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Original Article

The therapeutic effect of low-dose amitriptyline on patients with refractory diarrhea-predominant irritable bowel syndrome and its 1-year follow-up study

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Abstract: Aim: To comprehensively assess the efficacy of low-dose amitriptyline (AMT) on refractory diarrhea-predominant irritable bowel syndrome (D-IBS) and its follow-up study. Methods: A total of 170 patients fulfilled the criteria of refractory D-IBS and were randomly divided into the AMT group (n = 85) or the control group (n = 85). Over 4 wk, AMT (25 mg/day) was administered before bedtime along with *Lactobacillus acidophilus* (0.5 g tid), whereas the control group received only *L. acidophilus* (0.5 g tid). The main efficacy endpoint included the IBS symptom-severity score (IBS-SSS) and main-symptom relief rate. The secondary efficacy endpoint included the Pittsburgh Sleep Quality Index and the assessment of patients' quality of life. After AMT withdrawal at 4 wk, the patients were observed for a 1-year follow-up period. Side effects were also recorded. Results: Of the 85 AMT patients, 65 completed the trial. Their IBS-SSS scores and main-symptom relief rate improved significantly compared with the results for the control group. Finally, 63 patients of AMT group received drug withdrawal and a 1-year period of follow-up. Of these AMT-treated patients, 10 eventually presented with symptoms of recurrence and 8 were found to be sensitive to AMT. Conclusions: Low-dose AMT can improve refractory D-IBS patients' symptoms, quality of life, and sleep quality. Thus, AMT might be an effective alternative therapy for refractory D-IBS.

Keywords: Refractory irritable bowel syndrome, amitriptyline, effect, quality of life, side effect

Introduction

Irritable bowel syndrome (IBS) is one of the common gastrointestinal disorders with chronic symptoms. In the general population, IBS has an estimated prevalence between 5% and 20% [1] and can account for up to 25% of a gastroenterologist's workload in outpatient clinics [2, 3].

The management of refractory IBS symptoms remains challenging, although certain non-pharmacological therapeutic approaches have proved effective. Current IBS therapies mostly focus on regulating the intestinal flora and issuing a prescription for antispasmodic agents and antidepressants. Refractory IBS is defined as patients who fail to respond to conventional therapy, including education, dietary advice, spasmolytics, laxatives, and antidiarrheal medications administered for a minimum of 3 months in gastroenterology outpatient clinics; for these patients, the visual analog scale score is >50 points [4]. Refractory IBS patients often complain of persistent symptoms from which it is difficult to recover, and these symptoms often have a negative impact on a patient's quality of life and can significantly increase healthcare costs [5, 6]. Therefore, patients with refractory IBS gradually become a focus of gastroenterologists and participate in group-oriented therapy. Several studies have been conducted concerning psychological treatments for these patients, including cognitive behavior therapy, hypnotherapy, relaxation therapy, among others [7-9]. Although these treatments generally are beneficial, they have not been

Table 1. Demographic and baseline characteristics of the study patients

Variables	AMT group *N* = 85	Control group *N* = 85	*P* value
Gender (male/female)	43/42	45/40	>0.05
Age (years)	41.32±19.82	42.52±20.56	>0.05
BMI (kg/cm^2)	22.17±2.14	22.84±2.45	>0.05
Symptom duration (years)	14.13±10.15	15.78±9.68	>0.05
IBS-SSS	253.38±66.09	264.64±66.98	>0.05
PSQI	9.14±3.88	9.74±3.52	>0.05

AMT: Amitriptyline; BMI: Body mass index; IBS-SSS: Irritable bowel syndrome symptom-severity score; PSQI: Pittsburgh sleep quality index.

widely disseminated in the clinical management of patients.

Amitriptyline (AMT) is a representative tricyclic antidepressant (TCA) drug that, at a high dose (100 mg/day), has been used to treat IBS for many years; its use is limited, however, owing to potential adverse events. In recent years, low-dose AMT has been shown to be well tolerated and significantly effective for mollifying the symptoms associated with gastrointestinal disorders, so treatment with low-dose AMT has received widespread attention worldwide [10-12]. However, no research has been carried out concerning the efficacy of low-dose AMT for refractory diarrhea-predominant IBS (D-IBS), so no follow-up on withdrawal from the drug been reported. Therefore, we aimed to comprehensively assess the effect of low-dose AMT on refractory D-IBS, with the goal of providing reference data for clinical application. The primary endpoint was assessed using the IBS symptom-severity score (IBS-SSS) and the main-symptom relief rate. The secondary endpoint was assessed using the Pittsburgh Sleep Quality Index (PSQI) and quality of life (IBS-QOL) scores.

