Comparison of the efficacy of oral fenugreek seed extract and azithromycin in the treatment of acne vulgaris: a randomized, triple-blind controlled pilot clinical trial

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Background: Acne vulgaris is a multi-factorial disease affecting many aspects of life. This study was conducted to compare the efficacy of fenugreek seed extract and oral azithromycin in the treatment of acne vulgaris.

Methods: A total of 20 patients with acne vulgaris aged between 12 and 30 years old were entered into this 60-day, randomized, placebo-controlled, triple-blind study. The patients were randomly divided into two groups, (permuted block randomization, block size of 4), namely fenugreek and azithromycin groups. All the participants daily received two capsules containing 500 mg hydroalcoholic extract of fenugreek seeds or 125mg azithromycin, for two months. The patients were evaluated after 30 and 60 days from the start of the trial. The participants, investigators (the dermatologists who evaluated clinical responses), and statisticians who analyzed the data were blind for identity and allocation of the treatments.

Results: The baseline GAGS scores in azithromycin and fenugreek groups were respectively equal to 19.66 and 23.12, and there was a reduction in both azithromycin (GAGS2=14.33) (P-value=0.019) and fenugreek extract group (GAGS2=22.75) (P-value=0.780) during the experiment. There was a statistically significant difference among the two groups (F= (2, 24) = 3.861, P=0.035).

Conclusion: The effect of azithromycin was higher than fenugreek in the treatment of acne vulgaris.

Keywords: acne vulgaris, *trigonella*, azithromycin, therapeutics

INTRODUCTION

Acne vulgaris is the most prevalent skin disorder in young adults. Considerable prevalence of acne vulgaris and long-lasting sequelae make this disease important for dermatologists. The acne vulgaris was the 8th most common disease worldwide in 2015, and around 633 million people globally were affected by acne vulgaris [1].

Acne vulgaris is a multifactorial disease caused by inter-related and synergetic factors such as alteration of non-keratinized epithelial to keratinized one, androgen rise causing over secretion of the sebaceous gland, the proliferation of *Propionibacterium acnes,* and an increase in skin normal flora, which all of them lead to obstruct and inflame the sebaceous gland canal [2-4].

The prescription of oral antibiotic, especially azithromycin is a significant element to treat the moderate to severe acne vulgaris [5]. Consuming azithromycin can cause some adverse side effects, including gastrointestinal upset and cutaneous hypersensitivity reactions, leading researchers to find alternative medications to treat the acne.

Herbal drugs can be one of the alternatives [6,7].

The seeds and leaflet of *Trigonella foenum graecum* (fenugreek) are mostly used as a drug in various disorders in the Middle East and Mediterranean countries [8].

Recent studies have indicated that a significant amount of polyphenol compounds such as alkaloids and flavonoids distributed in fenugreek has some biological effects, including antioxidant effect, hydrogen donor ability, and free radical scavenging activity [9,10].

We conducted this randomized, triple-blind clinical trial study to compare the effect of oral azithromycin and fenugreek seeds extract to treat mild to moderate acne vulgaris.

MATERIALS AND METHODS

Trial Design

This research is a randomized, placebo-controlled, triple-blind (participants, investigator, and outcomes assessor) study conducted in 60 days and is also a mono-center clinical trial with parallel design. The participants were randomly divided into intervention and control groups (1:1 allocation ratio). Eligible patients were selected from November 2014 to June 2017; the last patient completed the study in September 2017.

Study Participants

The patients were aged between 12 to 30 years old, who were diagnosed with acne vulgaris by clinical manifestation recruited from the Dermatology Department, affiliated with Faghihi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran. Inclusion criterion was clinical diagnosis of mild to moderate acne vulgaris. The severity of the disease was determined by the global acne grading system (GAGS), which was previously introduced [14]. The GAGS scores of 1-18 and 19-30 were considered mild and moderate acne vulgaris, respectively.

Patients were removed from the study in the case of having any of the following conditions: (1) previous consumption of oral acne controller drugs in the past three months, such as antibiotics, isotretinoin, oral contraceptive pills; (2) consumption of drugs causing acne such as testosterone, progesterone, steroids, lithium, phenytoin, and isoniazid; (3) patients with symptoms of endocrine disorders, particularly hyperandrogenism, including polycystic ovarian syndrome (oligomenorrhea, polycystic ovaries, hirsutism), cushing syndrome (rapid weight gain, buffalo hump, moon face, excess sweating, purple or red striae on the body and hirsutism), congenital adrenal hyperplasia (CAH), androgen-secreting tumors, and acromegaly; (4) severe skin problem; and (5) women who were pregnant or lactating.

