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Effect of Fluoxetine Administration on Clinical and Echocardiographic Findings in Patients with Mitral Valve Prolapse and Generalized Anxiety Disorder: Randomized Clinical Trial

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Abstract

Background: Mitral valve prolapse (MVP) is accompanied by mental disorders including anxiety, which has similar presentations as MVP. It is hypothesised that treatment of anxiety might reduce the symptoms of MVP.
Objective: The aim of this study was to assess the clinical and echocardiographic effects of fluoxetine administration in patients with MVP and anxiety.
Methods: This randomized clinical trial was conducted on patients with documented MVP and generalised anxiety disorder (GAD) who were referred to Mashhad University of Medical Sciences cardiology clinics, Mashhad, Iran in 2015. Subjects were randomly assigned to intervention group who received propranolol and fluoxetine (both at 10 mg/day) and control group who received 10 mg/day propranolol. Assessments included echocardiography and GAD-7 questionnaire and rating of chest pain, that were performed at baseline and then weekly for 4 weeks. Analysis was performed using the Mann-Whitney U test and Two-way Repeated Measures Analysis of Variance (ANOVA).
Results: Sixty patients (25 male/ 35 female) with a mean age of 22.9 ± 2.5 years were studied in two groups of intervention (n = 30) and control (n = 30). GAD score was significantly higher in the intervention group (17.37 ± 1.61) compared with the control group (14.17 ± 0.83) ($p<0.001$). No significant difference was observed for changes in left atrium diameter, mitral annular diameter, left ventricular diameter or ejection fraction ($p>0.05$). Pain severity was reduced significantly more in control group (3.27 ± 1.26) compared to intervention group (2.80 ± 0.85) after treatment ($p<0.001$).
Conclusions: This study revealed that the co-administration of fluoxetine and propranolol may not only have no effective in improving echocardiographic changes of MVP but may also aggravate subjective findings of patients with MVP and GAD.
Trial registration: The trial is registered at the Iranian Clinical Trial Registry (IRCT.ir) with the IRCT identification number IRCT2014102819721N1.
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Keywords: Mitral valve prolapse, Anxiety, Fluoxetine, Propranolol

1. Introduction

Mitral valve prolapse (MVP) is a condition where the free edge of a leaflet of mitral valve remains above the annulus plane at the end of systole (1). MVP may be caused by any pathology that result in the elongation or rupture

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of cordial or papillary muscles (1). MVP is a common cardiac disorder that is estimated to occur in 2-3% of the general population (2). Mitral valve regurgitation is the most common complication of MVP and is significantly related to mortality (3). Other possible complications of MVP are atrial fibrillation, heart failure, peripheral arterial thromboembolism, endocarditis and sudden death (4). Although recent studies provide evidence for the superiority of 3D echocardiography, 2D echocardiography is considered as the gold standard for the diagnosis of MVP (4,5). The best treatment for MVP is surgery at the asymptomatic stage in the presence of expert surgeon and the underlying pathology (6). There are no medical treatment options for asymptomatic MVP while β-blockers and angiotensin converting enzyme (ACE) inhibitors may be useful in symptomatic stages where heart failure is developed (7). MVP is also seen in concordance with mental disorders including depression (23.1%), anxiety (26.7-35.9%) and panic disorder (0-50%) but no causal link has been identified for these coincidences (8). Some studies reported higher prevalence of symptoms of anxiety disorder in patents with MVP compared to healthy individuals and that these symptoms were reduced after psychotherapy or medication (9, 10). Contrary to these studies, recent studies have shown no difference in presentation on anxiety disorder symptoms in patients with MVP (8). Although there is doubt about the relationship between psychological disorders and MVP, it was previously shown that patients with MVP and anxiety comorbidity were found to have more intense emotional experiences compared with patients with MVP who do not express anxiety symptoms, and therefore might benefit from medical treatment for their condition (9). On the other hand, induced psychological stress was found to result in changes in rhythm (based on electrocardiogram) and amplitude of click in phonocardiogram (11). Regarding the fact that a number of symptoms of anxiety, including increased tachycardia, chest pain and blood pressure lability might aggravate MVP symptoms (12), it is hypothesized that treatment of the underlying or concomitant psychological disease might have a palliative effect on MVP signs and symptoms (13, 8–10). Previous studies have shown improvements in MVP symptoms and depth of the prolapse by psychotherapy or medical treatment of anxiety (benzodiazepines, β-blockers) (14, 15). Selective serotonin reuptake inhibitors (SSRIs) are considered as a treatment option for depression, anxiety and stress (16). Previous studies found no adverse effects for SSRI administration in cardiac valvular problems (17). On the other hand, a rodent study claimed improved antianxiety by the co-administration of a combination of β-blockers (atenolol) and benzodiazepine (alprazolam) and SSRI (escitalopram) (18). To the best of our knowledge no study has yet assessed the effect of SSRI on symptoms of MVP. The aim of this study was to assess the clinical and echocardiographic effects of fluoxetine administration to patients with MVP and anxiety.

