RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2024.2023-66
Cyprus J Med Sci 2024;9(5):316-322

Refractory Vasovagal Syncope Despite Tilt Training: Should Paroxetine be Included in the Treatment?

Lale Dinç Asarcıklı[1], Osman Beton[2], Burak Acar[3], Nur Beton[4], Hasan Birtan[5], Güzin Zekican[6], Nuryıl Yılmaz[7], Hakkı Kaya[8], Recep Kurt[9], Yeşim Akın[10], Mehmet Birhan Yılmaz[11]

[1]Department of Cardiology, University of Health Sciences Türkiye, Dr. Siyami Ersek Thoracic and Cardiovascular and Surgery Training and Research Hospital, İstanbul, Türkiye
[2]Department of Cardiology, Cyprus International University Faculty of Medicine, Nicosia, North Cyprus
[3]Department of Cardiology, Kocaeli University Faculty of Medicine, Kocaeli, Türkiye
[4]Clinic of Cardiology, Ankara City Hospital, Ankara, Türkiye
[5]Clinic of Cardiovascular Surgery, Dr. Burhan Nalbantoğlu State Hospital, Nicosia, North Cyprus
[6]Department of Cardiology, Dr. Burhan Nalbantoğlu State Hospital, Nicosia, North Cyprus
[7]Department of Psychiatry, University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital, İzmir, Türkiye
[8]Department of Cardiology, Onsekiz Mart University Faculty of Medicine, Çanakkale, Türkiye
[9]Department of Cardiology, Cumhuriyet University Faculty of Medicine, Sivas, Türkiye
[10]Department of Cardiology, Karabük University Faculty of Medicine, Zonguldak, Türkiye
[11]Department of Cardiology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye

Abstract

BACKGROUND/AIMS: To investigate the efficacy of selective serotonin reuptake inhibitors (SSRI) for preventing spontaneous vasovagal syncope (VVS) in patients with refractory VVS despite home-based tilt training (TT).

MATERIALS AND METHODS: We included 111 consecutive patients with VVS. All patients were instructed to increase salt and fluid intake, perform counterpressure maneuvers, and perform TT. The first control visit was scheduled within 2 months of the initial treatment. Paroxetine 20 mg was added to TT in patients with refractory VVS despite TT (TT plus SSRI group) at the first control visit, and patients without refractory VVS who continued TT (TT group). The clinical features of the patients, spontaneous VVS attacks before and after treatment, and follow-up data were recorded.

RESULTS: A total of 111 consecutive patients (67 females; age: 32±12 years) were treated with TT (64 patients) or TT plus SSRI (47 patients). The mean follow-up was 8.9±3.3 months after the first control visit. During follow-up, 38 (80.9%) patients in the TT + SSRI group and 30 (46.9%) in the TT group were asymptomatic ($p<0.001$). In the univariate analyses, TT plus SSRI treatment and TT treatment during follow-up were predictors of an asymptomatic course. Multivariate analysis showed that TT plus SSRI therapy (odds ratio: 4,785, 95% confidence interval: 4,784-11,501, $p<0.001$) as the sole predictor of asymptomatic course at follow-up.

CONCLUSION: The addition of paroxetine to the treatment of patients with recurrent VVS who do not respond to TT and conventional treatment is an effective and well-tolerated treatment method for preventing vasovagal attacks.

Keywords: Refractory vasovagal syncope, tilt training, drug treatment, selective serotonin re-uptake inhibitor, paroxetine

To cite this article: Dinç Asarcıklı L, Beton O, Acar B, Beton N, Birtan H, Zekican G, Yılmaz N, Kaya H, Kurt R, Akın Y, Yılmaz MB. Refractory Vasovagal Syncope Despite Tilt Training: Should Paroxetine be Included in the Treatment?. Cyprus J Med Sci. 2024;9(5):316-322

ORCID IDs of the authors: L.D.A. 0000-0002-7828-9487; O.B. 0000-0001-8540-428X; B.A. 0000-0003-3217-5000; N.B. 0009-0002-0066-2840; H.B. 0000-0002-4952-9402; G.Z. 0009-0004-6935-8454; N.Y. 0000-0002-6229-9197; H.K. 0000-0001-5230-635X; R.K. 0000-0001-6237-1585; Y.A. 0000-0002-1238-7439; M.B.Y. 0000-0002-8169-8628.

