude and baseline-adjusted analyses, with a small-to-moderate effect size value (Table 7).

Adverse Effects Evaluation

In the NAC group, one patient expressed mild scaling after the application of the agent but continued participating in the study. In the benzoyl peroxide group, two patients reported mild erythema, and two expressed scaling but continued to participate in the study.

Discussion

The present study aimed to investigate the effect of NAC gel in the treatment of moderate acne and compare it with benzoyl peroxide in a randomized controlled double-blind trial. The results of our study revealed that both benzoyl peroxide and NAC were effective in the acne treatment (Figures 3 and 4). However, NAC gel was more effective in the reduction of TLC, GAGS, CADI, and IGA scores. In addition, the significant differences observed in GAGS scores between the study groups at the second and third months of follow-up suggest that the intervention had a remarkable impact on acne severity over time, highlighting its potential clinical benefit.

Acne vulgaris is considered as one of the most common dermatological problems which can affect patients' quality of life [19]. Several studies have been done on various topical, systemic, and physical therapies for acne vulgaris. Photodynamic therapy, intense pulsed light (IPL), pulsed dye laser (PDL), neodymium: yttrium-aluminum garnet laser (ND:YAG), and erbium: glass laser (Er:glass) are among the novel physical treatments that can be used as monotherapy or in combination with other therapies [20]. Topical products are beneficial in dermatology because they can be applied directly to the involved area, reducing the amount absorbed into the body and allowing for better treatment of the hair follicles and sebaceous glands. Topical anti-inflammatory agents and antibiotics can effectively treat mild-to-moderate inflammatory acne. Various topical agents have been used in the treatment of acne vulgaris, including benzoyl peroxide, tretinoin, salicylic acid, Azelaic acid, and dapsone. Benzoyl peroxide is a topical disinfectant with various properties that make it effective in treating acne; it can unclog the pores and kill bacteria without affecting sebum production. It can also reduce the number of comedones on the skin. However, its major side effects, which are burning, dryness, erythema, peeling, or stinging, have limited its use [21].

Tetracyclines, particularly doxycycline and minocycline, remain the most prescribed oral antibiotics for acne vulgaris because of their efficacy, safety, and clinical experience. While all three major tetracyclines (tetracycline, doxycycline, and minocycline) are FDA-approved for infections, doxycycline and minocycline are preferred over tetracycline due to less frequent dosing, better absorption, increased lipophilicity, and lower resistance rates in Propionibacterium acnes [22].

Some studies have been done to find a safe and effective topical agent with the minimal side effects [23-25]. Topical clascoterone is a steroidal antiandrogen with anti-inflammatory effects. Its most common side effects are nasopharyngitis and headaches, but it has better efficacy in the treatment of acne compared with tretinoin 0.05% cream [23]. Herbert et al., in a two-phase randomized clinical trial, showed that clascoterone cream 1% demonstrates favorable efficacy and safety in the treatment of facial acne [25]. It should be noted that oral forms of anti-androgens such as spironolactone, cyproterone acetate, and flutamide are also among the treatment options in females with moderate-to-severe acne

Table 7. Efficacy of combination of doxycycline and topical N-acetyl cysteine versus doxycycline and topical benzoyl peroxide in the treatment of acne: evaluation of the study outcomes (Total lesion count) pre- and post-intervention according to different models.

