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Original Article

Effect of Citalopram and Olanzapine Combinations in the Treatment of Refractory Irritable Bowel Syndrome

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ABSTRACT

Background: Although plenty of medications have shown promise in the treatment of irritable bowel syndrome (IBS), none have relieved all complaints adequately to be considered as gold standard. Based on previous data regarding the effectiveness of olanzapine in other functional or psychosomatic disorders and clinical experience of the authors on its efficacy and safety, we considered to test this drug in combination with citalopram for IBS.

Materials and Methods: IBS patients who were refractory to conventional treatments were assigned randomly to take placebo or citalopram (C) with either placebo or olanzapine (O) by which, 38, 36 and 38 patients entered in the study in each group, respectively. The patients were evaluated for quality of life (IBS-QOL), severity and frequency of symptoms, depression and anxiety (HADS) before intervention and 4 and 12 weeks after initiation of the treatment. Thirty one of the placebo (P) group versus 13 patients of the control (C+P) and 17 of the case (C+O) completed the full course of study.

Results: While there was a trend toward better results in intervention groups compared to placebo alone, no statistically significant difference was observed among the three intervention groups in quality of life ($p = 0.799$); but, there was a significant improvement from pretest scores in both 4 and 12 week observations in all three groups ($p < 0.001$). Similar findings were detected between the two intervention groups for severity and frequency of symptoms as well as anxiety and depression scores. There was a significant rate of discontinuation of the study in the intervention groups compared to the placebo group.

Conclusion: Citalopram neither alone nor in combination with olanzapine added significant benefits to IBS symptoms in this study.

Keywords: IBS, Citalopram, Olanzapine

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INTRODUCTION

Irritable bowel syndrome (IBS) is a very common disorder characterized by abdominal pain or discomfort and altered bowel habits in the absence of detectable structural abnormalities. A considerable fraction of the patients also suffer from other functional disorders such as fibromyalgia, chronic headache, functional dyspepsia and non-organic chest pain. Worldwide prevalence of IBS is about 12 percent (1). The prevalence of IBS in Iran ranges from 5.6% to 16.4% depending on the sampling methods used (2, 3) and most studies show a female predominance (4-6). Despite the benign nature, IBS can considerably decrease quality of life and pose major financial burden by increasing days off work and extraordinary referral to medical service (7). IBS is classified according to the prominent symptom to constipation predominant IBS (IBS-C), diarrhea predominant IBS (IBS-D) and alternating or mixed symptoms (IBS-A or IBS-M) (8). Many experts suggest a trial of antidepressants in the IBS patients who have not responded to diet or symptomatic treatment to reduce their intestinal sensitivity even in the absence of overt anxiety or depressive symptoms (9). In the antidepressant family, there is an extensive experience on citalopram worldwide and in our clinic; moreover, the safety profile is quiet acceptable. On the other hand, the benefit of the neuroleptic drug, olanzapine in the functional disorders such as fibromyalgia has been reported (10). One of the ways to find a novel drug for a disorder like IBS is to assess the efficacy of a drug that is used to treat a condition that commonly coexists with, or is thought to have a similar pathophysiology with the disorder, such as fibromyalgia, anxiety, or depression (11). The aim of this study was to assess the effect of citalopram and olanzapine combination in the treatment of IBS and to compare it with that of citalopram or placebo.