2. Material and Methods

2.1. Research design and setting

This study is a randomized clinical trial which is conducted in Mashhad University of Medical Sciences cardiology clinics over a four month period; starting from March 2015.

2.2. Selection criteria

2.2.1. Inclusion criteria

Patients with diagnosed MVP who had symptoms of generalized anxiety disorder (GAD) were included in the study. GAD symptoms included chest pain and palpitation with at least one of the following symptoms; muscular fatigue, loss of energy, respiratory symptoms which were checked based on the previously validated GAD-7 questionnaire.

2.2.2. Exclusion criteria

Subjects were excluded if they had previous diagnoses psychological problems or medical diseases or conditions that result in anxiety including anaemia, hypoglycaemia, hyponatremia, hyperkalemia, alcohol/drug withdrawal syndrome, vertigo, thyrotoxicosis, hyperkapnea, central nervous system problems such as epilepsy, hypoxemia due to asthma or other causes, ischemic heart disease, malignancy and drugs that affect anxiety state including antiepileptics, antimicrobials, bronchodilators, digitalis, oestrogen, insulin, non-steroid anti-inflammatory drugs, antidepressants, antihistamins, calcium channel blockers, dopamine/levodopa, inotropic drugs, steroids as well as smoking .

2.3. Sampling

2.3.1. Sample size

Sample size was calculated using the GPOWER software version 3.1.7 for f test (repeated measures ANOVA, within-between interactions) using 0.25 as the effect size of f, error probability of 0.05, correlation among repeated measures of 0.5 and nonspheriscity correction of 1. The sample size calculated by the software was 27 subjects in each group. Considering 10% drop out, the final sample size was calculated as 60 subjects (30 subjects in each study group).

2.3.2. *Sampling method*
Subjects were identified based on the patient interview at the cardiology clinic. Subjects were approached and assessed for the inclusion and exclusion criteria and eligible subjects were approached and informed about the procedure and aims of the study. Subjects who were willing to participate in the study signed a written informed consent prior to participation in the study.

2.4. Blinding and allocation
Subjects were randomly assigned into control group, who received propranolol (10 mg/day), and intervention group, who received propranolol (10 mg/day) and fluoxetine (10 mg/day), for 4 weeks. Due to the number of drugs used (two medications in the intervention group and one medication in the control group), subjects could not be blinded in this study while the cardiologist was blinded regarding the type of medications used by the subjects.

2.5. Interventions
The control group received conventional treatment, which was Inderal 10mg three times per day while the intervention group received Inderal (10mg three times per day) and fluoxetine 10mg once a day. Except for the medication, subjects in both groups were managed similarly regarding visits and consultations. Subjects in both groups were assessed weekly for primary and secondary outcome measures.

2.6. Data Collection
Echocardiography was performed using the Esaote Mylab50 device by a cardiologist who was blinded regarding the intervention or control group. Subjects were asked to fill up a demographic questionnaire at the beginning of the study and report the severity of their chest pain based on an 11 scale rating system, where 0 indicates no pain and 10 indicates the highest ever pain. A questionnaire with same scoring system was filled for each subject in each follow up session. Also, Echocardiography finding of every subject were filled by the cardiologist. GAD severity was assessed using a validated 7-item questionnaire (GAD-7). GAD-7 was recognised as a screening tool for GAD (19) and its reliability (reported Cronbach's alpha of 0.86) and validity (against SCL-90-R questionnaire) has been previously assessed in a sample of the Iranian population (20).