Materials and method

Patients

Between October 2015 and May 2016, patients were recruited from the gastroenterology outpatient clinic of Guangzhou Nansha Central Hospital, Hedong branch of Guangzhou First People's Hospital, Guangdong province Second People's Hospital. The trial terminated in June 2017. The following inclusion criteria were adopted: (1) patients were between 18 and 65 years old and met the criteria for refractory D-IBS; (2) patients met the criteria for IBS-related stool types according to the Rome III criteria, namely loose (soft) or watery stools for ≥25% of bowel movements and lumpy or hard stools for <25% of bowel movements; and (3) patients understood all aspects of the trial and signed the informed consent form.

The following exclusion criteria were adopted: pregnancy, bowel surgery, a concomitant severe organic and/or psychiatric disease, hepatic or renal disease, prostatic disease, pregnancy or breast feeding, known glaucoma, history of seizures, history of thyroid or liver dysfunction, recent use of monoamine oxidase inhibitors, and moderate to severe anxiety or depression as assessed with the 14-item Hamilton Anxiety Rating Scale (a score of ≤17 points indicates mild anxiety, 18-24 points indicates mild to moderate anxiety, and 25-30 points indicates moderate to severe anxiety) and the 17-item Hamilton Depression Rating Scale (0-7 points are considered normal, and scores ≥20 indicate moderate, severe, or very severe depression).

Study design and procedures

This study was a prospective, randomized controlled trial of refractory D-IBS patients and was approved by the hospital ethics committee (clinical trial registration number: ChiCTR-TRC-12001969). Written informed consent was obtained from the patients according to the Declaration of Helsinki.

The 170 eligible patients were randomly divided into the AMT group or the control group by simple randomization with a computer-generated randomization schedule. The AMT group received AMT (25 mg/day) before bedtime along with *Lactobacillus acidophilus* (0.5 g tid), whereas the control group received only *L. acidophilus* (0.5 g tid). Ultimately, 85 patients received AMT treatment, and 85 patients served as controls. The primary endpoint was assessed using the IBS-SSS [13, 14] and main-symptom relief rate. The IBS-SSS and main-symptom scores were evaluated at baseline, on day 10, and at week 4. Main-symptom relief

Table 2. Comparison of IBS-SSS among study patients

	Abdominal pain	Days with pain	Abdominal distension	Satisfaction with bowel function	Interference with daily life	IBS-SSS
Baseline						
AMT group	52.58±14.71	56.06±27.09	32.84±24.38	53.03±17.89	58.79±22.26	253.38±66.09
Control group	54.29±13.68	57.96±25.56	37.35±22.44	54.95±18.04	59.29±21.14	263.83±66.98
P value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
10 days						
AMT group	30.91±20.13[a]	39.85±23.18[a]	21.26±17.55[a]	34.6±18.03[a]	37.78±22.53[a]	164.39±79.07[a]
Control group	51.89±15.79	59.29±21.46	38.98±18.16	55.87±15.68	58.01±20.4	254.03±59.99
P value	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
4 wk						
AMT group	27.42±23.88[a]	31.67±25.58[a]	19.29±18.37[a]	27.83±21.46[a]	32.37±25.74[a]	138.59±103.2[a]
Control group	43.11±18.37[a]	47.09±20.86[a]	29.39±19.56	43.11±16.3[a]	50.05±17.96[a]	212.76±70.85[a]
P value	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

The *P* value was for the comparison between the AMT group and control group. [a]Statistically significant difference from baseline, $P<0.05$.

rate was evaluated at baseline and at week 4. The scores of PSQI and IBS-QOL at baseline and at week 4 were the secondary endpoints [15, 16].

After 4 wk, the AMT group received drug withdrawal and 1-year period of follow-up. All patients entering this study recorded their side effects.

Evaluation of the effects of AMT

Relief of IBS symptoms was assessed with a yes/no response (see **Table 2**) to the question: "with regard to all your symptoms of D-IBS in the past 7 days, have you experienced any relief from these symptoms?" A relief from symptoms of >50% was defined as "effective". The evaluation of abdominal pain or discomfort, distention, bowel sound hyperfunction, and bowel satisfaction was defined as the visual analog scale score [4]. According to the Bristol stool chart calculation [1], an improvement of diarrhea symptoms was defined as an improvement of one or two levels with respect to the shape or hardness of the stool, and "invalid" meant that the stool shape or hardness remained at the original level or if a watery stool developed.

