Efficacy, safety, and tolerability of dapsone 5% gel and benzoyl peroxide 5% gel in combination with oral doxycycline in treating moderate acne vulgaris: a randomized clinical trial

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Background: Acne vulgaris is a common skin disease. Choosing an appropriate treatment modality is important. We compared benzoyl peroxide 5% gel vs. new topical dapsone 5% gel in combination with doxycycline to improve acne.

Methods: In a clinical trial, 60 cases with acne vulgaris aged 18-25 years were divided randomly into two groups, DD (dapsone 5% gel plus oral 100 mg doxycycline) and BD (benzoyl peroxide 5% gel plus oral 100 mg doxycycline). Topical dapsone 5% gel was made for the first time at Guilan University of Medical Sciences. The lesion counts, side effects, and acne severity (GAAS) were examined at baseline, 2, 4, 8, and 12 weeks. Satisfaction and improvement were assessed after 12 weeks. The Mann-Whitney, chi-squared, Wilcoxon, and Friedman tests were used for statistical analysis in SPSS v. 21.

Results: Inflammatory and non-inflammatory lesions were similar between the groups. Lesions were reduced within groups ($P > 0.05$). GAAS scores were similar between groups but decreased in both groups after 12 weeks ($P = 0.003$). Side effects (especially skin dryness) were less in the BD group after 12 weeks ($P = 0.017$), though erythema and skin irritation were less in the DD group ($P > 0.05$). Both groups reported a similar improvement rate (85%). However, satisfaction was more in the DD group (78%).

Conclusion: The new dapsone 5% gel seems to be as effective as benzoyl peroxide 5% in combination with doxycycline. Considering its good tolerability, safety, and acceptability, it is suggested as an appropriate treatment for moderate acne vulgaris. (Clinical trial number: IRCT2017072035195N1)

Keywords: Dapsone gel, Benzoyl Peroxide gel, Doxycycline, Acne, RCT

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INTRODUCTION

Acne vulgaris, the most common skin disease, can negatively affect the body's appearance and may lead to psychological disorders such as depression or anxiety. Inflammatory and non-inflammatory skin lesions characterize this disease [1]. According to reports by the Global Burden of Disease in 2015, the prevalence of acne vulgaris was estimated at 9.4%, ranked as the eighth most prevalent disease in the world [2]. Its prevalence was 87% in adolescents and 54% in adults [3]. Burden of acne vulgaris was

reported at 82.4% in 2017 [4].

Standard treatments for acne vulgaris include topical retinoid, benzoyl peroxide, azelaic acid, antibiotics (topical or oral), and oral isotretinoin [5-7]. The choice of therapy depends on the age, site, and severity of acne [8]. Advances in pharmacology have led to the production of topical dapsone 5% gel with long-term safety [5]. It works to treat acne vulgaris by directly blocking leukocyte traffic and inflammatory chemical mediators' production, and its indirect effect operates by reducing the level or activity of *Cutibacterium acnes* [9]. The efficacy of topical dapsone in the treatment of acne and in decreasing the number of inflammatory and non-inflammatory lesions is higher than that of the carrier drug [5]. In most studies, dapsone gel has been used as a single-drug therapy. However, it has also been safe and tolerable in combination with benzoyl peroxide or adapalene. The most common complications of dapsone gel are skin dryness and erythema. In long-term evaluation, there are no reports of significant side effects like hemolytic anemia, methemoglobinemia, or agranulocytosis, even in G6PD deficiency [10].

Benzoyl peroxide gel is another topical treatment for acne that inhibits the proliferation of antibiotic-resistant *Cutibacterium* strains, decreases the inflammatory and non-inflammatory lesions, and reduces the level of *C. acnes* [11]. No resistance to benzoyl peroxide has been reported so far. Contact dermatitis (mostly irritant rather than allergic) and whitening of clothes and bedding may occur with benzoyl peroxide [12].