2.7. Outcome
Subjects in each group were followed up every week for four weeks. In each follow up session subjects underwent echocardiography and were asked to rate their overall chest pain as well as filling up the GAD-7 questionnaire.
2.7.1. *Primary outcome measures*
The primary outcome measures were pain severity, echocardiographic findings including left atrial (LA) diameter, ejection fraction (EF), left ventricular (LV) diameter and mitral annular diameter. These variables were measured for all subjects at baseline and weekly for four weeks.
2.7.2. *Secondary outcome measures*
The secondary outcome measures were pain severity and palpitation severity. In order to assess the pain severity, subjects were asked to report the severity of their chest pain from a scale of zero, indicating no pain, to 10, indicating the worst pain ever. Palpitation severity was similarly reported by subjects based on a Likert scale ranging from zero (no palpitation) to 10 (extremely severe palpitation).

2.8. Research Ethics
This trial was approved by the ethical committee of the Sabzevar University of Medical Science (ethic committee code: 33/3/KPJ) and registered in Iranian Registry of Clinical Trials (IRCT) trial registration code IRCT2014102819721N1. Participants enrolling in this study were asked about drug adverse reactions in each visit. Also the participants were educated to report any cardio-respiratory or mood changes during the study.

2.9. Statistical analysis
The statistical package for social sciences (SPSS) version 21 (IBM Inc. Chicago, Il) was used to analyze the data. Continuous variables were checked for normality using the Shapiro-Wilk test. Continuous variables including age, mitral valve annular diameter, left atrium and ventricle diameter, ejection fraction, valve thickness and GAD score were shown as mean and standard deviation (SD) while frequency and percentage was used to describe categorical data including gender, education level, marital status and presence of mitral valve regurgitation. Mann-Whitney U test was used to compare GAD score between intervention and control groups. Two way repeated measures analysis of variance (ANOVA) was used to assess the effect of interventions on each mitral valve annular diameter, left atrium and ventricle diameter, ejection fraction and valve thickness. Moreover, two-way repeated measures

ANOVA was used to assess the effect of treatment methods over time on the pain and palpitation severity controlling for GAD score. Values of p smaller than 0.05 were considered as statistically significant.

3. Results

3.1. Baseline characteristics

A total of 60 subjects (30 subjects as intervention group and 30 subjects as controls) with a mean age of the 22.9 ± 2.5 years participated in this study (Figure 1). There was no significant difference in demographic parameters between intervention and control groups (Table 1).

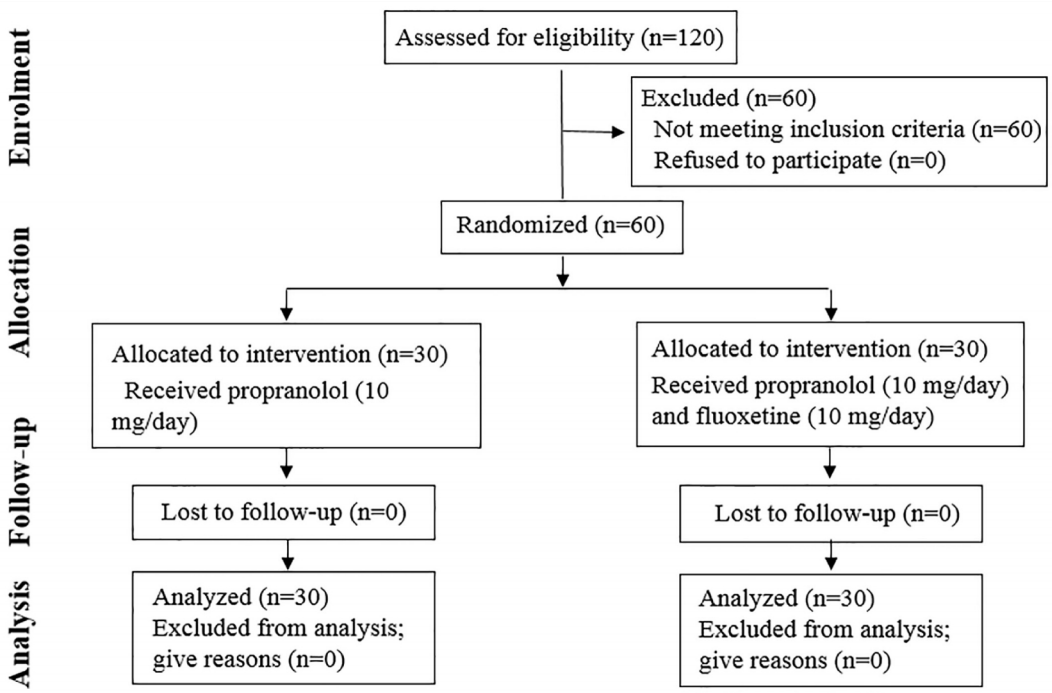

Figure 1. CONSORT statement flow diagram

Table 1. Demographic characteristics and their comparison between treatment groups

