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 Main Subject [Cardiology]



Original Article

Effect of Provocation by Sublingual Nitroglycerin on the Result of Tilt Table Test in Patients with Unexplained Syncope

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ABSTRACT

Article information

Received: 21-10-2023

Accepted: 11-12-2023

DOI:
 10.21608/IJMA.2023.243813.1844.

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Citation: Elshafey AEI, Ahmed AMZ, Abdul-Aziz AS, Al-Habbaa A. Effect of Provocation by Sublingual Nitroglycerin on the Result of Tilt Table Test in Patients with Unexplained Syncope. IJMA 2023 November; 5 [11]: 3808-3816. doi: 10.21608/IJMA.2023.243813.1844.

Background: Patients with unexplained syncope should undergo the tilt table test, it is the only clinical laboratory test indicated to identify susceptibility to vasovagal fainting.

The Aim of the work: To evaluate the effect of sublingual nitrates [Nitroglycerine] on the result of tilt table test in patients with unexplained syncope.

Patients and Methods: This was prospective observational study enrolled 60 patients with history of unexplained syncope. patients with cardiac or neurologic syncope were excluded. All patients were subjected to thorough history taking, physical examination [blood pressure, pulse and complete cardiac examination], standard 12 lead electrocardiography, transthoracic echocardiography, passive tilt table test for 45 minutes with negative response and provocation tilt table test by sublingual isosorbide dinitrate for 15 minutes.

Results: After provocation by isosorbide dinitrate 5 mg, 38 patients [63.3 %] turned from negative to a positive response. The most common type was Vasodepressor [35 %]. There was a statistically significant increase in heart rate from passive stage to provocation stage in positive patients [P <0.001] and in negative patients [P <0.001], While there was a statistically significant decrease in blood pressure in positive patients [P <0.001] and in negative patients [P <0.001]. There is no statistically significant difference between males and females regarding test results [P = 0.464] or type of response [P = 0.727]. There was no statistically significant difference between positive and negative patients regarding comorbidities, smoking [P =0.552], diabetes mellitus [P = 0.879], hypertension [P = 0.338], or medications, angiotensin converting enzyme inhibitors [P = 0.419], beta blockers [P = 0.636], calcium channel blockers [P = 0.616].

Conclusion: The sublingual nitroglycerine has positive impact on the result of tilt table test in individuals with unexplained syncope. Gender, comorbidities and medications didn't affect the result of tilt table test.

Keywords: Syncope; Provocation; Sublingual nitroglycerine; Tilt table test.



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INTRODUCTION

The term "syncope" refers to a brief period of unconsciousness brought on by global cerebral hypoperfusion. It has a rapid onset and short duration, and the patient recovers completely and normally on their own [1]. Around a third of people will get syncope at some point in their lives [2]. Syncope is a prevalent condition that causes about 1% of all visits to emergency rooms [3].

Cardiovascular, non-cardiovascular, or unexplained causes have been identified for syncope. Arrhythmias, coronary heart disease, as well as structural heart disease are the subsets of cardiovascular causes. Nervous system, psychiatric, metabolic, in addition to other disorders are non-cardiovascular causes [4]. Many of the patients with "unexplained" syncope experience neurally mediated syncope. In these patients, cardiovascular control may be stable for an extended period of time during orthostatic stress, and then there is a sudden decrease in blood pressure and heart rate which leads to cerebral hypoperfusion and syncope [5].

Tilt table test is the only clinical laboratory test recommended to determine susceptibility to neurally mediated fainting in patients with unexplained syncope. The cornerstone of the test is an orthostatic stress which is done by the upright tilting. A prolonged upright position is a known trigger of neurally mediated syncope, after an initial normal adaptation to standing, inappropriate vasodilatation or bradycardia appears, leading to occurring of symptoms and reproducing syncope. It is often carried out in hospital electrophysiology departments [6,7].

Tilt table test involves placing a patient on a flat table with a foot support, then tilting the table upward for a period of time to observe changes in blood pressure and heart rate. The patient is initially positioned supine and horizontal on the table, then tilted by degrees to upright position. During the study, blood pressure, heart rate, oxygen saturation, and cardiac rhythms are recorded and monitored carefully [8].

Tilt table test was initially described in 1986 by Kenny et al, since its introduction in clinical practice, it has been widely used, but no universally accepted protocol. At first it was only passive test with no provocative agents but with low sensitivity, then other protocols were used to enhance sensitivity [7,9].