Among oral treatments, doxycycline is the only available tetracycline product that shows anti-inflammatory effects other than antibiotic effects in the treatment of acne vulgaris [12]. Combination of oral doxycycline 100 mg with topical dapsone 5% gel or benzoyl peroxide gel 5% is an effective and well-tolerated regimen for moderate to severe acne vulgaris. Due to the lack of comparative studies to evaluate the efficacy of benzoyl peroxide versus the dapsone 5% gel, especially in combination with doxycycline, we aimed to compare benzoyl peroxide with topical dapsone 5% gel. In our study, dapsone 5% gel was made in the Faculty of Pharmacy of Guilan University of Medical Sciences, for the first time, due to the higher cost of the similar foreign ones [13]. This matter makes our study different from other studies. Besides, we assessed most treatment features including safety, tolerability, and patient satisfaction, in addition to treatment efficacy, which is less seen in other studies.

PARTICIPANTS AND METHODS

Trial design and participants

This study was a double-blinded, randomized clinical trial with a 1: 1 allocation ratio. Patients with acne vulgaris aged 18–25 years referring to the Dermatology Clinic of Razi Hospital (Rasht, Iran) from June to December 2019 were assessed for eligibility. Informed consent was obtained before the study. This study was approved by the Ethics Committee of Guilan University of Medical Sciences and was performed according to the Declaration of Helsinki (Ethics Code: IR.Gums.Rec.1396.26; IRCT ID: IRCT2017072035195N1).

Inclusion, exclusion, and withdrawal criteria

Inclusion criteria were patients with acne vulgaris with 15–50 inflammatory lesions and 20–100 non-inflammatory lesions, or a total of 30 to 120 lesions (ranked as moderate in the GAAS classification).

Exclusion criteria were secondary acne due to other diseases, using other oral or topical medicines to treat acne, G6PD deficiency, severe nodular cystic acne (ranked as very severe in the GAAS classification), and acne conglobata.

Withdrawal criteria were pregnancy, lactation, having an allergy to dapsone or sulfonic drugs, simultaneous taking of sulfone and anti-malarial drugs and cotrimoxazole, the presence of other skin diseases in the face, taking doxycycline simultaneously with barbiturates, phenytoin, or carbamazepine [14], patients with severe and intolerable local side effects or with disease progressing to severe nodulocystic lesions or acne conglobata, the use of acne-inducing or acne-aggravating medications, and patients quitting the study or not visiting the clinic at the given time.

Intervention method

At first, the inflammatory and non-inflammatory lesions and GAAS scores were evaluated. Then, patients were randomly assigned to two groups. The first group received dapsone 5% gel daily plus

100 mg doxycycline capsules daily for 12 weeks. Dapsone is an odorless white crystalline powder, whose composition is prepared in a water-borne gel for topical skin use. The dissolution rate of dapsone in water is very low, and it is also gradually oxidized. We used the solvent aid of monoethyl ether diethylene glycol and Tween 80 to improve the dissolution of dapsone in water and make the formula water-based. Also, sodium metabisulfite or other antioxidants were used in the formulation to reduce the oxidation process. The gel base was made from a polyacrylate base, preferably a carbomer. The dapsone product was prepared at a concentration of 5%. In its foreign formulation (ACZONE Gel 5%), the dapsone gel is water-borne, and there is 50 mg of dapsone per gram of carbomer 980 gel, diethylene glycol monoethyl ether, methylparaben, sodium hydroxide, and purified water [15]. The second group received benzoyl peroxide 5% gel plus 100 mg doxycycline capsules daily for 12 weeks. Both drugs were prepared in similar tubes. Patients were advised to apply a thin layer of dapsone gel or benzoyl peroxide gel (almost equal to a third of a finger) to the areas containing acne daily for 12 weeks after washing the face with a non-comedogenic, non-soap cleansing solution.