Address for Correspondence: Lale Dinç Asarcıklı
E-mail: mdlaledinc@gmail.com
ORCID ID: orcid.org/0000-0002-7828-9487

Received: 20.07.2023
Accepted: 27.05.2024

INTRODUCTION

Recurrent vasovagal (neurocardiogenic) syncope (VVS) is a common and important clinical presentation, accounting for 66% of syncope cases presenting to the emergency department.[1,2] The diagnosis of VVS, which causes deterioration in quality of life, limitation and inadequacy, increased hospital admissions, and serious health expenditures in many young patients, started to be made more frequently after the application of the head-up tilt test (HUTT).[3,4]

Although many randomized and non-randomized clinical trials have investigated various treatments for VVS, an effective treatment for VVS has not yet been identified.[3-7] Various pharmacological and non-pharmacological approaches are available for the treatment of VVS.[4-7] VVS treatment includes a multi-layered approach consisting of lifestyle changes, physical maneuvers, drug treatments, and, if necessary, pacemaker implantation. HUTT is greatly helpful in identifying younger patients but has also been shown to be beneficial in prophylactic treatment.[6,8,9] Tilt training (TT), or passive standing, is a non-pharmacological VVS treatment that involves repeated and prolonged exposure of the cardiovascular system to an orthostatic stimulus. However, there are inconsistencies in subsequent studies that vary according to the training protocol and patient compliance. Previous studies have shown that TT is a promising treatment for VVS.[9-12]

Non-invasive treatment of VVS includes both pharmacological and non-pharmacological interventions. Conversely, studies have been conducted on various drugs with different mechanisms of action for the treatment of VVS.[13] The central serotonergic system, which appears to be associated with the pathogenesis of VVS, has been investigated in several clinical studies.[13-15] In these studies, selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, and paroxetine, were shown to be effective in preventing vasovagal events.[15] In a placebo-controlled study involving severely symptomatic patients, paroxetine was found to be effective in preventing syncope attacks; however, this finding has not been supported by a small number of subsequent studies.[16] In this study, in patients with resistant VVS despite TT, the effectiveness of adding paroxetine to existing non-pharmacological therapy in preventing syncope attacks.

MATERIALS AND METHODS

The Study Group

This was a multicenter prospective observational study including 632 consecutive patients who were admitted to or referred to 3 different state hospital cardiology clinics with a diagnosis of transient loss of consciousness (TLoC) over a 1-year period. VVS was found in 183 (29.0%) patients, situational syncope in 38 (6.0%), carotid sinus syncope in 6 (0.9%), and orthostatic hypotension in 92 (14.6%) (including primary or secondary autonomic failure, postural orthostatic tachycardia syndrome and drug-induced), cardiac arrhythmia in 104 (16.5%), structural cardiovascular disease or pulmonary diseases in 27 (4.3%), neurological disorders (epilepsy, transient ischemic attack, non-epileptic drop attack) in 66 (10.4%), psychogenic disorders in 17 (2.7%), metabolic disorders (diabetic patients with or without hypoglycemia), in 34 (5.4%), inner ear-related vertigo in 5 (0.8%), and uncertain or unknown diagnosis (idiopathic) in 60 (9.5%) patients as the cause of TLoC.

Of the 183 patients with a diagnosis of VVS, 56 were excluded due to a history of syncope for 6 months (n=37), antidepressants, or anxiolytics use [(n=19) (12 of them using non-SSRI and 3 of them using SSRI antidepressants, and 4 of them using anxiolytics] (Figure 1). Of the remaining 127 patients with a diagnosis of VVS, those who attended at least 2 follow-up visits (provided that the first control visit was in the outpatient clinic) were included in the study. Patients who did not attend the second control visit were contacted via telephone, and a telephone-mediated control visit was conducted. Patients were advised to measure their own pulse and blood pressure, and if they could not measure it, they were advised to apply to the nearest health institution, and the obtained data were recorded. After treatment, 10 patients who did not come to the first control visit and 6 patients who could not be reached by telephone for the second control visit were excluded from the study. The remaining 111 patients constituted the study group (Figure 1). This study was conducted in accordance with the principles of the Declaration of Helsinki. The Institutional Ethical Committee of Türkiye's Yüksek İhtisas Training and Research Hospital approved the study (approval number: 091023-310-EPK). All patients enrolled in the study provided informed consent to participate in the study.

VVS Diagnosis

In the study group, patients with no pathological findings in the results of 12-lead electrocardiography (ECG), 72-hour Holter ECG follow-up, exercise ECG test, transthoracic echocardiography, and HUTT examinations were diagnosed with VVS. The HUTT (for 10 minutes in an upright position) was performed by an experienced nurse; previously it had been explained in a detailed version.[17]

Treatment and Follow-up

Patients were informed about the etiology of VVS, prodrome, and physical counterpressure maneuvers and how to avoid possible triggers. Adequate water and fluid intake, targeting 2-3 liters of fluid and 10 g of sodium chloride per day was recommended for the patients. In addition, the patients were educated about a strict daily TT program at home and additional flexible exercise training (ET) programs.

1. TT program: Patients were educated to practice TT at home while leaning against a wall (20 cm away from the wall with their ankles). The sessions were planned to be conducted in a safe and comfortable environment to prevent physical trauma and to be completed under the supervision of a family member. Patients were educated with sustained standing training and were encouraged to quit early if symptoms of presyncope developed; otherwise, TT was terminated at 30 minutes. Patients were informed that they would start the training with 5 min sessions twice a day, morning, and evening, increasing the session duration by 5 min each week, and extending the session duration up to 30 min. Two months later, patients were instructed to perform the alternate-day TT program.