MATERIALS AND METHODS

The IBS patients who were refractory to conventional treatment modalities were referred by gastroenterologists from December 2007 to February 2009 to the psychosomatic clinic of Noor hospital, Isfahan University of Medical Science to enroll in the study. The patients fulfilled the ROME III criteria (12) of IBS diagnosis. All types of IBS were accepted in the study and there were non-significant differences in distribution of these types among the groups. We excluded the patients who had a diagnosis of a major psychiatric or organic disorder based on the evaluations in gastroenterology and psychiatry clinics. All the patients evaluated for routine laboratory and thyroid function tests but the upper GI endoscopy, colonoscopy or sigmoidoscopy were accomplished according to the international guidelines with respect to the risk factors and age of the patients. After psychiatric evaluation and confirmation of eligibility, the patients signed a written informed consent. For randomization, the patients were assigned to one of the case, control and placebo groups alternately with the order of refer (keeping the order throughout the study) and received citalopram and olanzapine, citalopram and placebo identical to olanzapine or placebo, respectively. The case group was treated with olanzapine (Tehran Darou) at a dose of 1.25 mg during the first week with gradual increments up to one 5 mg tablet and citalopram (Tolid Daru) initially 10 mg and maximally one 20 mg tablet both bedtimes daily. The control group received citalopram coupled with placebo similar to olanzapine in shape with the same condition as the case group. The placebo group just received a placebo. The duration of 12 weeks was designated for the study and the patients were invited after 4 weeks and at the end of the study for a visit and filling the same questionnaires like the pretreatment interview. The patients who did not show up at the assigned date were called by telephone and asked for the reason of their absence. The patients were evaluated with the

questionnaire of quality of life for IBS patients (IBS-QOL) designed by Drossman and Patrick (13), severity of symptoms questionnaire acquired from Boyce et al (14). and the Hospital Anxiety and Depression Scores (HADS) for psychiatric assessment (15). Placebo group was only assessed for the quality of life. To exclude possible mistakes in filling the forms, all the questionnaires and specifications of the patients were filled by the patients under the supervision of clinical psychologists. Previous symptomatic treatment of the patients such as clidinium C, psyllium, loperamide, dicyclomine or antacids were continued for the patients who were taking them before the study but consumption of a new drug and any previously used psychotropic drug were prohibited during the study. The patients on the treatment with psychotropic drugs advised to stop the medication for 2 weeks before their first evaluation and initiation of the study.

Statistical Analysis: The statistical analysis was done with SPSS software version 15. Analysis of variance (ANOVA) with repeated measures was mainly used for comparison. The sample size of 27 was calculated for each group according to similar studies (16).

RESULTS

A total of 112 patients were studied, 65 (64.5 %) female and 38 (36.2 %) male. Mean age of the patients was 34.59 years (15 to 60 year-old) with no significant difference among 3 groups (p=0.741); 38 patients (36.2%) in the case group, 36 patients (34.3%) in the control group and 38 patients in the placebo group entered in the study and filled the questionnaires while only 17 and 13 patients in the case and control groups completed the study, respectively; 31 patients of the placebo group finished the schedule. There was no significant deference in age, marital status, level of education, baseline hospital anxiety and depression scores (HADS) among the three groups. Although most of our patients were diarrhea predominant, there was a significant alternation between initially diarrhea and constipation predominant subgroups.

Quality of Life: The quality of life was measured in each of the three groups and was considered as the primary aim of the study. Only the patients who finished all three steps of the study were considered for the analysis. Mean and standard deviation of the IBS-QOL scores are shown in table 1. Although there was a significant difference between pretreatment quality of life and 4th or 12th week scores within each group (p = 0.001), no significant difference was found between 4th and 12th week results. Likewise, the comparison among the three groups did not reveal a significant deference (p = 0.799).

Table 1: Mean (and standard deviation) of IBS-QOL

	Case (%)	Control (%)	Placebo (%)	Total (%)
Week 0	70.4 (7.9)	71.1 (12.6)	71.4 (13.6)	71.1 (11.9)
Week 4	78.3 (12.4)	79.0 (12.2)	74.9 (12.5)	76.7 (12.3)
Week 12	79.6 (13.3)	80.3 (14.0)	77.3 (13.3)	78.6 (13.3)

Severity and frequency of symptoms

Severity and frequency of symptoms of IBS were compared in case and control groups. The results are shown in tables 2 and 3. Statistical analysis showed a significant change of the base scores in weeks 4 or 12 (p = 0.017 and p<0.001, respectively) but not between weeks 4 and 12 (p = 0.336). Similar to the quality of life, no significant difference was detected between the two intervention groups (p = 0.946).