Outcome measurements

In this study, treatment efficacy, tolerability and safety, satisfaction, and improvement were assessed as follows:

Efficacy assessments

Efficacy was determined via acne lesion counts (inflammatory and non-inflammatory lesions). Efficacy was evaluated based on the proportion of subjects achieving success on GAAS, defined as (0: no lesion, 1: low, 2: mild, 3: moderate, 4: severe, and 5: very severe) [15]. Efficacy at 2, 4, 8, and 12 weeks after the intervention was assessed by comparing the mean GAAS score at baseline with the study endpoint as well as change from baseline.

Tolerability and safety

Erythema, burning, dryness, scaling, gastrointestinal complications, and phototoxicity were monitored and recorded throughout the study at 2, 4, 8, and 12 weeks.

Satisfaction and improvement

At week 12, subjects completed a questionnaire about their satisfaction with the treatment (1 = not satisfied, 2 = somewhat satisfied, 3 = satisfied, and 4 = very satisfied), and scored the acne improvement on a scale of 0 (worse) to 5 (complete improvement).

Sample size and statistical method

Using G-power software (version 3.0) and considering a power of 80%, the level of significance (alpha) of 0.05, an effect size of 0.8, and an anticipated drop-out rate of 10%. The required sample size was estimated to be 30 cases per group.

Randomization method

Patients with eligible criteria were divided into two groups using the randomized block design. The online website (https://www.sealedenvelope.com) was used to generate a randomized list based on the intended sample size and block size 4. After generating a list, each patient was identified with a unique code during the study.

The patient, prescribing physician, and outcome assessor were unaware of the drug type. The drugs were provided to patients at each visit by a dermatology ward staff who did not have a role in the diagnosis and treatment of patients.

Concealment mechanism

Using the sealed envelopes method, envelopes were prepared; each random sequence was recorded on a card, and the cards were placed in the envelopes. In order to maintain a random sequence, the envelopes were numbered in the same way on the outer surface. At the beginning of the registration of participants, according to the order of entry of eligible participants into the study, one of the envelopes of the letter was opened in order, and participants were identified with his/her code during the study.

Statistical method

Data were analyzed using SPSS software version

21. Median and interquartile range (IQR) were used to describe quantitative variables with non-normal distribution. The Mann-Whitney, chi-squared, and Fisher's exact tests were used to compare variables. The Wilcoxon and Friedman tests were used to assess the inflammatory and non-inflammatory lesions within the groups. The significance was set at $P < 0.05$.

RESULTS

A total of 124 patients were assessed for inclusion, and 64 cases were excluded because they did not meet the inclusion criteria. A number of 60 patients were analyzed in two groups (Figure 1). The mean age was 21.85 ± 2.45 years, with a median of 22 years. There was no significant difference in age between the groups ($P = 0.375$). The majority of patients were female (73.3%). There was no significant difference between the groups at baseline in terms of gender ($P = 0.559$), disease duration ($P = 0.292$), inflammatory lesions ($P = 0.211$), and non-inflammatory lesions ($P = 0.739$) (Table 1).

Efficacy results

The results of comparing groups in different assessment times showed no significant difference between the two groups in terms of inflammatory and non-inflammatory lesion counts at 2, 4, 8, and 12 weeks (Table 2). The results of comparing groups after 12 weeks in Table 3 showed no significant