2. ET program: Patients were educated about the flexible ET program consisting of 45-60 minutes exercise sessions three times a week. Each exercise session was planned to consist of stretching and relaxation exercises, such as 5 min stretching, 30-40 minutes cycling or brisk walking, 2-10 minutes local strengthening (sitting, pushing, and pulling), and 5 min stretching. In cases of symptoms, it was recommended to interrupt training and switch to a horizontal position.

The first control visit was planned within the first 2 months after the start of treatment. In the event of spontaneous syncope between the initiation of therapy and the first control visit, patients were

considered symptomatic, and 20 mg of paroxetine (at the first control visit) was added to the existing therapy. Patients without spontaneous syncope between the first treatment and the first control visit were considered asymptomatic, and their current treatment was continued. Asymptomatic patients who visited the first control visit were named the TT group, whereas symptomatic patients who were administered paroxetine were named the TT plus SSRI group.

Definitions and Data Collection

Side effects related to paroxetine or reasons for discontinuing paroxetine treatment were recorded at the control visits. The expected side effects are drowsiness, headache, transient sexual dysfunction, constipation, dry mouth, nausea, and diarrhea. The patients were examined by a psychiatrist. The psychiatrist applied the Beck Depression Inventory (Symptom Checklist-90) during the examination. Minor psychiatric disorders (MPD) diagnosed according to the DSM-IV-TR criteria[18] were included in the study. However, patients with dysthymia, major depressive episodes, or chronic psychiatric disorders were excluded from the study group by inclusion in the psychogenic syncope group (Figure 1). Routinely, each patient was asked to record the number of training sessions per day and their duration. In addition, each patient was asked to record their spontaneous and presyncope episodes. The efficacy of paroxetine treatment was evaluated by comparing the symptomatic status of patients in the TT and TT plus SSRI groups between the first and last control visits.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation in the presence of a normal distribution, as median (minimum-maximum) in the presence of an abnormal distribution, and categorical variables were expressed as percentages. For comparisons between patient groups, (χ^2 test was used for categorical variables, the t-test for independent groups for normally distributed continuous variables, and the Mann-Whitney U test for abnormally distributed variables. The paired t-test was used for normally distributed values, and McNemar test was used for categorical variables (percentages and ratios) to compare changes in the first and last control visit values. Univariate regression analysis was used to measure the relationship of variables with the asymptomatic (absence of syncope) condition during the first and last control visits. Variables with a p value of <0.1 in the univariate analysis were included in the multivariate analysis. The TT program, TT program plus SSRI, adequate ET program, average daily TT duration, and average daily TT number were included in the multivariate logistic regression analysis using the forward stepwise method to identify independent indicators of asymptomatic status during follow-up. Statistical analysis was performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

RESULTS

Study Population

The characteristics of the study population are shown in Table 1. A total of 111 consecutive patients were included in the study. Of these patients, 44 were male and 67 were female. The mean age was 32±12 years. The median numbers of syncopes and presyncope per year were 4 and 10, respectively. Twenty (15%) patients had a history of severe trauma due to a previous syncope attack. The median duration of VVS history was 2.5 years (Table 1). The first control visit was made to all patients in the cardiology outpatient clinic 28±5 days after the first treatment. During the period between the start of treatment and the first visit, 47 patients were symptomatic, whereas 64 (57.7%) patients were asymptomatic (Table 1, Figure 1).

The baseline characteristics of patients who were asymptomatic and symptomatic at the first control visit were similar (Table 1). Symptomatic patients presented to the first control visit earlier than asymptomatic patients (30±4 days versus 27±5 days; p=0.001). The mean duration and number of daily TTs were statistically higher in the asymptomatic group than in the symptomatic group (609±172 min compared to 54±7 min, p<0.001 and 421±187 min, 40±10 min, respectively; p<0.001). However, the mean duration and number of daily TT were statistically greater in the asymptomatic group than in the symptomatic group (20.0±3.0 min vs. 15.0±4.9 min and 1.8±0.1 vs. 1.5±0.3, respectively, p<0.001 for both). Compliance with an adequate ET program was statistically higher in the asymptomatic group than in the symptomatic group (73.4% compared to 42.6%; p=0.001), whereas there were no differences between the groups in compliance with adequate salt and fluid intake treatment (p=0.445) (Table 1).