Outcome	Model	Time	Group A (N=20) *	Group B (N=20) **	Mean Difference (95% CI)	Cohen's d (95% CI)	Partial Eta^2	P- value***	Adjusted R^2
Total lesion count	Crude	Pretreatment	24.45±14.15	24.25±12.69	0.2 (-8.40 to 8.80)				
		After 1 month	13.85±7.74	14.65±7.74	-0.8 (-5.75 to 4.15)	-0.10 (-0.72 to 0.52)	0.003	0.746	-0.023
		After 2 months	8.75±5.75	11.7±5.75	-2.95 (-6.63 to 0.73)	-0.51 (-1.14 to 0.12)	0.07	0.113	0.040
		After 3 months	5.7±3.99	9.95±3.99	-4.25 (-6.81 to -1.70)	-1.07 (-1.72 to -0.40)	0.23	0.002	0.210
	Adjusted[a]	Pre-treatment	24.45±14.15	24.25±12.69	0.2 (-8.40 to 8.80)				
		After 1 month	13.80±4.25	14.69±4.25	0.90 (-1.83 to 3.62)	-0.21 (-.83 to 0.41)	0.01	0.509	0.691
		After 2 months	8.72±4.52	11.73±4.52	-3.00 (5.90 to 0.11)	-0.67 (-1.30 to -0.02)	0.11	0.042	0.408
		After 3 months	5.68± 3.26	9.97± 3.26	-4.29 (-6.38 to -2.19)	-1.31 (-1.99 to -0.62)	0.32	<0.001	0.471
Inflammatory type lesions	Crude	Pretreatment	13.9± 8.89	18.8± 11.57	-4.9 (-11.51 to 1.71)				
		After 3 months	2.1± 3.83	5.9± 3.83	-3.8 (-6.25 to -1.35)	-.99 (-1.65 to -0.33)	0.20	0.003	0.185
	Adjusted[a]	Pretreatment	13.9± 8.89	18.8± 11.57	-4.9 (-11.51 to 1.71)				
		After 3 months	2.53±3.46	5.47±3.46	-2.93 (-5.18 to -0.68)	-0.84 (-1.49 to -0.19)	0.16	0.012	0.354
Non-inflammatory type lesions	Crude	Pretreatment	10.05±10.22	5.45± 7.38	4.6 (-1.11 to 10.31)				
		After 3 months	3.6± 2.75	3.75± 2.75	-0.15 (-1.91 to 1.61)	-0.05 (-0.67 to 0.57)	0.0007	0.863	-0.025
	Adjusted[a]	Pretreatment	10.05±10.22	5.45± 7.38	4.6 (-1.11 to 10.31)				
		After 3 months	3.21±2.38	4.13±2.38	-0.91 (-2.47 to 0.64)	-0.38 (-1.01 to 0.25)	0.04	0.241	0.253

*Doxycycline+N-acetylcystein; **Doxycycline+Benzoyl peroxide; ***Significant ($P \leq 0.05$); a: Adjusted for baseline pretreatment score (calculated based on 0ne-way ANOVA / ANCOVA model)

Table 5. Between-group comparisons (Group A vs. Group B) of GAGS score and total lesion counts at different time points versus baseline, using RM-ANOVA with Bonferroni correction.

Variables/ Comparison	Time point	Group A* (mean± SD)	Group B** (mean± SD)	Mean difference (95% CI with Bonferroni correction)	p-value***
GAGS (Group A vs Group B)	Baseline	23.65± 7.42	23.5± 6.04		
	1st month vs baseline	17.45± 5.99	20.15± 5.86	-2.85 (-8.97 to 3.27)	0.784
	2nd month vs baseline	13.6±4.27	20.5±6.37	-7.05 (-13.17 to -0.93)	0.018
	3rd month vs baseline	9.05±2.84	18.75±5.21	-9.85 (-15.97 to -3.73)	<0.001
Total lesion counts (Group A vs Group B)	Baseline	24.45±14.15	24.25± 12.69		
	1st month vs baseline	13.85±8.11	14.65±7.35	-1 (-10.21 to 8.21)	1.000
	2nd month vs baseline	8.75±6.01	11.7± 5.48	-3.15 (-12.36 to 6.06)	1.000
	3rd month vs baseline	9.05 ±2.84	18.75± 5.21	-4.45 (-13.66 to 4.76)	0.732

*Doxycycline+N-acetylcystein; **Doxycycline+Benzoyl peroxide; ***Significant ($P \leq 0.05$)

resistant to other therapies or with hyperandrogenism symptoms [26]. Topical trifarotene, a selective vitamin A analog, is another novel topical agent that has been used in trials for the treatment of acne and has shown excellent efficacy and potency [24].

In this study, we investigated the efficacy of NAC as an antioxidant in the treatment of facial acne. According to the mechanism of action of NAC, it has been observed that this drug can be effective in many vascular, pulmonary, psychiatric, and neurological diseases. Several case reports and clinical trial studies on the effect of this drug on skin diseases, including trichotillomania, severe drug sensitivity reactions and toxic epidermal necrolysis (TEN), melasma, connective tissue diseases, wound healing, ichthyosis, Xeroderma pigmentosum, and protection against sun damage, radiodermatitis and Raynaud's phenomenon, have been done. According to these studies, NAC has antiproliferative and antibacterial activity and also inhibits the release of inflammatory cytokines and oxygen-free radicals. Therefore, based on its mechanism of action, NAC can be effective in the treatment of acne [19,27].

