Original Article

The comparison of treatments with and without azithromycin in irritable bowel syndrome with diarrhea-predominant in gastrointestinal Clinic of Al-Zahra Hospital, Isfahan, Iran

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Abstract

Background: Irritable bowel syndrome (IBS) is a common gastrointestinal disorder. Recent studies suggest the importance of gut flora in the pathophysiology of it. Therefore, antibiotics have demonstrated a substantial benefit to reduce gut flora. Having few side effects, and applying one-dose per day, we studied the effect of azithromycin to treat IBS.

Materials and Methods: One hundred and twenty-six patients enrolled a randomized, double-blind, placebo-controlled study. The treatment group received azithromycin in addition to common treatment. Patients were followed for 12 weeks. Patients completed daily diaries documenting their symptoms.

Results: One hundred and thirteen patients completed the study. The onset of relief occurred significantly sooner, and duration of relief was significantly longer in azithromycin group. Movement, abdominal pain, bloating, and gas were significantly better in azithromycin group. Monthly results showed superior relief in bloating, gas, overall symptom, and overall bloating during 3 months. Significantly more patients in azithromycin group felt relief in bloating and gas and had greater consistency relief in almost all weeks.

Conclusion: In our study, azithromycin significantly relieved most symptoms, such as abdominal pain, bloating, and gas. Overall symptom and overall bloating were relieved significantly in more patients in the intervention group in all weeks.

Key Words: Azithromycin, diarrhea-predominant, gastrointestinal, irritable bowel syndrome

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INTRODUCTION

Irritable bowel syndrome (IBS) is a benign chronic condition and the most common gastrointestinal disorder[1,2] and characterized by abdominal pain or discomfort and alteration in bowel habits.[3,4] Although there are some hypotheses about the pathophysiology of IBS, the exact cause has remained unclear[5-7] and there is no organic or structural cause which can

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explain IBS symptoms.[2] The most accepted diagnostic criteria for IBS is the Rome criteria.[2,8]

As well as other parts of the world, IBS is one of the most common conditions which causes patients to refer to gastrointestinal clinics in Iran.[5,9] According to a systematic review in Iran, IBS prevalence is in the range of 1.1–25%.[9] The prevalence of IBS with diarrhea is approximately 3% among the general population in the UK[10] and ranged from 3% to 20% in North America.[11] IBS is more common in women than men.[2,12,13] SEPAHAN systematic review also showed the greater prevalence in women than men.[9]

IBS can generally be diagnosed beyond a careful history taking, a general physical examination, and common laboratory studies (without colonoscopy) in patients who have symptoms that meet the Rome criteria and who do not have warning signs.[11,14] According to bowel habits and stool characteristics, patients can be subclassified as having diarrhea-predominant IBS (IBS-D), constipation-predominant IBS, or mixed bowel habits.[11,14,15]

Recent studies suggest the importance of bacteria and gut flora in the pathophysiology of IBS.[8,16,17] These studies linked IBS to small intestinal bacterial overgrowth (SIBO).[6,18,19] SIBO is more common in diarrheal IBS than other subtypes.[20]

The conventional therapies are loperamide for IBS-D, however, because of the heterogeneous nature of the symptoms, patients are often treated with medications from more than one drug class to achieve relief.[2,11]

Since an abnormal composition of gut microbiota exists among IBS patients, using antibiotics seems to be appropriate to treat IBS.[20,21] According to previous studies, antibiotics such as rifaximin have demonstrated a substantial benefit to reduce gut flora.[8,16,17,19]

Some studies showed the role of different treatments such as loperamide, alosetron, and ondansetron on IBS syndrome.[2] Some scientists such as Pimentel *et al*., Saadi and McCallum and Menees *et al*. studied the effect of Rifaximin on patients with nonconstipation predominant IBS.[8,19,22] Pimentel *et al*. showed that a short course of rifaximin can ameliorate IBS symptoms.[8] Saadi and McCallum explained the benefits of rifaximin to treat IBS.[19] Despite the large number of studies on different treatments, especially different antibiotics such as rifaximin, few researches investigated the effect of azithromycin on IBS symptoms and the literature in this area is not substantial.