The sensitivity of tilt table test is improved when a pharmacological substance is utilized to enhance its effects, as contrasted with tilt table test conducted without any provocation. The first widely used pharmacological stimulant was intravenous isoproterenol; however, due to side effects and delivery route, sublingual nitroglycerine have replaced isoproterenol [10].

Nitroglycerin likely increases susceptibility to vasovagal syncope by venous dilation and reducing venous return to the heart and thereby enhancing cardiac activity and activating the reflex via central cardiac mechanoreceptors [11].

Our study aimed at evaluation of the effect of sublingual Nitroglycerine on the result of tilt table test in patients with unexplained syncope.

PATIENTS AND METHODS

This was a prospective observational study conducted in Cardiology department at Al-Azhar University Hospitals over a period of one year from June 2022 to July 2023.

Our study consists of one group of 60 patients with history of syncope of unknown origin and negative passive tilt table test for 45 minutes. Based on the result of passive tilt table test, patients with positive results were excluded from the study and patients with negative results were included into the study, then a provocation tilt table test for 15 minutes by sublingual isosorbide dinitrate 5 mg was done after 10 minutes of resuscitation and rest. Based on the result of provocation tilt table test for 15 minutes patients were classified into positive patients who had syncope and negative patients who didn't have syncope.

Informed consent: All participants or their immediate family members provided written informed permission after they were provided by information about the study [characters of the study, benefits, possible side effects]

Inclusion criteria: Patients with history of syncope of unknown origin with negative passive tilt table test for 45 minutes.

Exclusion criteria: [1] Patient refusal to be included into the study, [2] Presence of structural heart disease including: [a] Aortic stenosis, [b] Mitral stenosis, [c] Hypertrophic obstructive cardiomyopathy, [d] Cardiac tumors, [e] Pericardial effusion, [f] Pulmonary hypertension, [g] Left ventricular impairment.

[3] ECG abnormality suggestive of arrhythmic syncope, [4] Acute myocardial infarction, [5] Acute pulmonary embolism, [6] Family history of sudden death, [7] Persistent neurological deficit, [8] Features of epilepsy, [9] Lower extremities problems with inability to stand, and [10] Anemia with hemoglobin level < 10 [g/dl].

Sample Size: This study base on study carried out by *Buszko et al* ^[12], The sample size was measured utilizing Epi Info STATCALC, taking into account the following assumptions: The study was done utilizing a 95% two-sided confidence level and a power of 80%, with a margin of error of 5%. The ultimate maximum sample size extracted from the Epi-Info output, based on standard equation ^[13], was 54. Therefore, the sample size was augmented to include 60 cases in order to account for any drop out throughout the follow-up period.

Each patient included into the study was subjected to: [1] Full history taking and detailed analysis of syncopal attacks, [2] Clinical examination focusing on general and local examination of the heart, [3] Complete blood picture: for exclusion of anemia, [4] Standard 12 lead resting electrocardiography: for evidence of abnormalities suggestive of arrhythmic syncope, [5] Transthoracic echocardiography: for assessment of left ventricular systolic function, presence of valvular heart diseases, assessment of left ventricular mass and pericardium.

Tilt table test

Before the test, patients were instructed to fast 4 hours and all non-essential drugs should be withheld for a period exceeding their drug half-lives.

Laboratory environment: the environment in which the test undertaken had a great importance, the room was quiet at a pleasant temperature, and as unthreatening as possible. The illumination was dim, and the patient was given 20 minutes to relax in the supine position before the test started.

Table design: the test required a special tilt table which was a bed which rapidly moves the patient from a supine to an upright position, while the patient is secured to it with a foot board and restraints, the transition from supine to upright position was achieved smoothly and relatively rapidly, the table was able to be reset

quickly to the supine position [10 to 15 s]. The table was or electronically operated.

Recordings: Throughout the duration of the test electrocardiogram, blood pressure and oxygen saturation were continuously monitored by non-invasive measurements to record hypotension or bradycardia. Also, recording any symptoms or signs observed throughout the duration of the test.

Tilt angle: our patients were tilted at 70°, less angels did not seem to provide sufficient orthostatic stress, more angles seem to provide orthostatic stress more than required which may lead to false results.

Tilt table test stages and duration

[1] Pretest stage: 20 minutes at supine position.