The study by Nakai et al. (2015) demonstrated that topical application of 20% NAC solution twice daily for four weeks improves skin barrier function in patients with atopic dermatitis, as it increased skin hydration and decreased transepidermal water loss (TEWL) [28]. The randomized controlled trial by Rosato et al. (2009) demonstrated that intravenous NAC (15 mg/kg/hour every two weeks) reduces digital ulcers and Raynaud's phenomenon attacks in patients with systemic sclerosis (SSc). These findings showed that NAC may improve vascular dysfunction and tissue damage in SSc, likely through its vasoprotective and antioxidant effects [29]. Grant et al., in a randomized controlled trial (2016), found that oral NAC at doses of 1200–3000 mg/day significantly reduced nail biting behavior in patients with excoriation disorder, with 47% showing marked improvement compared to only 19% in the placebo group. This suggests that NAC may be an effective treatment for body-focused repetitive behaviors, possibly due to its modulation of glutamatergic pathways in the cortico-striatal circuits, which are implicated in compulsive disorders [30].

A limited number of studies have investigated the effect of NAC on patients with acne. A study conducted in 2012 by Haidar Al Anbari et al. investigated the effect of oral compounds of NAC, silymarin, and selenium in the treatment of acne and observed that all three oral compounds can be effective in reducing acne inflammatory lesions [31]. In another study conducted in 2012 by Ahmed Salih Sabib et al., the antioxidant effect of NAC, selenium, and silymarin in acne was investigated; they observed that these compounds are effective in treating papulopustular acne [32]. In these studies, inflammatory markers, including IL-8 and malondialdehyde (MDA) associated with acne, were measured, and they were reduced eight weeks after treatment with NAC. The number of inflammatory lesions was also reduced in patients with papulopustular acne. In contrast to these two studies, Divyesh Thakker and colleagues conducted a study for the treatment of patients with polycystic ovaries, showing that oral N-acetylcysteine had no effect on acne, hirsutism, weight gain, increased blood sugar, or insulin resistance, but

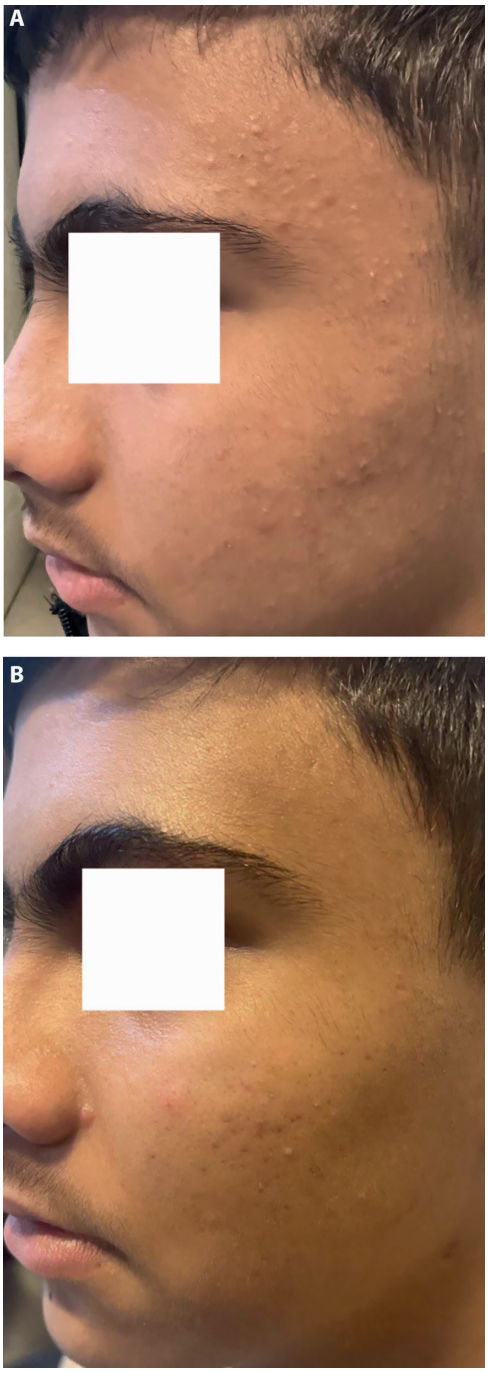

Figure 3. Therapeutic effect of NAC gel on acne: A) before treatment; B) after treatment.