Intervention

Subjects either took daily two oral capsules each one containing 500 mg hydroalcoholic extract of fenugreek seeds (Barij Essence Company, Kashan, Iran) or two azithromycin capsules (each one 125mg azithromycin plus 375 mg flour) (Barij Essence Company, Kashan, Iran) for two months. The azithromycin capsules have similar color, shape, size, and package to the fenugreek ones.

Primary and Secondary Outcomes

The primary consequence appeared as a change in the GAGS score. Lesions count changes were secondary consequences.

Follow-up

At baseline, all the studied subjects were examined fully. The subjects were recommended not to take any oral anti-acne drug during the study (except they allowed to wash their faces with anti-acne soap). We called the patients 30 and 60 days after the start of the trial to re-examine the clinical changes and asked them about the adverse effects by a standard questionnaire and capsule counts. Following up the study medications was measured by counting the remaining capsules. The patients were excluded from the study in the case where their remaining capsule count was 10% different from the expected ones. Allergic reactions, bloating, transient diarrhea, severe weight loss, heartburn, hypoglycemia symptoms, dizziness, and cold sweats were the side effects that the patients were asked about them.

Sample Size

A sample size of 10 patients per groups was

considered appropriate by assuming a drop-out rate of 10 to 20%, due to the exploratory (pilot) study design and lack of similar studies.

Randomization

Randomization was performed using the permuted block randomization with the block size of 4; the patients were randomly allocated to azithromycin and fenugreek groups. The randomization was performed by a single specifically appointed researcher to reduce selection bias and confounding factors. Each group had 10 participants.

Blinding

Participants, researchers (the dermatologists who measured the clinical response), and statisticians analyzing the data were blinded to identity and allocation of the treatments.

Ethical Approval

The local Ethics Committee of Shiraz University of Medical Sciences (CT-P-9362-6852) reviewed and approved the protocol, and the patients gave informed consent form. The study was registered at the Iranian Registry of Clinical Trials (IRCT)

(IRCT2015091123978N1; http://www.irct.ir/) and was conducted according to the principles of the Declaration of Helsinki (1996) and the Good Clinical Practice Guidelines (1996). All the subjects signed the written informed consent to participate in the study.

Statistical Analysis

Kolmogorov–Smirnov test was used to measure the normality distribution of data. Data with normal and non-normal distribution are reported as mean ± standard deviation and median (25th and 75th percentile), respectively. The changes between the two groups were compared by two way repeated measurements ANOVA reported as (F= (df (time*drug), df (error (time))) =X, P=XXX). The parameters between each group were compared by the independent t-test or Mann-Whitney U Test. The paired t-test was used to compare the baseline, and final GAGS score within the groups. SPSS 23.0 was used to analyze the data. A two-sided P value less than 0.05 was considered statistically significant.

RESULTS

A total of 20 patients met the inclusion criteria and included in the study after screening 50
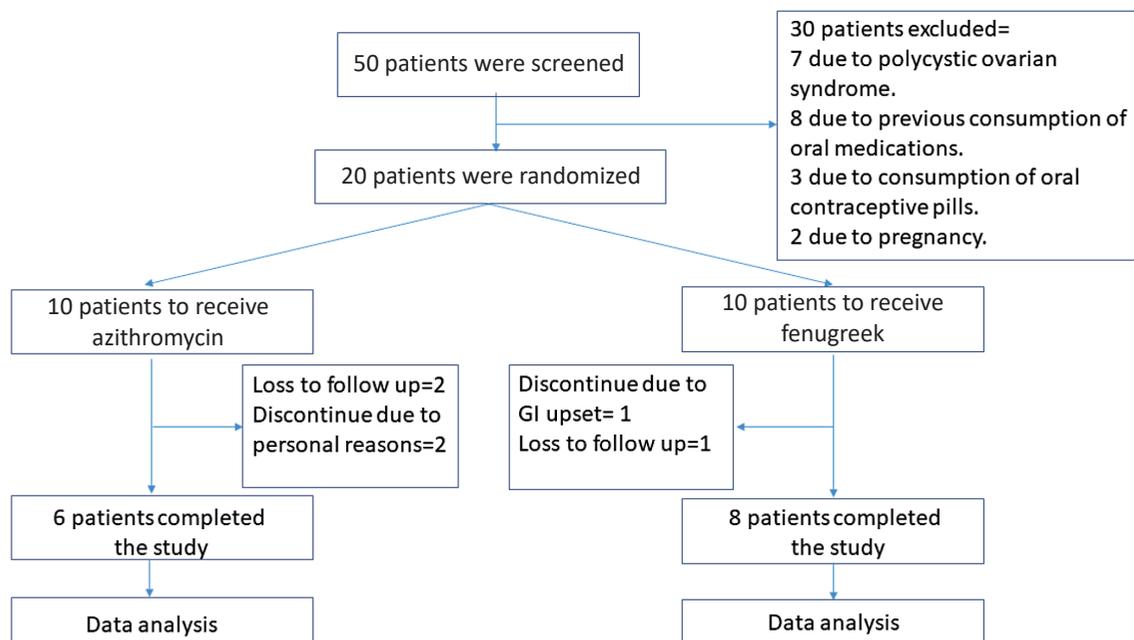