[2] The first [passive] stage: 45 minutes with tilting table upright to 70° for without provocation.

[3] Resuscitation and rest stage: 10 minutes at Supine position.

[4] The second [provocation] stage: 15 minutes with tilting table upright to 70° for after administration of sublingual isosorbide dinitrate 5 mg.

[5] Recovery stage: 20 minutes at supine position for follow up, rest resuscitation.

Positivity criteria of tilt table test: The tilt table test was judged positive when syncope [reproduction of patient's original symptoms] accompanied by hypotension, bradycardia or both.

Test termination: Test terminated and patients were brought to supine position after completion of the test with absence of symptoms or occurrence of syncope.

Interpretation of response to tilt table test varies depending upon the clinical setting

[1] When reflex hypotension/bradycardia was induced with reproduction of spontaneous syncope, the test was diagnostic for neurally mediated syncope.

[2] When reflex hypotension/bradycardia was induced without reproduction of syncope,

the test was suggestive of neurally mediated syncope.

[3] When no hypotension/bradycardia was induced but reproduction of syncope, the test was positive for pseudo syncope.

[4] When no hypotension/bradycardia was induced and no reproduction of syncope, the test was negative for neurally mediated syncope.

Classification of positive responses to tilt table test

[1] Type I [mixed]: The heart rate drops at the time of syncope, but not less than 40 beats/minute or drops less than 40 beats/minute for less than 10 seconds with or without asystole of less than 3 seconds. The blood pressure drops before the heart rate drops.

[2] Type IIa [Cardioinhibitory without asystole]: The heart rate drops less than 40 beats/minute more than 10 seconds without asystole of 3 seconds or more. The blood pressure drops before the heart rate drops.

[3] Type IIb [Cardioinhibitory with asystole]: Asystole for more than 3 seconds. The blood pressure drops before or with heart rate drop.

[4] Type III [Vasodepressor]: The heart rate does not drop more than 10 % compared to the peak at time of syncope.

Data management and statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows [SPSS Inc., Chicago, IL, USA]. Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test [χ^2] and Fisher exact were used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean \pm SD [Standard deviation] for parametric and median and range for non-parametric data. Independent T test and Mann Whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables respectively. Paired t-test was used to compare between two dependent groups of normally distributed variables while Wilcoxon signed ranks test was used for non-normally

distributed variables. All statistical comparisons were two tailed with significance Level of P-value, P-value \leq 0.05 indicates significant difference, while, P-value $>$ 0.05 indicates non-significant difference.

RESULTS

Baseline demographic characteristics

Regarding age, the mean age among all studied patients was 37.14 ± 18.07 years. Regarding sex there were 31 females [51.7%] and 29 males [48.3%] among all studied patients. Regarding frequency of syncopal episodes, range was between 1 and 7 in all studied patients with median number 2 episodes, in all studied patients. Regarding comorbidities, 19 of all studied patients [31.7%] were smokers, 14 [21.7%] were diabetics, and 10 [16.7%] were hypertensive. Regarding medications, 5 of all studied individuals [8.3%] were on angiotensin converting enzyme inhibitor [ACE-I], 7 [11.7%] were on beta blockers [BB], and 4 [6.7%] were on calcium-channel blockers [CCB] [table 1].

Result of tilt table test

Regarding tilt table test result ,38 of all studied patients [63.3%] had syncope while 22 [36.7 %] had negative response. Regarding type of positive response, 21 patients [35 %] were type III [vasodepressor], 12 patients [20 %] were type I [Mixed], 3 patients [5 %] were type IIb [cardioinhibitory with asystole] and 2 patients [3.3 %] were type IIa [Cardioinhibitory without asystole]. The most common type was type III [vasodepressor type]. Regarding time to positive response, the mean time to response was 8.71 ± 2.82 minutes from the start of provocation stage with range between 4.5 and 16 minutes [table 2].

Hemodynamics during different stages of tilt table test

Regarding comparison between hemodynamics during passive and provocation stages, there was significant statistical increase in heart rate from passive stage to provocation stage with [p-value $<$ 0.001] and significant statistical decrease in blood pressure from passive stage to provocation stage with [p-value $<$ 0.001] among patients who turned positive after provocation [n=38] and also in negative patients [n=22] [table 3].