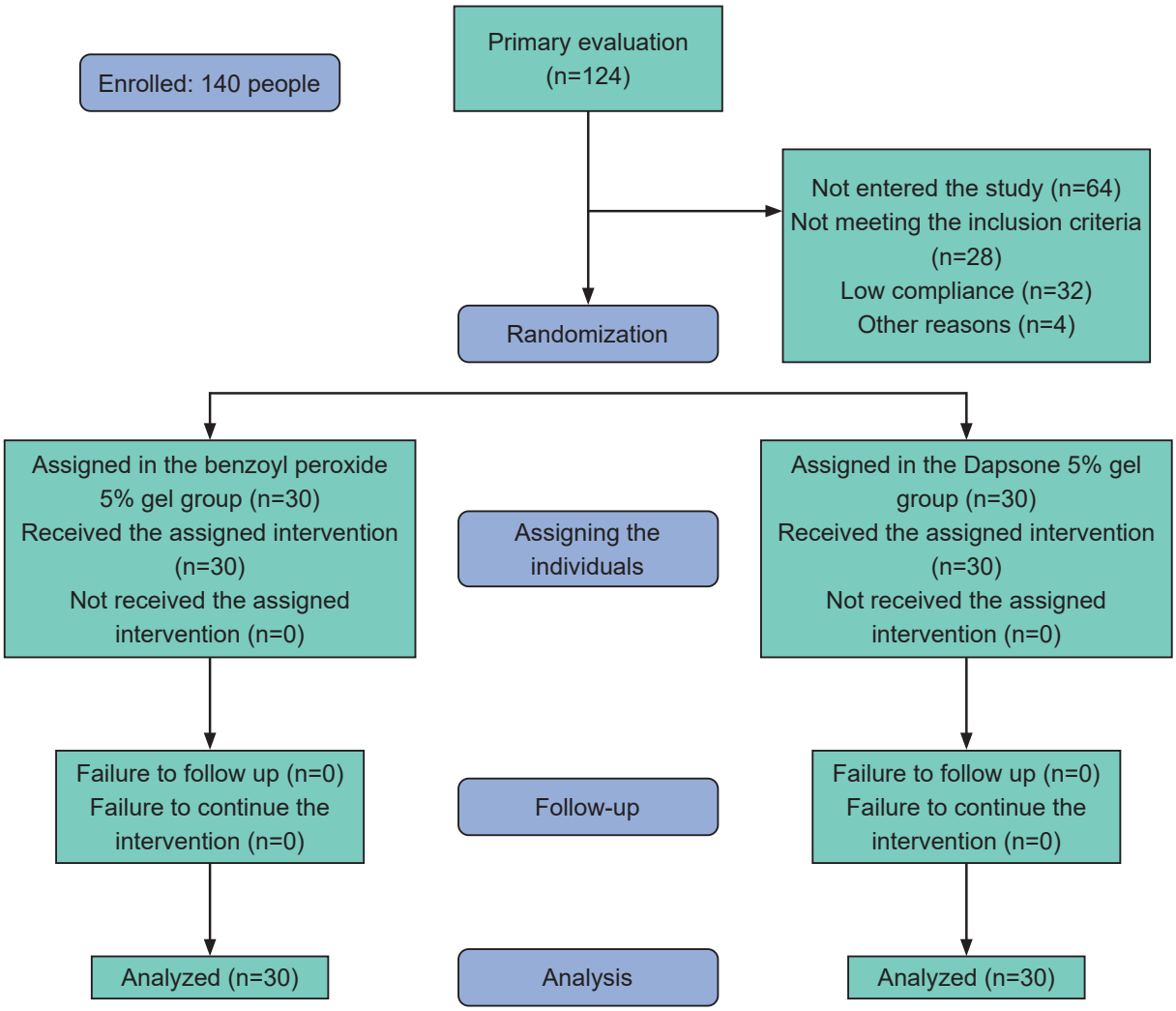

Figure 1. Design of the study.

Table 1. Characteristics of 60 patients with moderate acne vulgaris enrolled in this trial

Variable	BD (n = 30)	DD (n = 30)	Total	*P*
Age (years), Median (IQR [c])	21.50 (19.24-00.25)	22.00 (20.24-00.00)	22.00 (20.24-00.00)	0.375 [a]
Gender, n (%)				
Male	7 (23.3)	9 (30.0)	16 (26.7)	0.559 [b]
Female	23 (76.7)	21 (70.0)	44 (73.3)	
Disease duration (months), Median (IQR)	9 (5.13-50.50)	10.50 (6.24-75.00)	10.00 (6.22-00.00)	0.292 [a]
Inflammatory lesion counts, Median (IQR)	20.00 (19.25-00.00)	19.00 (16.25-75.25)	20.00 (17.25-00.00)	0.211 [a]
Non-inflammatory lesion counts, Median (IQR)	42.00 (38.48-75.50)	41.00 (37.50-75.00)	41.50 (38.50-00.00)	0.739 [a]