Follow-up Data After the First Control Visit

Additional paroxetine was added to TT (TT + SSRI group) for treating symptomatic patients (n=47) at the first control visit, and TT treatment was continued in asymptomatic patients (n=64) (TT group) (Figure 1). Patients were followed for 8.9±3.3 months after the first control visit (Table 2). During follow-up, 30 patients (46.9%) in the TT group and 38 (80.9%) in the TT plus SSRI group were asymptomatic (p<0.001). However, the mean number and duration of daily TT were statistically higher in the asymptomatic group than in the symptomatic group (12.6±2.0 min vs. 9.6±3.1 min and 1.1±0.1 vs. 0.9±0.2, respectively, p<0.001 for both). Compliance with an adequate ET program was higher in the asymptomatic group than in the symptomatic group (59.4% vs. 36.2%; p=0.016), whereas adequate salt and water intake levels were similar between the groups (p=0.487) (Table 2).

In the TT group, the mean daily TT duration, mean daily TT number, and adequate compliance with the ET program during follow-up were significantly decreased compared with the values at the first control visit (p<0.001, p<0.001, and p=0.004, respectively). Similarly, the mean daily TT duration and mean daily TT number during follow-up were significantly decreased in the TT plus SSRI group (p<0.001 and p<0.001, respectively). However, in the TT plus SSRI group, there was no significant difference in compliance with the ET program during follow-up compared with the value at the first control visit (p=0.250).

In 7 patients (14.9%) in the TT plus SSRI group, paroxetine-related side effects (drowsiness, transient sexual dysfunction, constipation, dry mouth, nausea, and diarrhea) were observed; however, treatment was continued in these patients. Paroxetine treatment was discontinued in one patient at the fifth month of follow-up because of weight gain (according to the patient, this was related to paroxetine). The patient was asymptomatic during the follow-up, and no syncope attacks were recorded after treatment was discontinued.

Independent Predictors of Asymptomatic Patients at Follow-up

The results of univariate and multivariate analyses performed to determine the predictors of asymptomatic status (absence of VVS attacks) during follow-up (the time between the first control visit and

Table 1. Characteristics of the study group

Variables	All patients, (n=111)	Asymptomatic during the first visit, (n=64)	Symptomatic during the first visit, (n =47)	p
Basal parameters				
Age	32±12	32±12	33±12	0.589
Female gender, n (%)	67 (60.4)	41 (64.1)	26 (55.3)	0.352
BMI, kg/m^2	23.6±4.6	23.2±3.9	24.2±5.3	0.266
Smokers, n (%)	45 (40.5)	27 (42.2)	18 (38.3)	0.680
Number of syncopes per year	4 (1-54)	4 (1-30)	4 (1-54)	0.388
Number of presyncope annually	10 (3-54)	8.5(13-50)	12 (3-54)	0.103
Number of syncopes per year >2, n (%)	99 (89.2)	57 (89.1)	42 (89.4)	1.0
Syncope causing severe trauma, n (%)	20 (15.0)	9 (14.1)	11 (23.4)	0.310
Prodromal symptoms, n (%)	78 (70.3)	49 (76.6)	29 (61.7)	0.138
History of positive HUTT, n (%)	75 (67.6)	43 (67.2)	32 (68.1)	0.920
VVS history duration (years)	2.5 (1-11)	2.5 (1-11)	2.5 (1-10)	0.507
History of head trauma, n (%)	16 (14.4)	8 (12.5)	8 (17.0)	0.692
Minor psychiatric disorders, n (%)	42 (37.8)	22 (34.4)	20 (42.6)	0.380
Parameters of the first control visit				
Systolic blood pressure (mmHg)	123±14	123±12	124±15	0.899
Diastolic blood pressure (mmHg)	71±10	73±10	72±10	0.590
Heart rate, beats per minute	75±11	76±10	75±12	0.687
Days of the first visit	28±5	30±4	27±5	0.001
Total number of TTs	48±11	54±7	40±10	<0.001
Total TT time (minute)	529±200	609±172	421±187	<0.001
Average daily TT time, minute	18.0±4.6	20.0±3.0	15.0±4.9	<0.001
Average number of daily TTs	1.7±0.3	1.8±0.1	1.5±0.3	<0.001
Adequate treatment adherence				
Salt and fluid intake, n (%)	92 (82.9)	55 (85.9)	37 (78.7)	0.445
ET program, n (%)	67 (60.4)	47 (73.4)	20 (42.6)	0.001

ET: Exercise training, HUTT: Head-up tilt test, TT: Tilt training, BMI: Body mass index, VVS: Vasovagal syncope.

the last follow-up visit) are presented in Table 3. Univariate analysis revealed that TT plus SSRI [odds ratio (OR): 4,785, 95% confidence interval (CI): 4,784-11,501, p<0.001)] and TT (OR: 0.209, 95% CI: 0.087-0.502, p<0.001) were predictors of asymptomatic patients at follow-up. Multivariate analysis revealed that only TT plus SSRI treatment (OR: 4,785, 95% CI: 4,784-11,501, p<0.001) was an independent predictor of asymptomatic patients at follow-up.