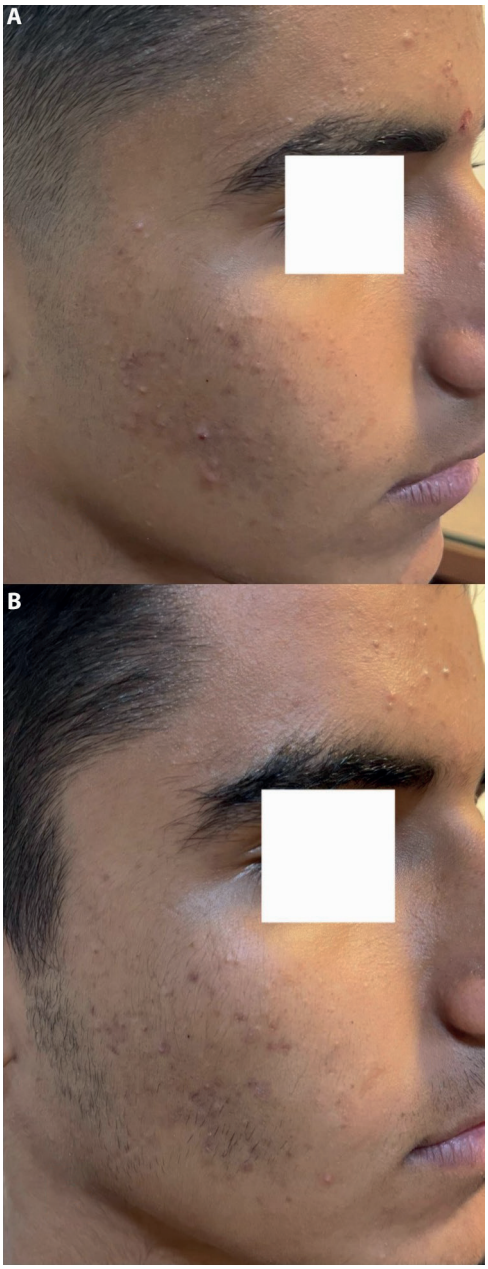

Figure 4. Therapeutic effect of benzoyl peroxide gel on acne: A) before treatment; B) after treatment.

they found that this drug significantly improved ovulation and increased the probability of pregnancy [32,33].

There has been only one study on the efficacy of topical NAC in the treatment of acne so far. Montes et al. investigated the effect of 5% NAC topical gel on acne in a double-blind placebo-controlled trial, and they observed that comedones were significantly reduced after eight weeks of treatment [34].

Limitations

This study has some limitations. Firstly, this study estimated the minimum sample size, but subgroup analyses and definitive conclusions require a larger sample size. Next, due to ethical concerns and the need to treat all patients with an established treatment, we could not prescribe NAC alone. Therefore, the effect of NAC and benzoyl peroxide could not be compared independently. To date, only one study has been done on the effect of topical NAC on acne. Additionally, all participants were from the same country, which may limit the generalizability of these findings to more diverse populations. Therefore, further studies with larger sample sizes and more heterogenous populations are needed to confirm and extend the results of our study. It should also be noted that acne is a multifactorial disease influenced by various factors such as body mass index (BMI) [35], race [36], systemic diseases [37], and medications [38]. Our study did not account