Demographic characteristics		Total	Fluoxetin+Inderal group (n = 30)	Inderal group (n = 30)	p-value
Age (years)		22.9±2.5	23.4±2.3	22.6±2.7	0.22
Gender, n (%)	Male	25 (41.7%)	12 (48.0%)	13 (52.0%)	0.79
	Female	35 (58.3%)	18 (51.4%)	17 (48.6%)	
Marital status, n (%)	Single	34 (56.7%)	16 (47.1%)	18 (52.9%)	0.60
	Married	26 (43.3%)	14 (53.8%)	12 (46.1%)	
Education level. n (%)	Illiterate	9 (15.0%)	3 (33.3%)	6 (66.7%)	0.17
	Primary school	13 (21.7%)	8 (61.5%)	5 (38.5%)	
	Secondary/Diploma	23 (38.3%)	14 (60.9%)	9 (39.1%)	
	Under graduate/Bachelor	14 (23.3%)	4 (28.6%)	10 (71.4%)	
	Post graduate	1 (1.7%)	1 (100%)	0 (0.0%)	

3.2. Comparison of outcomes

Mean GAD score of the subjects was 15.77 ± 2.05. GAD score was significantly higher in the intervention group (17.37 ± 1.61) compared with the control group (14.17 ± 0.83) ($U(1)=24.00$, $p<0.001$). Left atrium (LA) diameter and mitral annular diameter increased after treatment in both intervention and control groups but this increase was not significant between and within groups (Two-way repeated measures ANOVA $p=0.88$ and $p=0.09$ respectively). Similarly, although LV diameter decreased over the study duration, there was no significant difference between intervention and control groups neither within nor between groups (Two-way repeated measures ANOVA $p=0.05$). Ejection fraction was increased during the course of treatment in intervention group while it decreased in the control

group but no significant difference between or within groups was observed (Two-way repeated measures ANOVA p=0.73) (Table 2). Two-way repeated measures ANOVA analysis revealed that, after controlling for GAD score, although the pain severity decreased significantly in both groups (F=14.27, df=2.92, df Error=1.21, p<0.001), it was reduced significantly more in control group compared with intervention group after treatment (F=44.36, df=1, df Error=57, p<0.001) (Table 2, Figure 2). Two way repeated measures ANOVA analysis revealed that, after controlling for GAD score, although the palpitation severity decreased significantly in both groups (F=10.15, df=1.23, df Error=127.11, p=0.54), there was no significant difference between intervention and control groups after treatment (F=0.29, df=1, df Error=57, p=0.59) (Table 2, Figure 3).

Table 2. Comparison of cardiologic variables before and after intervention between intervention and control groups

Echocardiograpich varibales (mean ± SD)	Fluoxetin+Inderal group		Inderal group		F	df[4]	df Error	p-value
	Baseline	After	Baseline	After				
LA[1] diameter (mm)	29.37±0.76	29.57±0.82	29.17±1.18	29.40±0.97	0.02	1	58	0.88
EF[2] (%)	61.10±1.88	61.27±1.41	60.80±1.63	60.53±1.14	2.33	1	58	0.13
LV[3] diameter (mm)	50.20±0.92	48.83±5.17	50.63±1.32	49.70±3.68	0.14	1	58	0.71
Mitral annular diameter (mm)	28.80±0.85	29.37±0.96	28.80±1.13	29.03±1.07	2.95	1	58	0.09
Pain severity	10.00±0.00	3.93±1.51	10.00±0.00	1.40±0.67	44.36	1	112.74	<0.001*
Palpitation severity	10.00±0.00	1.33±0.55	10.00±0.00	1.33±0.66	0.29	1	89.77	0.59