Having few side effects, and applying one-dose per day, we studied the effect of azithromycin to treat IBS, in this study.

MATERIALS AND METHODS

This study was a double-blind, placebo-controlled, randomized trial. The study was approved by the Ethical Committee of Isfahan University of Medical Sciences (project number: 393469; the number of Ethical Committee: IR.mui.rec. 1393030469).

The purpose of the protocol was explained to each subject and written informed consent was obtained from each participant.

Subjects

Subjects were selected from IBS-D patients, which referred to the gastrointestinal clinic of Al-Zahra Hospital, Isfahan, Iran, during 2012. The diagnosis of IBS-D for each patient was confirmed on the basis of Rome III criteria.[3] The possibility of celiac, disaccharidase deficiency, and bacterial overgrowth was rejected by a gastroenterologist, by an exact history taking and clinical examination for each subject. The probability of malignancy was rejected by colonoscopy and biopsy.

The sample size was calculated from Cochran's formula in which the probability of type I error was preserved at 0.05, and the test power was 80%. The sample size for each group was 62, however, to consider the dropout, 65 subjects studied in our research. One hundred and twenty-six patients who met Rome III criteria for IBS-D enrolled in the study and randomly received either intervention treatment (azithromycin) or placebo. All subjects gave written informed consent. For each subject, a checklist including demographic information, physical examination results, and clinical symptoms was completed at baseline.

Rome III diagnostic criteria for irritable bowel syndrome

Recurrent abdominal pain, at least three times a month, consistent in last 3 months, with at least two following symptoms of the pain: Relieved by defecation, associated with a change in frequency of stool, associated with a change in form (appearance) of stool. The criteria should be resisted in last 3 months, and the onset of symptoms should be at least 6 months before diagnosis.[2]

Inclusion criteria

(1) IBS-D clinical diagnosis, (2) age 18–50 years, (3) not allergic to azithromycin, (4) not using antibiotics in last 1 month,[23] (5) consent to participate in the study.

Exclusion criteria

(1) Refuse to continue the study, (2) develop any serious azithromycin's side effects, and (3) not to comply the study protocol, (4) taking drugs that interact with azithromycin, (5) contraindications of azithromycin, (6) any evidence of inflammatory bowel disease, active peptic ulcer, diagnosed microscopic colitis, gallbladder's active disorder.

Study design and follow-up

All patients in both groups received common treatment include loperamide (2–4 mg, twice a day) and dicyclomine (10–20 mg, four times a day), and limitation on alcohol, caffeine, and fat consumption.[2] The treatment group received azithromycin by following order: 500 mg on the 1st day of trial, and 250 mg from the 2nd day, over 5 days, as one dose, 2 h after lunch. The control group received matched appearance and taste placebo, with the same order as azithromycin.

Participants were followed for 12 weeks. Each patient referred to clinic on days 7 (a day after completion of antibiotic course), 21, 35, and 84 (12th week) of study, to follow-up and physical examination. Furthermore, they were followed by telephone calls on days 49 and 63 of study. On all follow-up days, (by refer or phone call) patients were monitored about the main symptoms of IBS, bloating, drug side effects, using any other drug, and symptoms improvement, according to checklist.

Weekly overall symptom relief and bloating relief were collected weekly as self-reported relief as, "yes" or "no" to the following question: "In regard to all your symptoms of IBS, as compared with the way you felt before you started the study treatment, have you, in the past 7 days, had adequate relief of your IBS symptoms?"[8] Monthly relief was defined as relief in at least 2 of the 4 weeks of a month.

For each symptom such as stool consistency, abnormal bowel movement, abdominal pain, bloating and gas, patients completed a daily checklist, documenting their symptoms, and rated them as Likert scoring systems, during 84 days. The average of scores of each symptom was calculated for each subject.