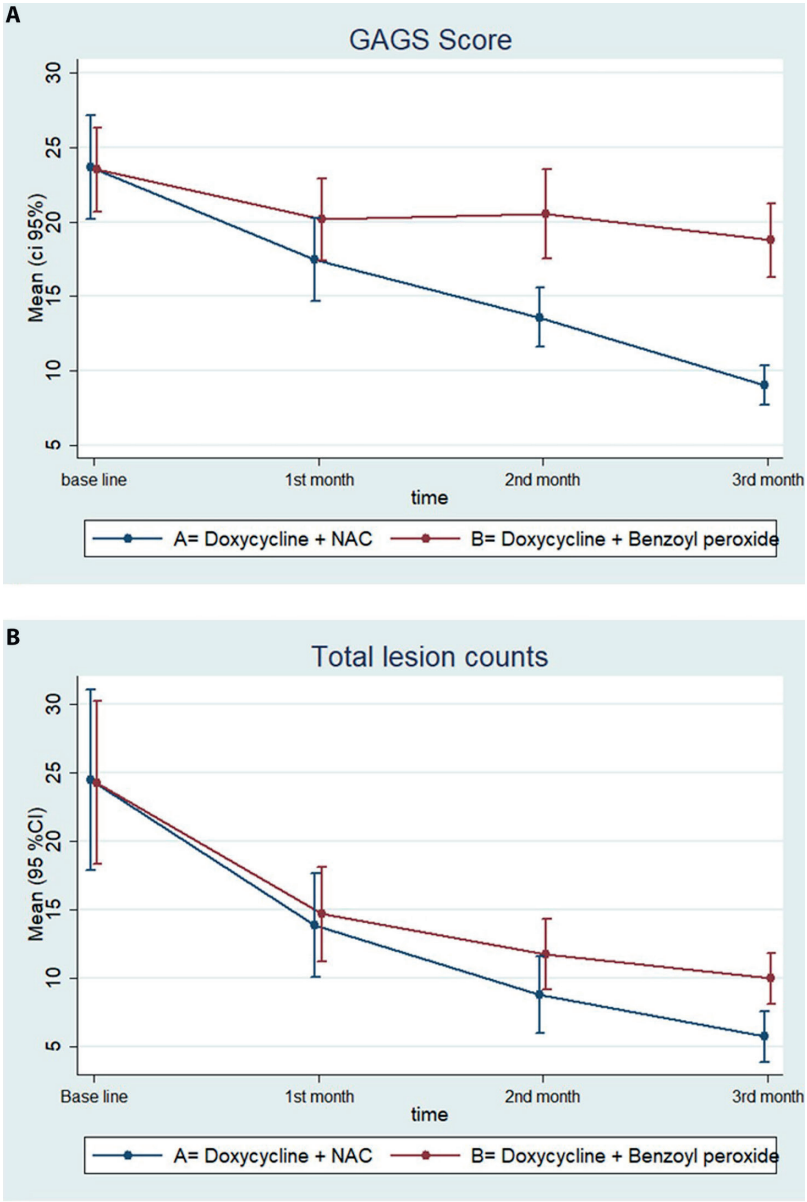

Figure 2. A) changes in GAGS scores across the study groups during three months of follow-up; B) changes in total lesion counts across the study groups during three months of follow-up.

for these variables and their potential impact on acne severity and treatment responsiveness. It is recommended to consider these factors in future studies.

Furthermore, this study was conducted on patients with moderate acne vulgaris; patients with mild or severe acne vulgaris were not included. It is recommended investigating the effect of NAC as an adjuvant treatment in mild, moderate, and severe acne vulgaris in future studies.

In addition, this study is a clinical trial that investigated the clinical outcomes of applying NAC but did not explore its direct effect on the cytokine levels. It is recommended that future studies investigate the direct effects of NAC on the cytokine level in addition to clinical outcomes. Conversely, while most effect sizes indicating the efficacy of the interventions for acne treatment fell within a large effect interval, the wide ranges of the 95% confidence intervals suggested that these results were inconclusive; therefore, further studies with larger sample sizes are strongly recommended.

Conclusion

In the present study, we evaluated the efficacy of NAC gel using IGA, CADI, and GAGS scores. The results showed that after treatment with NAC, all scores were significantly reduced. There was also a significant decrease in TLC after treatment. As only one patient reported mild scaling after treatment with NAC, this agent may be a suitable option for dermatologists to treat patients with mild to moderate facial acne.