Statistical analysis

Data were analyzed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA), and measured data are presented as the mean ± SD using analysis of variance ANOVA, followed by Student-Newman-Keuls test for multiple comparisons. Counting data were compared across groups using the χ^2 test. $P<0.05$ was considered to reflect statistical significance.

Results

Study participants

The study enrolled 170 patients with refractory D-IBS. Of these patients, 10 did not follow doctors' orders, 7 patients stopped taking their medication because of side effects, and 14 patients were lost during follow-up. A total of 139 patients (AMT group 65, control group 74) completed the study (**Figure 1**). **Table 1** presents the baseline characteristics of the patients. There were no differences between the two groups with respect to age, gender, body mass index, symptom duration, IBS-SSS score, or PSQI score.

Primary efficacy endpoint

Compared with the control group, the degree of abdominal pain, days with pain, degree of abdominal distension, degree of satisfaction with bowel habits, quality of life, and IBS-SSS scores of the AMT group improved significantly both at day 10 and week 4 ($P<0.05$ for all; **Table 2**). Compared with baseline, the IBS-SSS scores of the AMT group were significantly lower at both day 10 and week 4 ($P<0.05$ for all). However, with the exception of abdominal distention, the indexes of the control group were significantly lower only after 4 wk of treatment.

After 4 wk of treatment, the main-symptom relief rate values (including abdominal pain, distention, bowel sound hyperfunction, and