Table 2: Mean (and standard deviation) of severity of symptoms

	Case (%)	Control (%)	Total (%)
Week 0	4.8 (3.1)	6.0 (2.9)	5.3 (3.1)
Week 4	3.7 (3.1)	3.4 (3.1)	3.6 (3.0)
Week 12	3.3 (3.3)	2.5 (2.2)	3.0 (2.9)

Table 3: Mean (and standard deviation) of frequency of symptoms

	Case (%)	Control (%)	Total (%)
Week 0	6.0 (4.0)	6.8 (4.2)	6.3 (4.0)
Week 4	4.7 (4.1)	5.5 (4.5)	5.0 (4.2)
Week 12	4.3 (4.5)	4.0 (3.5)	4.2 (4.0)

Depression and Anxiety: The results of HADS depression and anxiety scores of the patients are shown in tables 4 and 5. There was a significant improvement of both scores in weeks 4 and 12 compared to pre-intervention scores (p=0.013 and p<0.001) but, there was not a significant change from weeks 4 to 12 (p=0.054). The difference between case and control groups was not significant as well (p=0.10).

Table 4: Mean (and standard deviation) of HADS depression score summary

	Case (%)	Control (%)	Total (%)
Week 0	9 (3.7)	8.3 (4.2)	8.7 (3.9)
Week 4	8.4 (3.1)	6.4 (3.5)	7.5 (3.3)
Week 12	6.8 (2.6)	5.8 (3.0)	6.3 (2.8)

Table 5: Mean (and standard deviation) of HADS anxiety scores summary

	Case (%)	Control (%)	Total (%)
Week 0	11.8 (2.2)	10.4 (4.1)	11.2 (3.1)
Week 4	10.2 (3.6)	8.3 (5.2)	9.4 (4.4)
Week 12	9.5 (3.2)	7.4 (4.2)	8.6 (3.8)

The reason of refusal of the patients to continue the study was assessed in the clinic or asked via a phone call to the patients who did not refer in the expected days. In some cases, contact with the patients was not possible due to address change or wrong phone numbers. Table 6 summarizes the data in this regard.

Table 6: Patients related reasons of failure to continue the study

	Side effects	Unsatisfied with treatment	Idea of harmful effect of the drugs	Improvement with shorter course of treatment	Unknown	Total
Case	3	3	1	4	12	23
Control	3	3	2	1	12	21
Placebo	-	2	-	2	4	8

DISCUSSION

None of the currently available medications of IBS can control all symptoms properly and IBS still impose a significant health burden. Most of the medications for constipation or diarrhea are ineffective in alleviation of abdominal discomfort or even worsen it (17, 18). Despite promising results of alosetron, an inhibitor of serotonergic 5HT3 receptor approved for diarrhea, and tegaserod, a partial agonist of 5HT4 receptor effective in constipation, abdominal pain and bloating, their application is restricted due to significant cardiovascular side effects. Nevertheless, the prominent effect of these serotonergic drugs coupled with a considerable mass of studies in the literature confirms the basic role of serotonin (5HT) in pathogenesis of IBS (8). On the other hand, a considerable overlap of IBS with psychiatric disorders especially depression, anxiety disorders and sexual abuse in childhood justifies the recommendation of antidepressants in IBS (19, 20). Tricyclic antidepressants (TCAs) are commonly used in treatment of IBS and it seems to be effective in low doses in IBS and pain related conditions such as migraine headache, functional dyspepsia, non-organic chest pain, neuropathic or cancer related pains (1). The effect of this class of antidepressants might be due to regulation of central of peripheral pain perception, amelioration of psychiatric co-morbidity or modification of gastrointestinal motility via a local effect (21). Although the effectiveness of this family of antidepressants has been shown in a meta-analysis by Ford et al (22). another meta-analysis of the best quality randomized controlled trials (RCTs) by Quartero et al. failed to observe a beneficial effect of TCA compared to placebo (23). Although the overall evidence suggests a therapeutic role for TCA in IBS, a significant discontinuation rates due to side effects is reported (9). Regarding therapeutic effect of SSRI antidepressants, even less RCTs are available of which paroxetine is the most studied drug. The largest study on 257 patients, compared paroxetine and psychotherapy with routine management by a gastroenterologist and