Patients rated daily abdominal pain, bloating and gas as a score of 6-point Likert scoring system (with 1 indicating not at all; 2: Slight; 3: Mild; 4: Moderate; 5: Severe; and 6: Worst imaginable). Weekly relief regarded as "not at all," "slight," and "mild," at least ½ day of the week.[8]

Patients rated daily stool consistency as a 5-point Likert scale (with 1 indicating hard; 2: Formed; 3: Loose; 4: Very loose; and 5: Watery). Weekly relief regarded as "hard" and "formed" at least ½ day of the week.[8]

Monthly relief regarded as at least 2 weeks relief in a month.

The onset and duration of overall symptom relief were also assessed. The onset of relief was considered as the 1st week after treatment in which the patient had experienced adequate relief in symptom. Duration of relief was evaluated as the number of consecutive weeks, after onset of relief, that patient's symptom was relieved.

All subjects were become aware of serious drugs side effects and were asked to refer to hospital or call researchers in case they were developed any symptom. No subject reported drugs side effect.

Randomization method

The study was a double-blind clinical trial. Both azithromycin oral cap and placebo were produced by Farabi Pharmaceutical Company. Placebos had completely the same appearance as azithromycin oral cap. Both intervention treatment and placebo were encoded by Pharmaceutical Company and neither researchers nor patients were aware of randomization. The company produced packages include either azithromycin or placebo. Each package was contain enough treatment for follow-up duration and had a unique code. Packages had been given to participants by a nurse. The consort table is depicted in Figure 1.

Clinical evaluation and treatment effect were determined by one of the research team members, who were blinded about packages continent.

After the completion of the study, pharmaceutical company opened the codes. Therefore, all participants stayed blind until the study, data collection and assessments were completed.

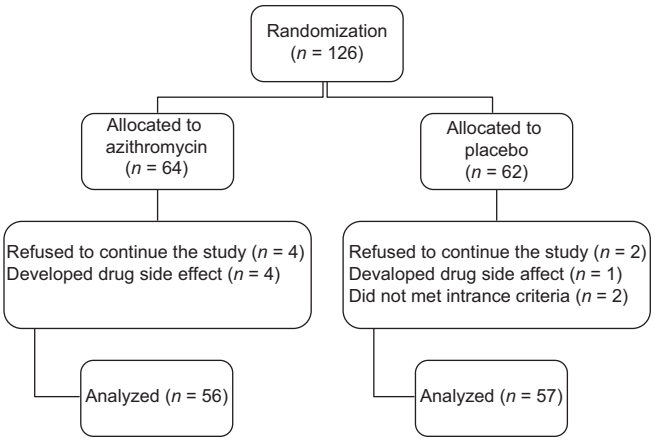

Figure 1: Flow diagram of the trial

Statistical analysis

Information entered onto SPSS package version 20; California. Statistical tests include Student's *t*-test, Kolmogorov–Smirnov, Mann–Whitney U-test, and Chi-square, were applied in this study. Here, we applied Student's *t*-test, to compare normally distributed variables between intervention and placebo groups. Chi-square was applied to compare the relief proportion between two groups. To compare the onset of relief and duration of relief between two groups, Mann–Whitney U-test was performed. Significant level was set at $P < 0.05$.

RESULTS

Although during the year 2012, a total of 126 participants were enrolled in the study, 113 patients completed the study, 56 subjects in treatment and 57 in placebo group. Subjects in the treatment group received azithromycin in addition to common treatment, and patients in placebo group received placebo instead of azithromycin, in addition to common treatment.

Mean (standard deviation) of age were 34.28 (12.033) and 32.75 (9.416) in treatment and placebo groups, respectively. In this study, age was normally distributed (Kolmogorov–Smirnov $P = 0.166$), and the mean age did not differ significantly between two groups (Student's *t*-test, $P = 0.452$).

Twenty (35.7%) patients in treatment group and 17 (29.8%) patients in placebo group were male. Therefore, sex proportion did not differ between two groups (Chi-square test, $P = 0.505$).