DISCUSSION

The main findings of this study, which investigated the effect of adding paroxetine (SSRI) to the treatment of resistant VVS despite TT, are as follows: 1) TT treatment initially seemed effective in preventing syncope attacks; however, loss of efficacy was observed during follow-up, probably due to decreased compliance of patients with TT programs; 2) the addition of paroxetine to TT treatment resulted in a reduction in syncope attacks in patients with resistant syncope attacks despite TT; 3) paroxetine has been shown to have a lasting effect on preventing syncope attacks in patients with TT-resistant VVS, as long as it is used; 4) paroxetine was observed to be well-tolerated in patients with VVS; 5) TT plus SSRI treatment was found to be the only independent predictor of being asymptomatic during follow-up.

To date, few pathophysiological suggestions have been made regarding the underlying mechanisms of VVS.[3,4,6] Susceptibility to VVS has been associated with insufficient sympathetic activation, resulting in sympathetically mediated peripheral vascular resistance reduction.[10,18] Upright posture induces gravity-induced pooling of venous blood in the lower extremities. This pooling and displacement of intravascular volume decreases cardiac output, activates arterial baroreceptor reflexes, and increases sympathetic stimulation. The activation of ventricular mechanoreceptors produces a strong afferent signal in the brainstem and inhibits sympathetic stimulation.[16] Another possible mechanism is stimulation of the Bezold-Jarisch reflex because of strong contraction of the myocardium against insufficient filling of the heart chamber, resulting in paradoxical hypotension and bradycardia; this may also be responsible for VVS. In general, VVS is caused by three main mechanisms: low vasoconstrictor reserve variability, increased autonomic tone, and changes in baroreflex sensitivity. Most triggers consist of prolonged sitting or standing in an upright position, or muscle activation with a reduction in cardiac preload.[6]

VVS has different treatment options, and it continues to be an important health problem. Various non-pharmacological approaches are effective for treating VVS.[6] The initial strategy is patient education, which is very helpful and necessary. Patients should be advised to avoid heat

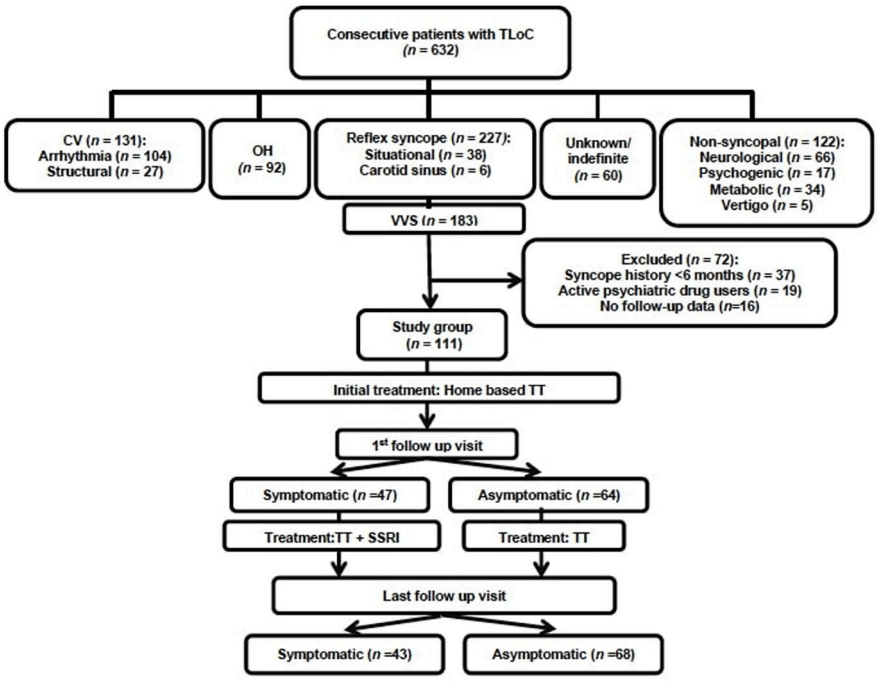

Figure 1. Flow chart showing patients who participated in the treatment-based study at follow-up and the distribution of patients into subgroups according to drug therapy.

TLoC: Transient loss of consciousness; CV: Cardiovascular, TT: Tilt training, OH: Orthostatic hypotension, SSRI: Selective serotonin reuptake inhibitor, VVS: Vasovagal syncope.