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References

1. Yan HM, Zhao HJ, Guo DY, Zhu PQ, Zhang CL, Jiang W. Gut microbiota alterations in moderate to severe acne vulgaris patients. *J Dermatol*. 2018;45(10):1166-1171. DOI:10.1111/1346-8138.14586.
2. Purdy S, de Berker D. Acne vulgaris. *BMJ Clin Evid*. 2011;2011:1714. PMID:21477388.
3. Dréno B. What is new in the pathophysiology of acne, an overview. *J Eur Acad Dermatol Venereol*. 2017;31:8-12. DOI:10.1111/jdv.14374.
4. Li X, He C, Chen Z, Zhou C, Gan Y, Jia Y. A review of the role of sebum in the mechanism of acne pathogenesis. *J Cosmet Dermatol*. 2017;16(2):168-173. DOI:10.1111/jocd.12345.
5. Liu Y, Sun Q, Xu H, Ma G, Wu P. Serum level changes of inflammatory cytokines in patients with moderate to severe acne vulgaris treated with dual-wavelength laser. *Chinese Journal of Plastic and Reconstructive Surgery*. 2023;5(2):47-52. DOI:10.1016/j.cjprs.2023.05.001.
6. Eichenfield DZ, Sprague J, Eichenfield LF. Management of acne vulgaris: a review. *JAMA*. 2021;326(20):2055-2067. DOI:10.1001/jama.2021.17633.
7. Samuels DV, Rosenthal R, Lin R, Chaudhari S, Natsuaki MN. Acne vulgaris and risk of depression and anxiety: a meta-analytic review. *J Am Acad Dermatol*. 2020;83(2):532-541. DOI:10.1016/j.jaad.2020.02.040.
8. Sood S, Jafferany M, Vinaya Kumar S. Depression, psychiatric comorbidities, and psychosocial implications associated with acne vulgaris. *J Cosmet Dermatol*. 2020;19(12):3177-3182. DOI:10.1111/jocd.13753.
9. Mohsin N, Hernandez LE, Martin MR, Does AV, Nouri K. Acne treatment review and future perspectives. *Dermatol Ther (Heidelb)*. 2022;35(9):e15719. DOI:10.1111/dth.15719.
10. Tobiasz A, Nowicka D, Szepietowski JC. Acne vulgaris—Novel treatment options and factors affecting therapy adherence: A narrative review. *J Clin Med*. 2022;11(24):7535. DOI:10.3390/jcm11247535.
11. Baldwin H. Oral antibiotic treatment options for acne vulgaris. *J Clin Aesthet Dermatol*. 2020;13(9):26-32. PMID:33133338.
12. Kircik LH. Doxycycline and minocycline for the management of acne: a review of efficacy and safety with emphasis on clinical implications. *J Drugs Dermatol*. 2010;9(11):1407-1411. PMID:21061764.
13. Narsa AC, Suhandi C, Afidika J, Ghaliya S, Elamin KM, Wathoni N. A Comprehensive Review of the Strategies to Reduce Retinoid-Induced Skin Irritation in Topical Formulation. *Dermatol Res Pract*. 2024:5551774. DOI:10.1155/2024/5551774.
14. Pei Y, Liu H, Yang Y, et al. Biological activities and potential oral applications of N-acetylcysteine: progress and prospects. *Oxid Med Cell Longev*. 2018;2018(1):2835787. DOI:10.1155/2018/2835787.
15. Alsulaimani H, Kokandi A, Khawandanh S, Hamad R. Severity of Acne Vulgaris: Comparison of Two Assessment Methods. *Clin Cosmet Investig Dermatol*. 2020;13:711-716. DOI:10.2147/ccid.S266320.
16. Bae IH, Kwak JH, Na CH, Kim MS, Shin BS, Choi H. A Comprehensive Review of the Acne Grading Scale in 2023. *Ann Dermatol*. 2024;36(2):65-73. DOI:10.5021/ad.23.094.
17. Aghaei S, Mazharinia N, Jafari P, Abbasfard Z. The Persian version of the Cardiff Acne Disability Index. Reliability and validity study. *Saudi Med J*. 2006;27(1):80-82. PMID:16432599.
18. Serdar CC, Cihan M, Yücel D, Serdar MA. Sample size, power and effect size revisited: simplified and practical approaches in pre-clinical, clinical and laboratory studies. *Biochem Med (Zagreb)*. 2021;31(1):27-53. DOI:10.11613/BM.2021.010502.
19. Mardani N, Mozafarpoor S, Goodarzi A, Nikkhah F. A systematic review of N-acetylcysteine for treatment of acne vulgaris and acne-related associations and consequences: Focus on clinical studies. *Dermatol Ther (Heidelb)*. 2021;34(3):e14915. DOI:10.1111/dth.14915.
20. Jean-Pierre P, Tordjman L, Ghodasara A, Nwosu C, Nouri K. Emerging lasers and light-based therapies in the management of acne: a review. *Lasers Med Sci*. 2024;39(1):245. DOI:10.1007/s10103-024-04196-8.
21. Fox L, Csongradi C, Aucamp M, Du Plessis J, Gerber M. Treatment modalities for acne. *Molecules*. 2016;21(8):1063. DOI:10.3390/molecules21081063.
22. Del Rosso JQ. Oral Doxycycline in the Management of Acne Vulgaris: Current Perspectives on Clinical Use and Recent Findings with a New Double-scored Small Tablet Formulation. *J Clin Aesthet Dermatol*. 2015;8(5):19-26. PMID:26029331.
23. Han JJ, Faletsky A, Barbieri JS, Mostaghimi A. New acne therapies and updates on use of spironolactone and isotretinoin: a narrative review. *Dermatol Ther (Heidelb)*. 2021;11(1):79-91. DOI:10.1007/s13555-020-00481-w.
24. Naik PP. Trifarotene: a novel therapeutic option for acne. *Dermatol Res Pract*. 2022;2022(1):1504303. DOI:10.1155/2022/1504303.
25. Hebert A, Thiboutot D, Gold LS, et al. Efficacy and safety of topical clascoterone cream, 1%, for treatment in patients with facial acne: two phase 3 randomized clinical trials. *JAMA dermatol*. 2020;156(6):621-630. DOI:10.1001/jamadermatol.2020.0465.
26. Gao J, Mahto A. Anti-Androgen Therapy in Female Adult Acne. *J Dermatol Res Ther*. 2016;2(2):23. DOI:10.23937/2469-5750/1510023.
27. Janeczek M, Moy L, Riopelle A, et al. The potential uses of N-acetylcysteine in dermatology: a review. *J Clin Aesthet Dermatol*. 2019;12(5):20-26. PMID:31320973.
28. Nakai K, Yoneda K, Murakami Y, et al. Effects of Topical N-Acetylcysteine on Skin Hydration/Transepidermal Water Loss in Healthy Volunteers and Atopic Dermatitis Patients. *Ann Dermatol*. 2015;27(4):450-451. DOI:10.5021/ad.2015.27.4.450.
29. Rosato E, Borghese F, Pisarri S, Salsano F. The treatment with N-acetylcysteine of Raynaud's phenomenon and ischemic ulcers therapy in sclerodermic patients: a prospective observational study of 50 patients. *Clin Rheumatol*. 2009;28(12):1379-1384. DOI:10.1007/s10067-009-1251-7.
30. Grant JE, Chamberlain SR, Redden SA, Leppink EW, Odlaug BL, Kim SW. N-Acetylcysteine in the Treatment of Excoriation Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*. 2016;73(5):490-496. DOI:10.1001/jamapsychiatry.2016.0060.
31. AlAnbari H, Sahib A, Raghif A. Effects of silymarin, N-acetylcysteine and selenium in the treatment of papulopustular acne. *Oxid Antioxid Med Sci*. 2012;1:201-207. DOI:10.5455/oams.290912.or.019.
32. Sahib A, Al-Anbari H, Salih M, Abdullah F. Effects of oral antioxidants on lesion counts associated with oxidative stress and