1: LA= Left atrium, 2: EF= Ejection fraction, 3: LV= Left ventricle, 4: df=degree of freedom
* Significant effect of time and trial on pain severity

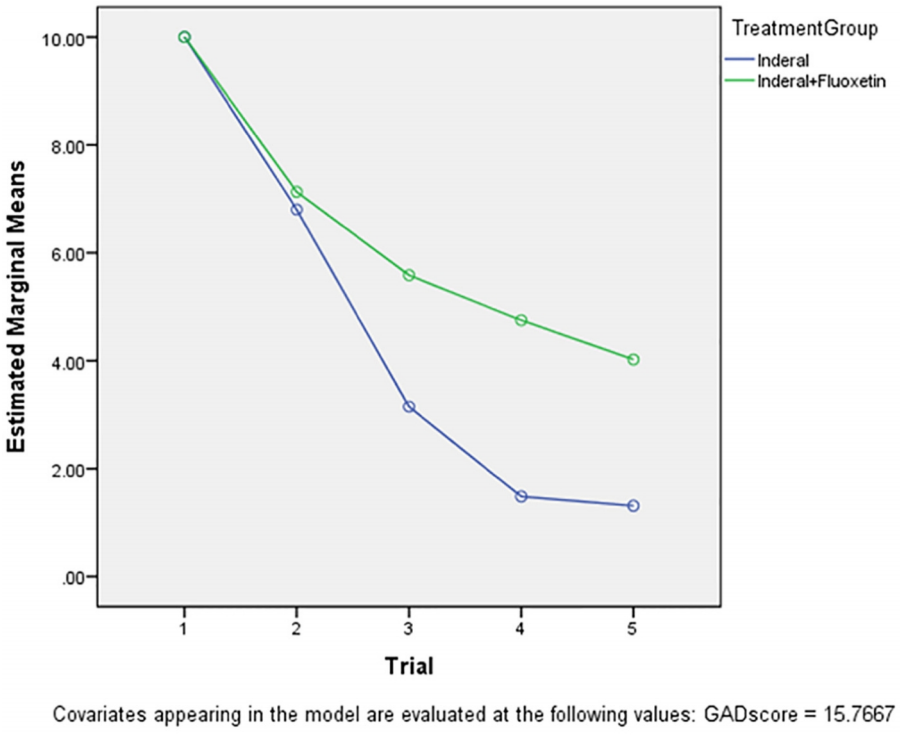

Figure 2. Effect of treatments on pain severity

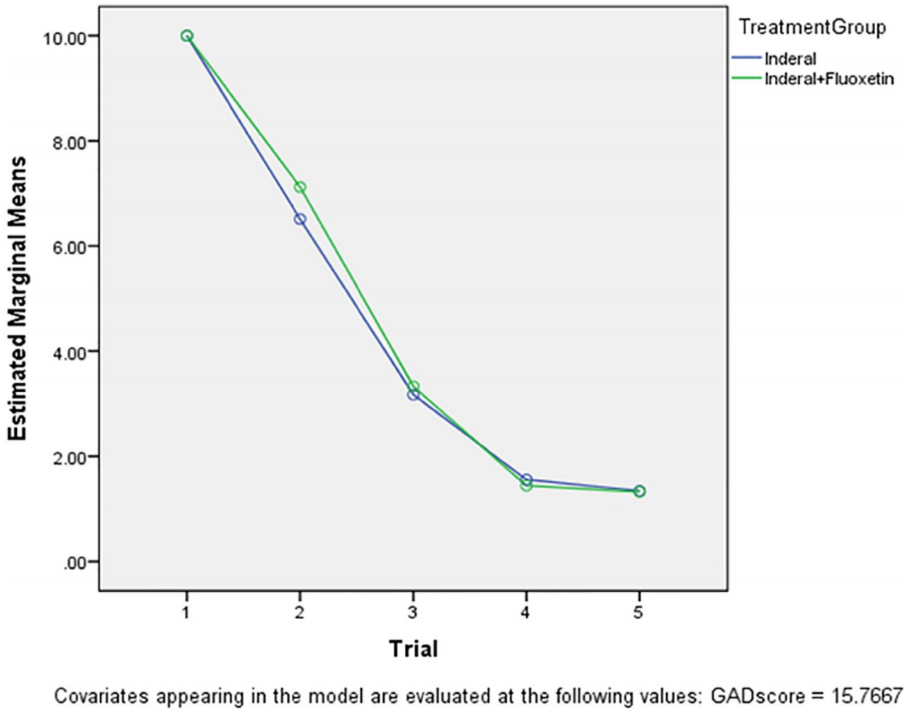

Figure 3. Effect of treatment on palpitation severity

4. Discussion

This study found an increase in LA diameter and decrease in LV diameter during the course of follow up period in both intervention and control groups but these changes were not statistically significant. This finding was in line with the findings of previous studies which showed only a significant increase in LA diameter in moderate to severe mitral regurgitation (21, 22). This finding indicates that none of the two modalities could reverse the progression of MVP. In this study LV diameter and ejection fraction were decreased in both groups, but this decrease was not statistically significant. It was previously shown that beta-II blockers improve LV function in MVP and Mitral regurgitation (23). It was previously shown that adrenergic receptor upregulation exists in mitral valve prolapse, which results in autonomic dysregulation in MVP patients (12, 24). The findings of this study were in line with the hypothesis of high sympathetic activity in MVP. On the other hand, there is a high sensitivity to sympathetic activity in some types of anxiety disorder that can be regulated by administration of propranolol (25). Furthermore propranolol administration reduced severity of chest pain to a significantly lower level in control group compared with intervention group. It was previously shown that prolapse of the mitral valve may result in traction of papillary muscles that, in turn, result in the stimulation of cardiac stretch receptors resulting in chest pain. In addition, this stimulation might trigger abnormal autonomic nerve feedback (26). The regulatory effect of propranolol on sympathetic activity might be the reason for the reduced chest pain in this study. SSRIs were shown to have a high potency in reducing the occurrence of non-cardiac chest pain (27, 28). This finding was the basis of a hypothesis that serotonin might have a more powerful role in non-cardiac chest pain compared to norepinephrine (28). The extent of chest pain improvement of subjects in this study with propranolol alone compared to co-administration of fluoxetine and propranolol may indicate that the basis of chest pain in MVP may be more of a cardiac reason, therefore SSRIs may not serve as a therapeutic adjuvant for cardiac symptoms in non-complicated MVP. This study also found that co-administration of SSRI may reduce the effect of beta blocker