Table 2. Follow-up data of the study group after the first control visit

Variables	All patients, (n=111)	TT group, (n=64)	The TT + SSRI group, (n=47)	p
Systolic blood pressure (mmHg)	123±14	124±14	122±14	0.276
Diastolic blood pressure (mmHg)	71±8	70±9	73±8	0.134
Heart rate, beats per minute	74±11	73±12	76±9	0.259
Duration until last visit (months)	8.9 ±3.3	9.0±3.3	8.8±3.2	0.717
Asymptomatic at follow-up, n (%)	68 (61.3)	30 (46.9)	38 (80.9)	<0.001
Syncope during follow-up, n (%)	43 (37.8)	34 (53.1)	9 (19.1)	<0.001
Syncope causing severe trauma, n (%)	11 (9.9)	10 (15.6)	1 (2.1)	0.023
Average TT time per day, minute	11.4±2.9	12.6±2.0	9.6±3.1	<0.001
Average number of daily TTs	1.1 ±0.2	1.1±0.1	0.9±0.2	<0.001
Adequate treatment adherence				
Salt and fluid intake, n (%)	97 (84.7)	56 (87.5)	38 (80.9)	0.487
ET program, n (%)	55 (49.5)	38 (59.4)	17 (36.2)	0.016

ET: Exercise training, TT: Tilt training, SSRI: Selective serotonin re-uptake inhibitor.

and beware of early prodromal symptoms. Aydin et al.[19] showed that a significant reduction in syncope frequency could be achieved using the standard training protocol. Isometric muscle contractions increase cardiac output and arterial blood pressure while reducing syncope in non-randomized and randomized studies.[20,21] Communication with the patient is important during treatment because treatment is usually tailored to the patient's response. TT was developed after repeated HUTT observations. It has been suggested that repetitive HUTTs gradually increase peripheral sympathetic nervous system function and may decrease positive test results.[8,22]

Several studies have shown that training for continuous exposure to orthostatic stress effectively reduces the risk of syncope recurrence.[9,22] Ector et al.[8] found that patients could tolerate all HUTTs after 3-6 sessions, if they repeated daily HUTTs to hospitalized patients until the patients developed a vasovagal response and tolerated the entire test period. Therefore, many researchers have prescribed TT at home, which involves standing against a wall for 30 minutes twice a day; however, it was reported that outpatient TT has no beneficial effect on spontaneous episodes of syncope during follow-up.[10,23] It has been reported that patient compliance is necessary for a continuous TT program, and it may be difficult to achieve a high rate of patient compliance in each patient

Table 3. Univariate and multivariate predictors of asymptomatic at follow-up

	Univariate			Multivariate		
Variables	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
TT + SSRI	4,785	4,784-11,501	<0.001	4,785	4,784-11,501	<0.001
TT program	0.209	0.087-0.502	<0.001			
ET program	0.489	0.223-1,058	0.069			
Number of presyncope annually	1,026	0.987-1,067	0.199			
TT duration per day	0.862	0.746-0.997	0.045			
TT per day	0.116	0.009-1,430	0.093			

CI: Confidence interval, ET: Exercise training, TT: Tilt training, OR: Odds ratio, SSRI: Selective serotonin reuptake inhibitor.

group.[24] A study conducted by Foglia-Manzillo et al.[25] revealed that only 34% of patients fulfilled all the requirements of the TT session, even at short-term follow-up. In our study, it was found that patient compliance with TT was better at the beginning and decreased significantly over time. In our study, 53.1% of the patients who were asymptomatic at the first follow-up visit became symptomatic during follow-up, in parallel with a decrease in compliance with TT. Numerous physical therapy strategies and maneuvers have been tried for the treatment of VVS.[6] The ET program was formerly widely used because it increases blood volume and improves or modulates baroreceptor function.[25,26] Aerobic and core strengthening exercises were also included in these studies.[26,27]

Serotonin is a neurotransmitter known to affect blood pressure and heart rate by modulating the central nervous system. Several studies have investigated the use of SSRIs for treating VVS.[13,15,16] In a randomized, double-blind, placebo-controlled study, Di Girolamo et al.[16] showed that compared with placebo, paroxetine significantly reduced episodes of syncope in patients with refractory VVS who did not respond to conventional therapy during a 2-year follow-up. Theodorakis et al.[13] published the results of a randomized, placebo-controlled, double-blind study showing that fluoxetine and propranolol were not superior to placebo for the treatment of VVS. Paroxetine has high selectivity and low affinity for adrenergic, cholinergic, and histamine receptors.[16] Therefore, not all SSRIs are equally effective against recurrent VVS. In this case, the group effect of SSRIs for treating VVS can be misinterpreted.

A high rate of MPD has been reported in patients with VVS.[28,29] These disorders are associated with increased vasovagal reflex excitability and relatively high rates of VVS attack.[30] Leftheriotis et al.[30] showed that psychiatric drug therapy can improve VVS attacks and psychiatric symptoms in MPD patients.