inflammation in patients with papulopustular acne. *J Clin Exp Dermatol Res*. 2012;3(163):2. DOI:10.4172/2155-9554.1000163.
33. Thakker D, Raval A, Patel I, Walia R. N-acetylcysteine for polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. *Obstet Gynecol Int*. 2015;2015(1):817849. DOI:10.1155/2015/817849.
34. Montes LF, Wilborn WH, Montes CM. Topical acne treatment with acetylcysteine: clinical and experimental effects. *Skinmed*. 2012;10(6):348-351. PMID:23346662.
35. Lajevardi V, Ghodsi SZ, Daneshpazhooh M, Kazemi H, Aryanian Z, Goodarzi A. The relationship between body mass index and the severity of acne. *Iranian Journal of Dermatology*. 2014;17(1):13-17.
36. Barbieri JS, Shin DB, Wang S, Margolis DJ, Takeshita J. Association of race/ethnicity and sex with differences in health care use and treatment for acne. *JAMA Dermatol*. 2020;156(3):312-319. DOI:10.1001/jamadermatol.2019.4818.
37. Uzuncakmak TK, Karadag AS, Akdeniz N. Acne and systemic diseases. *EMJ Dermatol*. 2015;3:73-78. DOI:10.33590/emjdermatol/10314085.
38. Kazandjieva J, Tsankov N. Drug-induced acne. *Clin Dermatol*. 2017;35(2):156-162. DOI:10.1016/j.clindermatol.2016.10.007.