Figure 1. CONSORT diagram of the effect of fenugreek on the treatment of acne vulgaris compared to azithromycin.

Table 1. Baseline data of the patients

Parameter	Azithromycin Mean (SD)	Fenugreek Mean (SD)	P-value
Age (year)	22.50 (5.96)	16.63 (3.07)	0.033*
Acne duration (year)	6.67 (3.01)	3.25 (1.83)	0.022*
GAGS score	19.66 (3.93)	23.12 (3.36)	0.101*
Total lesion count	55.50 (31.99)	83.62 (38.49)	0.173*
Inflammatory lesion count	27.66 (17.76)	47.12 (23.58)	0.108a
Non-inflammatory lesion count	27.83 (31.50)	36.50 (30.57)	0.614*

*Independent Samples Test
a Mann-Whitney U Test

patients. Four patients did not complete the trial after two months in the azithromycin group, two patients did not take azithromycin fully, and another 2 did not continue the study due to personal reasons (traveling to another city). In the fenugreek group, one patient did not take the drug, and one patient did not complete the study due to gastrointestinal (GI) upset (bloating and heartburn). The observation was conducted on six patients treated with azithromycin (Group A), and eight patients treated with the extract of fenugreek seeds (Group B) (Figure 1).

The mean age of group A was 22.50, while the mean age of Group B was 16.63 3.068 (p-value=0.033). Table 1 shows the baseline and demographic data of the patients.