[a] Mann-Whitney test; [b] chi-squared test; [c] interquartile range
Abbreviations: DD, dapsone and doxycycline; BD, benzoyl peroxide and doxycycline

Table 2. Comparison of inflammatory and non-inflammatory lesion counts in DD group vs. BD group at different weeks

Time	Inflammatory lesions counts			Non-inflammatory lesions counts		
	BD Median (IQR)	DD Median (IQR)	*P* [a]	BD Median (IQR)	DD Median (IQR)	*P* [a]
Week 2	20.00 (18.24-75.00)	19.50 (16.25-75.25)	0.401	40.00 (36.46-00.00)	41.00 (34.50-55.25)	0.812
Week 4	18.50 (15.24-00.25)	18.00 (15.25-00.00)	0.790	35.50 (30.49-75.50)	39.00 (27.50-75.00)	0.673
Week 8	16.00 (11.30-00.00)	17.00 (12.25-75.00)	0.836	24.00 (21.52-00.75)	31.50 (22.55-00.25)	0. 359
Week 12	12.00 (10.30-00.50)	14.00 (7.30-50.00)	0.784	18.00 (15.60-25.00)	20.00 (17.62-25.50)	0.415

[a] Mann-Whitney test
Abbreviations: DD, dapsone and doxycycline; BD, benzoyl peroxide and doxycycline

difference between groups in terms of inflammatory ($P = 0.745$) or non-inflammatory lesions ($P = 0.739$) totally. The lesion counts were reduced within BD and DD groups after 12 weeks. However, the changes from pre to post were not significant within the groups (Table 3; Figures 2 and 3)

The GAAS score was not different between the groups. The GAAS scores in the BD group were significantly different from pre to post-intervention ($P = 0.003$). The results also showed that GAAS scores in the DD group were significantly different from pre to post-intervention ($P = 0.006$) (Table 4).

Tolerability and safety results

The side effects differed between the groups at week 12, being significantly lower in the BD group (7 (23.3%)) than in the DD group (16 (53.3%)) ($P = 0.017$). Also, skin dryness in the BD group was less than in the DD group at weeks 4, 8, and

Table 3. Inflammatory/non-inflammatory lesion counts in DD group vs. BD group before and after the intervention

Lesion	Time	BD (n = 30)	DD (n = 30)	*P* [a]
		Median (IQR)	Median (IQR)	
Inflammatory lesions (count)	Baseline	20.00 (19.25-00.00)	19.00 (16.25-75.25)	0.745
	Week 12	12.00 (10.30-00.50)	14.00 (7.30-50.00)	
	P-value [b]	0.369	0.399	
Non-inflammatory lesions (count)	Baseline	42.00 (38.48-75.50)	41.00 (37.50-75.00)	0.739
	Week 12	18.00 (15.60-25.00)	20.00 (17.62-25.50)	
	P-value [b]	0.191	0.399	

[a] Mann-Whitney test for between groups; [b] Wilcoxon test for within groups
Abbreviations: DD, dapsone and doxycycline; BD, benzoyl peroxide and doxycycline