Several pathophysiologic mechanisms similar to the vasovagal reflex are believed to be mediated by changes in central serotonin levels.[31] Grubb[32] proposed that SSRIs downregulate postsynaptic serotonin receptors by promoting neuronal transmission. This reduction in receptor density is thought to blunt the response to rapid changes in central serotonin levels.[14,15,32]

Study Limitations

This study has a few limitations. First, this was a prospective observational study and did not have a randomized placebo-controlled design. Second, the sample size was relatively small. Third, patients from three health centers followed by different healthcare providers were included in the study. Fourth, it would have been more beneficial for all patients to undergo a psychiatric evaluation to better understand the response to the SSRI. Fifth, to better understand the pathophysiological impact of SSRIs, patients could be evaluated using pre- and post-treatment quality of life and psychiatric measures. Sixth, quantitative methods can be used to assess patient adherence to TT and ET. Last but not least, the follow-up period of our study was relatively short compared with that of other randomized studies on SSRIs. Therefore, large-scale, multicenter, randomized, and prospective studies are needed to determine the efficacy of paroxetine in VVS.

CONCLUSION

TT is an acceptable treatment for VVS for motivated patients who are willing to follow the program. However, the effectiveness of TT in preventing VVS attacks decreased during the follow-up period, probably due to decreased compliance of patients with the TT program. In patients with recurrent VVS who do not respond to conventional treatments, the addition of paroxetine appears to be an effective and well-tolerated treatment modality for preventing vasovagal attacks.

MAIN POINTS

- TT treatment initially appeared effective in preventing syncope; however, a loss of efficacy was observed during follow-up.
- Paroxetine has a lasting effect on preventing syncope attacks in patients with TT-resistant VVS.
- Paroxetine was well tolerated in patients with VVS.
- Tilt training plus paroxetine treatment was the only independent predictor of asymptomatic patients during follow-up.

ETHICS

Ethics Committee Approval: The Institutional Ethical Committee of Türkiye's Yüksek İhtisas Training and Research Hospital approved the study (approval number: 091023-310-EPK).

Informed Consent: All patients enrolled in the study provided informed consent to participate in the study.

Authorship Contributions

Concept: L.D.A., O.B., Y.A., M.B.Y., Design: L.D.A., O.B., Y.A., M.B.Y., Data Collection and/or Processing: L.D.A., O.B., B.A., N.B., H.B., G.Z., N.Y., H.K., R.K., Y.A., Analysis and/or Interpretation: L.D.A., O.B., B.A., N.B., H.B., G.Z., N.Y., H.K., R.K., M.B.Y., Literature Search: B.A., N.B., H.B., G.Z., N.Y., H.K., R.K., Y.A., Writing: L.D.A., O.B., B.A., N.B., H.B., G.Z., N.Y., H.K., R.K., M.B.Y.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study had received no financial support.