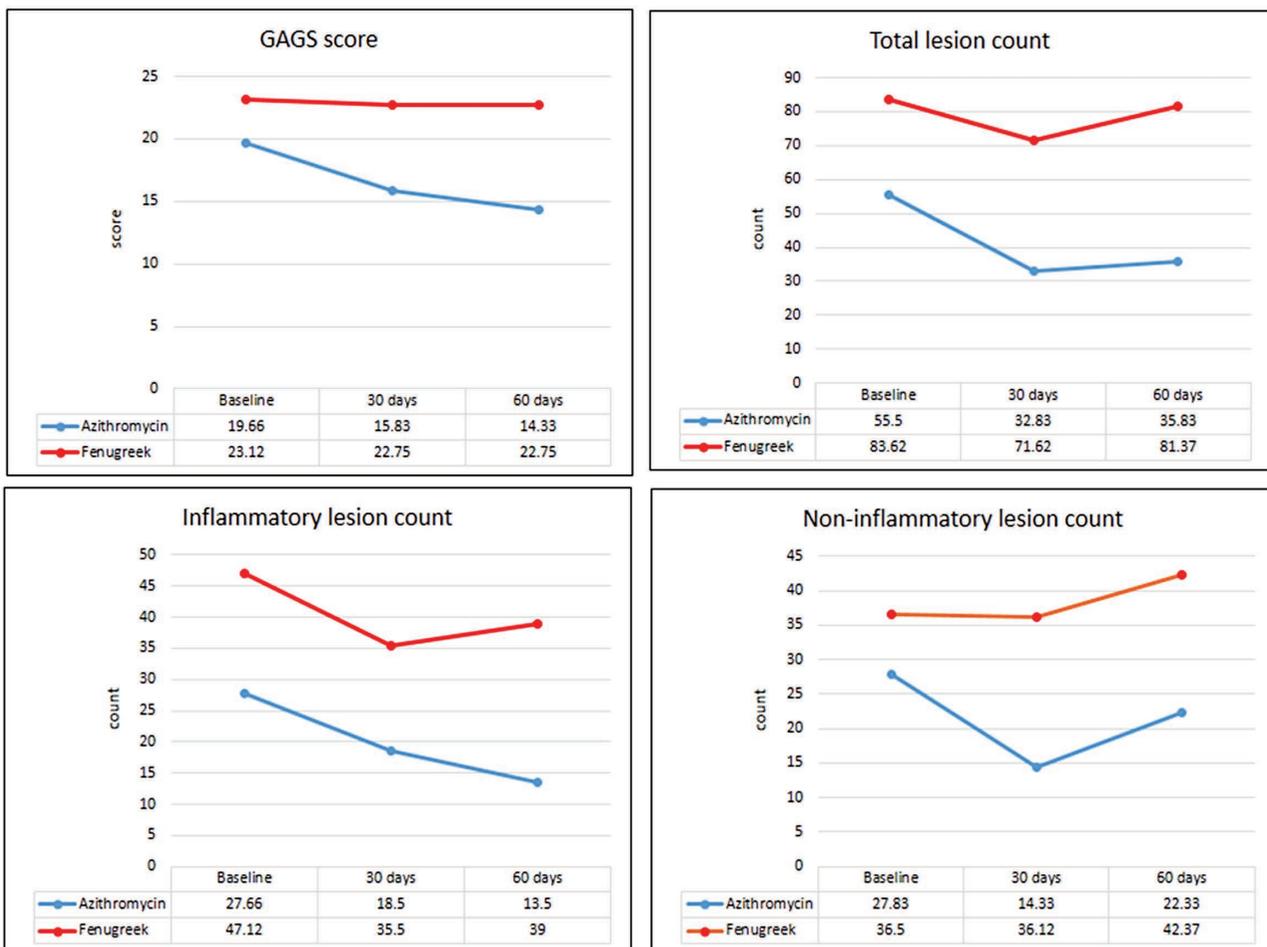The baseline GAGS score in Group A and Group B was 19.66 and 23.12, respectively, and there was

Figure 2. The trend of the GAGS score, total lesion count, inflammatory lesion count, and non-inflammatory lesion count in the two groups.

a reduction in both azithromycin (GAGS2=14.33) (P value=0.019) and fenugreek extract groups (GAGS2=22.75) (P-value=0.780) during the experiment. There was a statistically significant difference between the two groups (F= (2, 24) = 3.861, P=0.035).

There was no statistically significant changing trend of the mean total lesion count (F= (2, 24) = 0.482, P=0.547), inflammatory lesion count (F= (2, 24) = 0.421, P=0.576), and non-inflammatory lesion count (F= (2, 24) = 0.437, P=0.567) between the two groups.

Table 2 and Figure 2 summarize the trend of the GAGS score, total lesion count, inflammatory lesion count, and non-inflammatory lesion count.

DISCUSSION

This paper aimed to compare the efficacy of two oral drugs, azithromycin, and fenugreek in the treatment of acne vulgaris for eight weeks. The results showed that azithromycin had a more therapeutic effect on acne vulgaris.

A range of pathogenesis factors triggers acne vulgaris, but follicular hyperkeratinization, increased sebum production, *Propionibacterium acnes*, and inflammation are thought to be the leading causes [3]. *Propionibacterium acnes* is the main microorganism in the pathogenesis of acne vulgaris. The proliferation of this bacteria causes T helper 17 (Th17) and Th1 cells to produce IL-17 and other pro-inflammatory cytokines causing inflammation by activate caspase-1 and finally increasing secretion of IL-1 beta [11,12]. Furthermore, the increased activity of inflammatory enzymes such as 5-lipoxygenase (5-LOX) [13], and peroxisome proliferator-activated receptors (PPARs) [14] and reduced activity of antioxidant enzymes such as catalase, glutathione peroxide, and superoxide dismutase [15] are important factors in the pathogenesis of acne vulgaris. Moreover, recent studies have indicated that systemic disease such as diabetes mellitus and polycystic ovary syndrome are associated with acne vulgaris by peripheral insulin resistance as the same pathogenesis [16]. It is clear that the prevalence of acne is higher in people who are overweight [17].