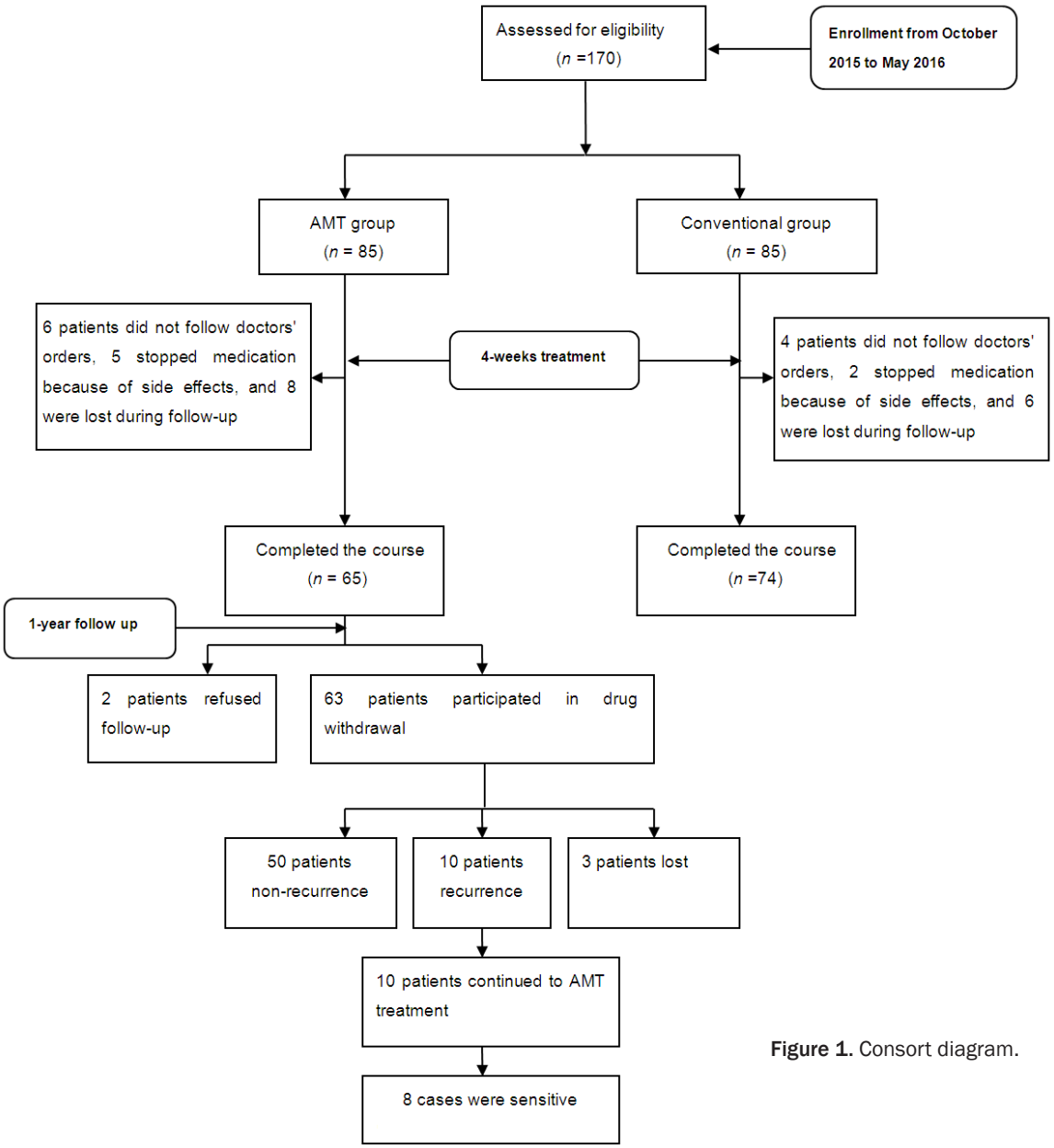

Figure 1. Consort diagram.

diarrhea) of the AMT group were significantly greater than those of the control group ($P<0.05$ for all, **Table 3**).

Secondary efficacy endpoints

Compared with the control group, the AMT group exhibited significant improvements in dysphoria, interference with activity, health worries, food avoidance, social reaction, and personal relationship scores of the IBS-QOL ($P<0.05$ for all; **Table 4**). Compared with baseline, the AMT group exhibited significant improvements in dysphoria, interference with activity, health worries, food avoidance, social reaction, personal relationships, and sexual function ($P<0.05$ for all). The control group experienced significant improvements in only dysphoria, health worries, and sexual function ($P<0.05$ for all; **Table 4**).

The AMT group also showed a significant improvement in PSQI compared with the control group ($P<0.05$, **Table 3**). Also, compared with baseline, the AMT group exhibited significant improvement. However, there was no significant difference in PSQI between baseline and the control group ($P>0.05$).

Table 3. Comparison of index in patients

Variables	AMT group *N* = 65	Control group *N* = 74	*P* value
Main-symptom relief rate			
Abdominal pain n/m (%)	59/65 (89.7%)	24/74 (32.4%)	<0.05
Distention n/m (%)	35/60 (57.3%)	13/64 (20.3%)	<0.05
Diarrhea n/m (%)	54/65 (81.8%)	18/74 (24.3%)	<0.05
Bowel sound hyperfunction n/m (%)	16/26 (61.5%)	6/30 (21.4%)	<0.05
PSQI (mean ± SD)	5.27±2.61	8.87±3.14	<0.05
Side effects			
Dry mouth	50/65 (75.8%)	15/74 (20.2%)	<0.05
Sleepiness	52/65 (78.8%)	15/74 (20.2%)	<0.05
Dizziness	16/65 (24.2%)	8/74 (10.8%)	<0.05
Constipation	14/65 (20.2%)	5/74 (6.7%)	<0.05
Palpitations	3/65 (3.1%)	0/74 (0%)	>0.05
Malaise	3/65 (4.1%)	0/74 (0%)	>0.05

The *P* value is for the comparison between the AMT group and the control group. n, the number of patients considered for statistical analysis; m, the total number of patients used for statistical analysis; PSQI: Pittsburgh sleep quality index.

Table 4. Comparison of IBS-QOL subscale scores among the study participants

Variables	Groups	Baseline	Week 4	*P* value
Dysphoria	AMT	61.14±16.31	78.09±11.97[a]	<0.05
	Control	59.53±16.71	64.09±14.28[a]	
Interference with activity	AMT	71.28±17.02	81.44±13.59[a]	<0.05
	Control	68.84±18.51	72.81±14.74	
Body image	AMT	88.89±16.55	89.33±16.34	>0.05
	Control	86.48±17.32	88.46±16.31	
Health worry	AMT	60.27±15.28	72.09±15.53[a]	<0.05
	Control	56.55±17.68	61.9±14.25[a]	
Food avoiding	AMT	61.61±26.56	72.03±19.08[a]	<0.05
	Control	62.75±26.82	65.65±24.38	
Social reaction	AMT	80.37±15.34	88.76±12.27[a]	<0.05
	Control	78.12±17.18	81.06±14.81	
Sexual function	AMT	83.09±17.89	87.37±16.89[a]	>0.05
	Control	82.82±18.67	85.84±17.37[a]	
Personal relationship	AMT	81.48±17.23	91.07±13.16[a]	<0.05
	Control	82.57±18.62	84.52±17.09	

[a]Statistically significant difference compared with baseline, *P*<0.05.