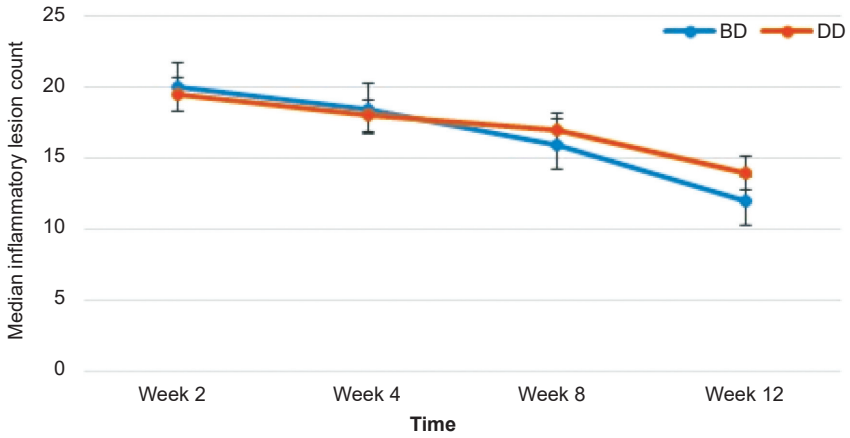

Figure 2. Median inflammatory lesion count in each group. DD: dapsone and doxycycline; BD: benzoyl peroxide and doxycycline.

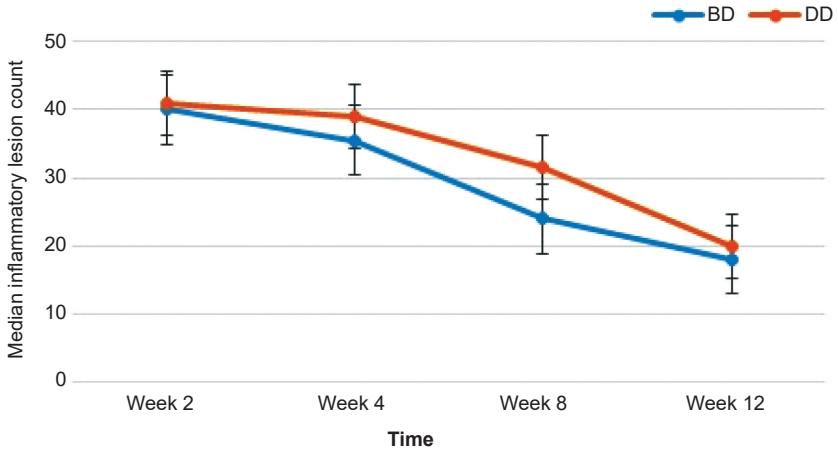

Figure 3. Median non-inflammatory lesion count in each group. DD: dapsone and doxycycline; BD: benzoyl peroxide and doxycycline.

Table 4. Comparison of GAAS scores in DD group vs. BD group at different weeks

Time	Score	BD n (%)	DD n (%)	*P* [a]
Week 2	3	14 (46)	14 (43)	0.175
	4	16 (53)	17 (56)	
Week 4	2	-	4 (13.3)	0.052
	3	30 (100)	25 (83.3)	
	4	-	1 (3.3)	
Week 8	1	-	1 (3.3)	0.089
	2	3 (10.0)	10 (33.3)	
	3	23 (76.7)	16 (53.3)	
	4	4 (13.3)	3 (10.0)	
Week 12	0	-	1 (3.3)	0.935
	1	6 (20.0)	5 (16.7)	
	2	12 (40.0)	10 (33.3)	
	3	7 (23.3)	9 (30.0)	
	4	5 (16.7)	5 (16.7)	

[a] Fisher's exact test
Abbreviations: DD, dapsone and doxycycline; BD, benzoyl peroxide and doxycycline

12 (P = 0.038). Erythema and skin irritation during different weeks were somewhat less in the DD group, though this difference was insignificant. Gastrointestinal complications and phototoxicity effects were not observed in either group (Table 5).

Satisfaction and improvement results

According to the results, the two groups were similar in patients' improvement. Both groups reported approximately 85% moderate to complete improvement in their acne. The percent of satisfaction with their treatment was 78% in the DD group and 69% in the BD group.