Analysis was performed both weekly and monthly; however, weekly analysis did not release here completely.

The proportion of weekly consistency relief was greater in azithromycin group for all weeks except for week 8; however, this difference was not significant. According to the Chi-square test's results, the proportion of weekly relief for consistency was significantly greater in azithromycin group only in week 2 ($P = 0.028$).

Except for weeks 9 and 11, abnormal bowel movement was more relieved in placebo group. However, the different was not significant except for week 8.

The proportion of patients which experienced pain relief was greater in azithromycin group, until week 7. However, the proportion difference was significant only in week 3.

More patients in azithromycin felt the relief of daily bloating and gas in all 12 weeks. Relief differences were significant for both bloating (except for 1st week) and gas in 12 weeks ($P < 0.0001$).

The overall symptom was relieved in more patients in the intervention group than placebo, in all weeks. The observed difference was significant in weeks 1, 2, 3, 9, and 12.

Overall bloating relieved in more patients in azithromycin group in all 12 weeks. The observed differences were significant in all weeks except for weeks 7 and 8.

Onset of relief for subjects was considered as the 1st week that each patient had relief of overall symptoms. According to the explanation, lower values are more suitable. As it is depicted in Table 1, onset of relief occurred significantly sooner in patients in azithromycin group ($P = 0.001$).

Duration of symptom relief was considered as the number of weeks, after the onset of relief, that each patient experienced relief in overall symptoms. This means that greater values are more suitable. According to the test result, duration of relief was significantly longer in azithromycin group ($P = 0.006$). The result is represented in Table 1.

As explained before, monthly relief was determined as at least 2 weeks relief in a month. Monthly relief in each group and the comparison between the groups relief are indicated in Table 2.

According to the results, the proportion of consistency relief was 82.1% in azithromycin and 63.2% in placebo group in a 1st month. *P* value of Chi-square test was 0.024, which means that significantly more patients in azithromycin group had consistency relief in the 1st month of study. The proportion differences between two groups were not significant for 2nd and 3rd months (both $P > 0.05$).

The proportion of abnormal bowel movement relief and pain relief were the same for two groups in 3 months. Daily bloating and gas were relieved significantly more in azithromycin than placebo group in all 3 months ($P < 0.001$).

Table 1: Comparison of onset and duration of relief

Efficacy outcome	Mean rank		*P*†
	Azithromycin	placebo	
Onset of relief	46.58	67.24	0.001*
Duration of relief	65.38	48.76	0.006*

†Mann-Whitney U-test, **P*<0.05 considered as significant

Table 2: Comparison of percent relief between two groups

Symptom	Month 1			Month 2			Month 3		
	Azythromicin†	Placebo†	*P*‡	Azythromicin†	Placebo†	*P*‡	Azythromicin†	Placebo†	*P*‡
Consistency	46 (82.1)	36 (63.2)	0.024*	50 (89.3)	45 (78.9)	0.133	49 (87.5)	45 (78.9)	0.224
Abnormal bowel movement	51 (91.1)	54 (94.7)	0.448	50 (89.3)	51 (89.5)	0.974	53 (94.6)	50 (87.7)	0.195
Pain	48 (85.7)	43 (75.4)	0.168	52 (92.9)	49 (86.0)	0.234	50 (89.3)	53 (93.0)	0.489
Daily bloating	38 (67.9)	14 (24.6)	<0.0001*	43 (76.8)	21 (36.8)	<0.0001*	48 (85.7)	21 (36.7)	<0.0001*
Gas	40 (71.4)	9 (15.8)	<0.0001*	45 (80.4)	12 (21.1)	<0.0001*	45 (80.4)	9 (15.8)	<0.0001*
Overall symptom	49 (87.5)	35 (61.4)	0.001*	53 (94.6)	53 (93.0)	0.714	54 (96.4)	48 (84.2)	0.028*
Overall bloating	39 (69.6)	6 (10.5)	<0.001*	48 (85.7)	43 (75.4)	0.168	50 (89.3)	36 (63.2)	0.001*

†Number (percent) of relief, ‡Chi-square test, **P*<0.05 considered as significant

More patients in azithromycin had overall symptom relief and overall bloating relief. The difference in each issue was significant for 1st and 3rd month.