Side effects

Table 3 presents the various adverse events reported by patients in both groups. Dry mouth, sleepiness, dizziness, and constipation were more frequently reported by the AMT group than the control group (P<0.05 for all; **Table 3**). We found that sleepiness and dizziness almost disappeared within 1 wk. Patients who had both dry mouth and constipation symptoms experienced significant relief after receiving AMT for 2 wk. No serious adverse events occurred in the control group.

Follow-up study

For the AMT group, 65 patients completed the study, and 63 received drug withdrawal and a 1-year follow-up. Among the 63 patients, 10 experienced a recurrence of symptoms within 1 year (i.e., recurrence rate = 15.87%), and 3 were lost during follow-up. Of the 10 patients who experienced recurrence, 8 were found to be sensitive to AMT retreatment, so the AMT retreatment effective rate was 80% (**Figure 1**).

Discussion

The diagnosis of D-IBS is generally based on clinical symptoms and can be made using various criteria, but the etiology remains unknown. The most popular pathogenetic theories are visceral hypersensitivity, disturbances of gut motility and secretion, autonomic nervous system dysfunction, deregulation of the brain-gut axis, altered gut microbiota, and inflammation

of the gut wall [17, 18]. This potential multiplicity of causes has given rise to a variety of treatment approaches [19]. The current mainstays of pharmacotherapy include bulking agents, antidiarrheal agents, laxatives, antispasmodics, antidepressants, serotonergic agonists or antagonists, antibiotics, and probiotics [20-22]. Despite numerous studies evaluating the treatment of D-IBS, however, there is still no universally accepted satisfactory treatment for this condition [8]. Patients with D-IBS tend to have relatively more severe depression and anxiety than healthy persons. Therefore, antidepressants, e.g., TCAs, selective serotonin reuptake inhibitors, etc., have been extensively used to treat IBS [23]. Whereas selective serotonin reuptake inhibitors are used to treat C-IBS, i.e., owing to their prokinetic effect, TCAs are effective for D-IBS because they prolong the whole-gut transit time [24]. The TCA antidepressants are effective for improving global D-IBS symptoms and reducing abdominal pain, but the clinical use of TCAs for D-IBS patients is limited because of safety and tolerability considerations [24].

AMT is an antidepressant that acts through a mechanism similar to that of the TCAs, and AMT is efficacious for treating patients with IBS. In 1998, Rajagopalan *et al* [25] were the first to attempt a prospective, randomized, double-blinded, placebo-controlled trial investigating the effectiveness of low-dose AMT (25-75 mg/d) for treating patients with IBS. After 12 wk of treatment, the response of the AMT group was significantly greater than that of the placebo group (63.6% vs 27.3%). Vahedi *et al* [26] used a smaller dose (10 mg/d) to treat patients with D-IBS, and again the response of the AMT group was significantly greater than that of the placebo group (68% vs. 40%) after 4 wk of treatment, and the side effects were nominal that those reported by the placebo group. In our study, the IBS-SSS scores of the AMT group improved more than those of the control group after 10 d of treatment. After 4 wk of treatment, the main-symptom relief rate and IBS-QOL score of the AMT group were significantly greater than those of the control group. These results suggest that low-dose AMT (25 mg/d) significantly lessens the symptoms refractory D-IBS.

Several potential mechanisms have been proposed to explain the benefit of AMT for treating IBS. These include alteration of gut motility and visceral sensitivity and prolongation of whole-gut transit time [27]. We previously observed that low-dose AMT could reduce visceral sensitivity using the noninvasive drinking-ultrasonography test with healthy volunteers [28]. Dysregulation of central pain perception in the brain-gut axis is considered to play a pivotal role in the pathophysiology of IBS, and thus AMT might reverse the dysfunction of the pain-regulatory system via a central analgesic action. Morgan *et al* [29] demonstrated that the doses of AMT required for central analgesia are lower than doses required for antidepressant treatment. One study, however, found that AMT can negatively impact the sleep patterns of IBS patients [30]. Our present study also confirmed that AMT could significantly improve sleep quality compared with the control group. Therefore, the beneficial effects of AMT may be multifactorial, comprising an improvement central pain threshold, anticholinergic effects, regulation of gastrointestinal transit time, and peripheral anti-neuropathic effects.

To our knowledge, this was the first prospective, randomized, controlled trial investigating the effectiveness of a therapeutic low dose of AMT for refractory D-IBS. Notably, our study included a 1-year period of patient follow-up. In conclusion, low-dose AMT was well tolerated and might be effective for reducing the severity of symptoms of patients with refractory D-IBS while also significantly improving sleep quality and quality of life. Therefore, AMT should be considered as an alternative regimen for the treatment of refractory D-IBS.

Disclosure of conflict of interest

None.

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