Azithromycin is an approved, and effective antibiotic for acne [5]. One study conducted by Bardazzi et al. [18] showed that azithromycin was

Table 2. Follow-up data of the patients

Parameter	Time of measurement	Azithromycin							Fenugreek							Within-Subjects Effects*
		Mean	Minimum	Maximum	Standard Deviation	95% Confidence Interval		Mean	Minimum	Maximum	Standard Deviation	95% Confidence Interval		
						Lower Bound	Upper Bound					Lower Bound	Upper Bound	
GAGS score	Baseline	19.66	15	25	3.93	16.457	22.876	23.12	20	29	3.36	20.346	25.904	F=(2, 24) = 3.861, P=0.035
	1 month	15.83	11	24	5.04	10.986	20.680	22.75	16	31	5.73	18.552	26.948	
	2 month	14.33	6	22	5.96	9.244	19.423	22.75	16	31	5.55	18.343	27.157	
Total lesion count	Baseline	55.50	11	88	31.99	23.545	87.455	83.62	38	145	38.49	55.951	83.625	F=(2, 24) = 0.482, P=0.547
	1 month	32.83	10	53	20.31	8.249	32.833	71.62	30	123	31.86	50.334	71.625	
	2 month	35.83	7	116	42.04	-11.123	35.833	81.37	21	192	59.29	40.710	81.375	
Inflammatory lesion count	Baseline	27.66	8	55	17.76	8.679	46.655	47.12	27	100	23.58	30.681	63.569	F=(2, 24) = 0.421, P=0.576
	1 month	18.50	2	43	17.46	2.091	34.909	35.50	15	73	19.12	21.290	49.710	
	2 month	13.50	2	37	12.34	-13.239	40.239	39.00	5	120	37.95	15.844	62.156	
Non-inflammatory lesion count	Baseline	27.83	0	80	31.50	0.296	55.370	36.50	7	100	30.57	12.652	60.348	F=(2, 24) = 0.437, P=0.567
	1 month	14.33	0	44	15.47	-2.777	31.444	36.12	5	67	21.52	21.307	50.943	
	2 month	22.33	0	79	31.51	-11.291	55.957	42.37	13	135	41.72	13.256	71.494	

*Two-way repeated measures ANOVA.

successful within eight weeks of treatment in 88.5% of patients. Three patients suffered from gastrointestinal upset.

The main reason for the antibacterial activity is less-polymerized free phenols in fenugreek. Coumarin derivatives are one of the components in addition to phenols that can significantly enhance bactericidal activity of fenugreek in both gram-positive like *Propionibacterium acnes* and gram-negative bacteria by interacting with prokaryotes electron chain transport mechanism [19]. Recent studies have indicated that the extract of fenugreek seeds contains steroid saponins having wound healing and epithelization properties in addition to anti-inflammatory and anti-oxidative properties [20]. Fenugreek significantly decreased the IL-1β level in Freund's adjuvant-induced arthritis in albino rats [21]. Fenugreek had anti-inflammatory effects by reducing the activity of 5-lipoxygenase, cyclooxygenase [22] and PPARs [23]. Anti-oxidative properties are explained by increasing the activity of catalase, glutathione peroxidase, and superoxide dismutase [22,24].

While systemic diseases are related to acne, several studies showed the effect of fenugreek on metabolic and systemic disorders. The pharmaceutical effect of fenugreek on diabetes mellitus is associated with reduction of the gastrointestinal glucose absorption, improvement of the peripheral glucose utilization, and increase of the insulin response [25,26]. Furthermore, the use of Fenugreek can cause weight loss and improve acne vulgaris [27].

Our study had some limitations, including a low number of participants in each group, which was due to restricting inclusion and exclusion criteria. Another problem was discontinuation of study due to reasons unrelated to the medication. Moreover, low response to treatment can be caused by a short period of the treatment and an improper dose of fenugreek.

CONCLUSION

There is not strong or sufficient evidence to prove the efficacy of fenugreek extract seed in acne vulgaris in this paper. Therefore, it is recommended that further long-term clinical trials be conducted with higher doses of fenugreek to measure the possible effects of fenugreek on the treatment of acne vulgaris.

Data Availability

Acknowledgments

Conflict of Interest: None declared.

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