DISCUSSION

Choosing the appropriate treatment modality

Table 5. Comparing safety and tolerability in DD group vs. BD group at different weeks

Time	Symptom	Category	BD n (%)	DD n (%)	*P*
Week 2	Erythema	Yes	5 (16.7)	4 (13.3)	0.989 [a]
		No	25 (83.3)	26 (86.7)	
	Irritation	Yes	4 (13.3)	2 (6.7)	0.671 [a]
		No	26 (86.7)	28 (93.3)	
	Dryness	Yes	1 (3.3)	5 (16.7)	0.195 [a]
		No	29 (96.7)	25 (83.3)	
	Side effects	Yes	9 (30.3)	12 (40.0)	0.417
		No	21 (70.0)	18 (60.0)	
Week 4	Erythema	Yes	9 (30)	5 (16.7)	0.36 [a]
		No	21 (70)	25 (83.3)	
	Irritation	Yes	6 (20.0)	3 (10.0)	0.472 [a]
		No	24 (80.0)	27 (90.0)	
	Dryness	Yes	2 (6.7)	8 (26.7)	0.038 [b*]
		No	28 (93.3)	22 (73.3)	
	Side effects	Yes	14 (46.7)	20 (66.7)	0.118
		No	16 (53.3)	10 (33.3)	
Week 8	Erythema	Yes	6 (20)	2 (6.7)	0.254 [a]
		No	24 (80)	28 (93.3)	
	Irritation	Yes	6 (20.0)	2 (6.7)	0.254 [a]
		No	24 (80.0)	28 (93.3)	
	Dryness	Yes	2 (6.7)	8 (26.7)	0.038 [b*]
		No	28 (93.3)	22 (73.3)	
	Side effects	Yes	13 (43.3)	17 (56.7)	0.302
		No	17 (56.7)	13 (43.3)	
Week 12	Erythema	Yes	1 (3.3)	1 (3.3)	0.989 [a]
		No	29 (96.7)	29 (96.7)	
	Irritation	Yes	4 (13.3)	2 (6.7)	0.671 [a]
		No	26 (86.7)	28 (93.3)	
	Dryness	Yes	2 (6.7)	8 (26.7)	0.038 [b*]
		No	28 (93.3)	22 (73.3)	
	Side effects	Yes	7 (23.3)	16 (53.3)	0.017 [b*]
		No	23 (76.7)	14 (46.7)	

[a] Fisher's exact test; [b] chi-squared test
Abbreviations: DD, dapsone and doxycycline; BD, benzoyl peroxide and doxycycline
*Significant at the level of 0.05

for acne vulgaris is important considering its side effects and morbidity. We compared the efficacy of benzoyl peroxide 5% gel vs. dapsone 5% gel in combination with doxycycline for moderate acne vulgaris. Results of our study showed that the number of inflammatory and non-inflammatory lesions was not different between the two groups at weeks 2, 4, 8, and 12. However, both groups experienced a decrease in both the inflammatory and non-inflammatory lesions over time. Side effects (especially skin dryness) were significantly less in the BD group after 12 weeks, though erythema and skin irritation were slightly less in the DD group. The GAAS score was similar between the two groups but significantly decreased over time.

Jawade *et al.* demonstrated that dapsone 5% gel was efficacious and well-tolerated in non-inflammatory and inflammatory acne lesions at the end of 12 weeks [5]. In a similar report, dapsone 5% gel decreased the inflammatory and non-inflammatory lesion counts, so its effect was significant at week 4, especially for inflammatory lesions, which may be due to its anti-inflammatory effects [16]. In a study by Kircik, dapsone 5% gel twice daily was prescribed along with doxycycline hyclate 100 mg once daily for 12 weeks. Subjects who achieved a qualifying improvement at week 12 continued with only dapsone 5% gel twice daily. Their results showed that the combination of oral doxycycline

100 mg with topical dapsone 5% gel twice daily was an effective and well-tolerated regimen for moderate to severe acne vulgaris [17]. In the present study, dapsone 5% gel as combination therapy showed an improvement at week 12. Dapsone gel may have different effects by gender; one study found that once-daily dapsone 5% gel was efficacious for acne regardless of baseline lesion count and was more effective in females [18]. In the present study, females comprised the majority (73.3%) of our participants, and its related finding may not be valid.