found both interventions superior to routine management in improving the quality of life without a significant decrease in severity of symptoms. In this study 50 % discontinuation of paroxetine mostly due to side effects was reported (24). The results of fluoxetine is conflicting (25, 26) but citalopram has been acceptably supported in studies. In one RCT, citalopram 20 mg daily in the first 3 weeks and 40 mg thereafter, significantly improved the overall well being and severity of symptoms including abdominal pain and frequency of flatus without a considerable change in the bowel habit. These effects were not related to the improvement of depression or anxiety and began before the usual 3 week lag needed to detect antidepressant effect of the drug; however, dose increment potentiated the effects. The failure of the study to detect a significant improvement in intervention groups may be attributed to lower doses in comparison to the dose of 40 mg used in similar studies. We decided to apply 20 mg daily doses to reduce dose dependant side effects and improve the compliance of patients (16, 27). Moreover, the results of intervention groups despite lack of significance were better than the results of placebo group which suggest a possibly significant difference if a larger sample size were studied. Although some authors may only suggest the SSRI antidepressants in moderate to severe impairment of the quality of life (8) most meta-analysis and review articles support wider application of these antidepressants in IBS. Ford et al. in an analysis of all SCTs about SSRI reported a significant improvement of symptoms with an efficacy comparable with TCAs (22). Although no one of the antidepressants is approved by US food and drug administration (FDA) for treatment of IBS, it is suggested that the patients who fail to respond to the symptomatic treatment receive a trial of antidepressants even in the absence of overt anxiety or depressive symptoms. While there is more experience on TCA antidepressants, SSRIs have a better safety and tolerability profile (9). Olanzapine by its own or in combination has been effective on IBS symptoms in the literature. Effect of the neuroleptic drugs including olanzapine has been reported in the treatment of other functional disorders as well (28) Multiple case series report the treatment of fibromyalgia with olanzapine (10, 29, 30) and response of a case with both IBS and fibromyalgia symptoms to olanzapine is reported (31). The rational of treatment of IBS with olanzapine was the reports of acceptable response to the drug in fibromyalgia, other functional and pain disorders and IBS itself, as well as the good experience of the authors in this regard in psychosomatic clinic. In this study, addition of olanzapine to the citalopram regimen caused no significant difference with citalopram alone. One explanation of the obtained result is the possible unreported noncompliance or missing of some doses of the drug due to side effects. Other possible factors are lower doses (5 mg or less compared to 10 to 20 mg in fibromyalgia studies), (10, 30) gradual raising the dosage, short course of the treatment and small sample size. We decided to try lower doses in the pilot study to avoid expected side effects in intermediate or high doses. The significant rate of discontinuation, which is considerably higher in intervention than in placebo group, is reported by some other authors as well (30). We trusted to the patients' reports and memories in each interview sessions for monitoring the compliance and registering possible side effects. Considering the fluctuating nature of IBS in contrary to fibromyalgia, missing of the doses in less symptomatic days due to failure to recall or belief of being unnecessary is predictable. More precise monitoring and exclusion of noncompliant case possibly could change the results. The study may imply that the routine administration of the psychotropic drug is not rational, yet it dose not exclude this option for appropriate cases. Before prescription of antidepressant or neuroleptic drugs for IBS patients,

special attention should be paid to selection of the patients regarding the symptoms profile and tolerability of the drugs.

CONCLUSION

Citalopram neither alone nor in combination with olanzapine added significant benefits to IBS symptoms in this study.

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