on chest pain in MVP. To the best of our knowledge no similar study has assessed the effect of SSRIs alone or in combination with other drugs in reducing the severity of MVP syndrome. Furthermore, this study showed that propranolol administration with or without SSRI co-administration resulted in significant reduction in palpitation. It was previously shown that beta-blocker administration was beneficial in reducing palpitation in MVP (23). SSRIs were shown to have no significant effect on palpitation in postural orthostatic tachycardia syndrome (POTS), but may result in refractory tachycardia in the first 2 weeks of the initiation of treatment, although this finding was shown to have no effect on the overall symptom relief effects of SSRI (29, 30). Based on the reported findings of the previous studies and the findings of the present study, it can be hypothesized that the effect of co-administration of propranolol and fluoxetine on palpitation, may be attributed to propranolol and the non-significant less success in palpitation reduction might be due to adverse

effect of fluoxetine. While Using GAD-7 questionnaire was not the only possible tool for evaluating anxiety disorder, we decided to use this questionnaire because of simplicity and previous validation in our country. Other studies may get different results because of using other questionnaires. Also, we relied on participant's reports about using medications and avoidance of using other drugs. About documenting the pain and palpitation status, patients may have reported inaccurate answers because of possible life events prior to each of their visits. In order to minimize these bios we suggested they could fill their questionnaires some hours later if they think they may provide inappropriate answers.

5. Conclusions

The findings of this study suggest the use of fluoxetine with propranolol may aggravate the effects of propranolol in MVP patients. This effect might be due to a different physiological mechanism for anxiety in MVP, which halts the effects of SSRIs on cardiac symptoms of the subjects. The findings of this study may help physicians make a more accurate judgment on the use of medications in order to reduce the financial and medical costs of their treatment for MVP patients with anxiety. However, more research is required to identify the mechanism of the observed effect of fluoxetin and also on the effects of other SSRI drugs on the echocardiographic and symptomatic characteristics of MVP patients with anxiety.

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Trial registration:

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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