Although the effectiveness of dapsone or benzoyl peroxide in treating acne has been studied extensively, researchers have not previously investigated the efficacy of dapsone gel vs. benzoyl peroxide gel. In a clinical trial, the lesion counts in dapsone 5% gel and isotretinoin were significantly lower than in isotretinoin alone [19]. Kamoji *et al.* (2018) showed that 0.1% adapalene and 1% clindamycin had good efficacy with fewer side effects than dapsone gel 5% for mild to moderate acne vulgaris [20]. Results of a clinical trial showed the significantly greater efficacy of benzoyl peroxide gel and adapalene 0.3% vs. vehicle, offering good safety in the treatment of moderate to severe inflammatory acne. A significantly better therapeutic effect was observed as compared with benzoyl peroxide gel as monotherapy, especially at weeks 8 and 12 [21-23]. Another study (2019) reported no significant difference between benzoyl peroxide or adapalene in combination with other therapies [24]. These previous reports implied that either dapsone gel or benzoyl peroxide gel as a combination therapy might be more effective in the treatment of acne vulgaris, in agreement with the results of our study with no difference in efficacy between the two drugs.

Our data revealed that the GAAS score was not different between the two groups, but it decreased within the groups over 12 weeks. Del *et al.* (2015) reported that dapsone 5% gel significantly reduced the GAAS score by week 12 [25]. Alexis *et al.* reported that 42.9% of subjects were responders to topical treatment with dapsone gel based on the GAAS at week 12 [26]. These previous reports are in accordance with the results of our study.

To our knowledge, most studies looked at the efficacy of dapsone gel, but few proceeded to other outcomes. In this study, safety and tolerability, patients' satisfaction, and improvement were also evaluated. According to previous reports, the side effects of dapsone 5% gel were low, and most complications were reported at the site of use with a mild to moderate severity [27,28]. Ibrahim *et al.*, in a cohort study, demonstrated that dapsone 5% gel by itself was effective and safe in the healing of acne vulgaris with minimal side effects of erythema and skin irritation. In their study, the clinical response to dapsone 5% gel was excellent in 12.5%, good in 67.5%, moderate in 17.5%, and mild in 2.5%, and treatment satisfaction was 20% very satisfied, 60% satisfied, and 20% somewhat satisfied. Side effects were low, and only 5% of cases had mild irritation [29]. Shashikumar *et al.* found that 60.6% of patients showed an excellent to good response, and 16.2% of patients showed a fair response, but only 7.2% had a poor response [30]. Lynde *et al.* (2014) and Alagheband *et al.* (2015) reported that topical dapsone is well-tolerated with minimal side effects [31,32].

In a study by Del *et al.* (2015), facial application of dapsone 5% gel for 12 weeks reduced the percentage of subjects reporting erythema (> 10%), dryness (5%), oiliness (> 20%), and peeling (< 5%) compared with baseline in both adolescent and adult females [25]. In our study, the low frequency of erythema and skin irritation in the dapsone group had increased the acceptability rate of this drug, which may be due to dapsone's anti-inflammatory effects and the climatic conditions of the study area (high humidity in the North of Iran). Keating *et al.* demonstrated that the most common side effect in combination gel of benzoyl peroxide with adapalene was skin dryness in the long-term use in mild to moderate severity acne [33]. In our study, the combination of benzoyl peroxide with doxycycline led to a low frequency of skin dryness.

CONCLUSION

We conclude that in combination with doxycycline, our novel dapsone 5% gel product is as effective as benzoyl peroxide 5%. Considering the good tolerability, safety, and acceptability of dapsone 5% gel, it is suggested as an appropriate treatment for improving moderate acne vulgaris. Large-scale studies with longer follow-up periods are required for confirmation of our findings.

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