REFERENCES

1. Disertori M, Brignole M, Menozzi C, Raviele A, Rizzon P, Santini M, et al. Management of patients with syncope referred urgently to general hospitals. Europace. 2003; 5(3): 283-91.
2. Brignole M, Menozzi C, Bartoletti A, Giada F, Lagi A, Ungar A, et al. A new management of syncope: prospective systematic guideline-based evaluation of patients referred urgently to general hospitals. Eur Heart J. 2006; 27(1): 76-82.
3. Kułakowski P. Syncope update 2013: diagnosis and treatment. Kardiol Pol. 2013; 71(3): 215-23.
4. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018; 39(21): 1883-948.
5. Vyas A, Swaminathan PD, Zimmerman MB, Olshansky B. Are treatments for vasovagal syncope effective? A meta-analysis. Int J Cardiol. 2013; 167(5): 1906-11.
6. Coffin ST, Raj SR. Non-invasive management of vasovagal syncope. Auton Neurosci. 2014; 184: 27-32.
7. Kuriachan V, Sheldon RS, Platonov M. Evidence-based treatment for vasovagal syncope. Heart Rhythm. 2008; 5(11): 1609-14.
8. Ector H, Reybrouck T, Heidbüchel H, Gewillig M, Van de Werf F. Tilt training: a new treatment for recurrent neurocardiogenic syncope and severe orthostatic intolerance. Pacing Clin Electrophysiol. 1998; 21(1 Pt 2): 193-6.
9. Reybrouck T, Heidbüchel H, Van de Werf F, Ector H. Tilt training: a treatment for malignant and recurrent neurocardiogenic syncope. Pacing Clin Electrophysiol. 2000; 23(4 Pt 1): 493-8.
10. Raj SR, Coffin ST. Medical therapy and physical maneuvers in the treatment of the vasovagal syncope and orthostatic hypotension. Prog Cardiovasc Dis. 2013; 55(4): 425-33.
11. Duygu H, Zoghi M, Turk U, Akyuz S, Ozerkan F, Akilli A, et al. The role of tilt training in preventing recurrent syncope in patients with vasovagal syncope: a prospective and randomized study. Pacing Clin Electrophysiol. 2008; 31(5): 592-6.
12. Gurevitz O, Barsheshet A, Bar-Lev D, Zimlichman E, Rosenfeld GF, Benderly M, et al. Tilt training: does it have a role in preventing vasovagal syncope? Pacing Clin Electrophysiol. 2007; 30(12): 1499-505.
13. Theodorakis GN, Leftheriotis D, Livanis EG, Flevari P, Karabela G, Aggelopoulou N, et al. Fluoxetine vs. propranolol in the treatment of vasovagal syncope: a prospective, randomized, placebo-controlled study. Europace. 2006; 8(3): 193-8.
14. Grubb BP, Samoil D, Kosinski D, Kip K, Brewster P. Use of sertraline hydrochloride in the treatment of refractory neurocardiogenic syncope in children and adolescents. J Am Coll Cardiol. 1994; 24(2): 490-4.
15. Grubb BP, Wolfe DA, Samoil D, Temesy-Armos P, Hahn H, Elliott L. Usefulness of fluoxetine hydrochloride for prevention of resistant upright tilt induced syncope. Pacing Clin Electrophysiol. 1993; 16(3 Pt 1): 458-64.
16. Di Girolamo E, Di Iorio C, Sabatini P, Leonzio L, Barbone C, Barsotti A. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol. 1999; 33(5): 1227-30.
17. Fitzpatrick AP, Theodorakis G, Vardas P, Sutton R. Methodology of head-up tilt testing in patients with unexplained syncope. J Am Coll Cardiol. 1991; 17(1): 125-30.
18. Béchir M, Binggeli C, Corti R, Chenevard R, Spieker L, Ruschitzka F, et al. Dysfunctional baroreflex regulation of sympathetic nerve activity in patients with vasovagal syncope. Circulation. 2003; 107(12): 1620-5.
19. Aydin MA, Mortensen K, Salukhe TV, Wilke I, Ortak M, Drewitz I, et al. A standardized education protocol significantly reduces traumatic injuries and syncope recurrence: an observational study in 316 patients with vasovagal syncope. Europace. 2012; 14(3): 410-5.
20. Krediet CT, de Bruin IG, Ganzeboom KS, Linzer M, van Lieshout JJ, Wieling W. Leg crossing, muscle tensing, squatting, and the crash position are effective against vasovagal reactions solely through increases in cardiac output. J Appl Physiol (1985). 2005; 99(5): 1697-703.
21. van Dijk N, de Bruin IG, Gisolf J, de Bruin-Bon HA, Linzer M, van Lieshout JJ, et al. Hemodynamic effects of leg crossing and skeletal muscle tensing during free standing in patients with vasovagal syncope. J Appl Physiol (1985). 2005; 98(2): 584-90.
22. Di Girolamo E, Di Iorio C, Leonzio L, Sabatini P, Barsotti A. Usefulness of a tilt training program for the prevention of refractory neurocardiogenic syncope in adolescents: A controlled study. Circulation. 1999; 100(17): 1798-801.
23. On YK, Park J, Huh J, Kim JS. Is home orthostatic self-training effective in preventing neurally mediated syncope? Pacing Clin Electrophysiol. 2007; 30(5): 638-43.
24. Kinay O, Yazici M, Nazli C, Acar G, Gedikli O, Altinbas A, et al. Tilt training for recurrent neurocardiogenic syncope: effectiveness, patient compliance, and scheduling the frequency of training sessions. Jpn Heart J. 2004; 45(5): 833-43.
25. Foglia-Manzillo G, Giada F, Gaggioli G, Bartoletti A, Lolli G, Dinelli M, et al. Efficacy of tilt training in the treatment of neurally mediated syncope. A randomized study. Europace. 2004; 6(3): 199-204.
26. Mtinangi BL, Hainsworth R. Effects of moderate exercise training on plasma volume, baroreceptor sensitivity and orthostatic tolerance in healthy subjects. Exp Physiol. 1999; 84(1): 121-30.
27. Mtinangi BL, Hainsworth R. Increased orthostatic tolerance following moderate exercise training in patients with unexplained syncope. Heart. 1998; 80(6): 596-600.
28. Gracie J, Newton JL, Norton M, Baker C, Freeston M. The role of psychological factors in response to treatment in neurocardiogenic (vasovagal) syncope. Europace. 2006; 8(8): 636-43.
29. Linzer M, Varia I, Pontinen M, Divine GW, Grubb BP, Estes NA 3rd. Medically unexplained syncope: relationship to psychiatric illness. Am J Med. 1992; 92(1A): 18-25.
30. Leftheriotis D, Michopoulos I, Flevari P, Douzenis A, Koborozos C, Kostopoulou A, et al. Minor psychiatric disorders and syncope: the role of psychopathology in the expression of vasovagal reflex. Psychother Psychosom. 2008; 77(6): 372-6.
31. Kosinski D, Grubb BP. Neurally mediated syncope with an update on indications and usefulness of head-upright tilt table testing and pharmacologic therapy. Curr Opin Cardiol. 1994; 9: 53-64.
32. Grubb BP. Neurocardiogenic Syncope: What Role for Serotonin?. In: Raviele A (ed). Cardiac Arrhythmias 1997. Springer, Milano, 1998, pp. 411-21. https://doi.org/10.1007/978-88-470-2288-1_54