For each symptom patients rated their symptoms as a Likert scoring systems. The average of scores of each symptom was calculated for each subject. As these averages were normally distributed, the scores were compared between intervention and placebo groups by using *t*-test. Results are depicted in Table 3.

According to Table 3, abdominal pain, bloating and gas had significantly lower average in azithromycin group ($P < 0.05$). The average score for consistency was lower in azithromycin group; however, the difference was not statistically significant ($P = 0.637$). The average of movement was considerably higher in azithromycin group ($P = 0.036$).

Table 3: Comparison of the average of daily scores

Symptom	Mean (SD)		*P*
	Azithromycin	Placebo	
Consistency	2.31 (0.363)	2.34 (0.454)	0.637†
Movement	2.26 (0.248)	2.15 (0.299)	0.036*
Abdominal pain	2.70 (0.703)	2.97 (0.574)	0.023*
Bloating	3.03 (0.852)	3.95 (0.627)	<0.001*,†
gas	2.96 (0.727)	4.20 (0.388)	<0.001*,†

Each value is represented as: Mean (SD). †Equality of variances not assumed, **P*<0.05 considered as significant. SD: Standard deviation

DISCUSSION

Because of the heterogeneous nature of the symptoms, conventional therapies for IBS-D such as loperamide have not provided sufficient benefit.[2,11] Since an abnormal composition of gut microbiota exists among IBS patients, using antibiotics seems to be appropriate to treat IBS.[20,21] Here, we studied the effect of azithromycin to treat IBS, because of few side effects and applying one-dose per day.

In this study, 113 patients analyzed 56 subjects in azithromycin and 57 in placebo group. There was no significant difference between the two groups regarding to age and sex. Analysis was performed weekly and monthly.

Azithromycin had significantly superior effect on onset and duration of relief, compared with placebo.

In our study, the proportion of stool consistency relief was higher in azithromycin group for almost all weeks; however, the difference was not significant except for week 2. The proportion was significantly higher in azithromycin group, in 1st month. Pimentel *et al*. showed a significant effect of rifaximin on stool consistency,[8] however other studies, found no difference between rifaximin and placebo groups in this issue.[24,25]

Patients in azithromycin group experienced more pain relief, in 1st 7 weeks and 1st 2 months. However, the differences were not significant (except for week 3). In a study on rifaximin, abdominal pain relieved more in rifaximin group compared with placebo.[8]

Daily bloating and gas were relieved significantly more in azithromycin compared with placebo in all 3 months and 12 weeks. Other studies yielded significantly greater rate of bloating relief in rifaximin compared with placebo.[8,24] Bloating improvement was more evident in patients with mild to moderate symptoms at baseline, but in patients with severe IBS symptoms, rifaximin did not significantly improve bloating versus placebo.[11] Results of a meta-analysis showed more bloating relief in rifaximin compared with placebo.[22]

In our study, overall symptom and overall bloating relieved significantly more in weeks 1, 2, 3, 9, and 12, and 1st and 3rd months. Studies on neomycin showed a significant reduction in IBS symptoms compared with placebo.[26,27] Other studies showed significant improvements in overall symptoms in rifaximin versus placebo ($P = 0.02$).[8,24]

Another study compared the effect of rifaximin with some other antibiotics, including neomycin, doxycycline, amoxicillin/clavulanate, and ciprofloxacin.

The results reported superior improvement of abdominal symptoms in patients treated with rifaximin compared to those who received other antibiotics.[28]

According to the results of this study, azithromycin provides better relief of overall symptoms of IBS and bloating. Consistency relief, gas, and daily boating relieved more in azithromycin group. Furthermore, patients in azithromycin experienced earlier and longer relief. Therefore, azithromycin can be used as a therapeutic approach for disease.

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Conflicts of interest

There are no conflicts of interest.

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