Regarding hemodynamics at the time of syncope, mean heart rate was 74.41 ± 30.83 beat/min, mean systolic blood pressure was 65.2 ± 11 mmHg, and mean diastolic blood pressure was 38.56 ± 7.98 mmHg which means that there was more decrease in systolic and diastolic blood pressure and decrease in heart rate in patients with positive response [table 4].

Relation between gender and result of tilt table test

Regarding gender effect on the test results, there was no statistically significant difference between males [n = 29] and females [n = 31] regarding the result [P = 0.464] and type of response [P = 0.727] [table 5].

Relation between comorbidities, medication and result of tilt table test

Regarding comorbidities effect on the result of tilt table test there was no statistically

significant difference between positive and negative patients, smoking [P = 0.552], diabetes mellitus [P = 0.879], hypertension [P = 0.338], Regarding medications effect on the result of tilt table test there was no statistically significant difference between positive and negative patients, angiotensin converting enzyme inhibitors [P = 0.419], beta blockers [P = 0.636], calcium channel blockers [P = 0.616] [table 6].

Regarding comorbidities effect on types of positive response there was no statistically significant difference between different types of response, smoking [P = 0.336], diabetes mellitus [P = 0.689], hypertension [P = 0.651], Regarding medications effect on types of positive response there was no statistically significant difference between different types of response with angiotensin converting enzyme inhibitors [P = 0.810], beta blockers [P = 0.651], calcium channel blockers [P = 0.267] [table 7].

Table [1]: Baseline demographic characteristics of all studied individuals

Demographic characteristics		Patients [n=60]
Age [years]	Mean \pm SD	37.14 ± 18.07
	Range	14 – 78
Sex n [%]	Female	31 [51.7%]
	Male	29 [48.3%]
Body Mass Index [kg/m ²]	Mean \pm SD	24.92 ± 3.65
	Range	18.6 – 30.2
Comorbidities n [%]	Smoking	19 [31.7%]
	Diabetes Mellitus	13 [21.7%]
	Hypertension	10 [16.7%]
Medications n [%]	Angiotensin converting enzyme inhibitors	5 [8.3%]
	Calcium channel blockers	4 [6.7%]
	Beta blockers	7 [11.7%]
Syncope frequency [episodes]	Median	2
	Range	1 – 7

SD, Standard deviation

Table [2]: Tilt table test result and type distributions of all studied patients

Patients [n=60]		
Test result n [%]	Negative	22 [36.7%]
	Positive	38 [63.3%]
Type of positive response n [%]	I [Mixed]	12 [20%]
	IIa [Cardioinhibitory without asystole]	2 [3.3%]
	IIb [Cardioinhibitory with asystole]	3 [5%]
	III [Vasodepressor]	21 [35%]
Time to response[min]	Mean \pm SD	8.71 ± 2.82
	Range	4.5– 16

SD, Standard deviation

Table [3]: Comparison between hemodynamics during Passive and provocation stages among patients with negative and positive response

Hemodynamics	Negative patients [n=22]		P-value
	Passive stage	Provocation stage	
Max HR [beat/min] Mean ± SD	96.48 ± 18.17	116.1 ± 19.73	<0.001
Min HR [beat/min] Mean ± SD	76.62 ± 14.93	82.14 ± 21.26	.307
Max SBP [mmHg] Mean ± SD	122.62 ± 13.83	114.29 ± 15.14	.002
Min SBP [mmHg] Mean ± SD	107.33 ± 13.52	92.38 ± 19.18	<0.001
Max DBP [mmHg] Mean ± SD	84.57 ± 11.65	74.43 ± 10.13	.001
Min DBP [mmHg] Mean ± SD	71.52 ± 9.99	59.14 ± 13.17	<0.001
Hemodynamics	Positive patients [n=38]		P-value
	Passive stage	Provocation stage	
Max HR [beat/min] Mean ± SD	94.83 ± 13.48	113.3 ± 18.84	<0.001
Min HR [beat/min] Mean ± SD	76.12 ± 11.68	77.69 ± 25.02	.748
Max SBP [mmHg] Mean ± SD	129.77 ± 20.57	114.57 ± 16.92	<0.001
Min SBP [mmHg] Mean ± SD	110.5 ± 19.18	65.91 ± 11.78	<0.001
Max DBP [mmHg] Mean ± SD	82.53 ± 12.8	76.63 ± 12.86	.016
Min DBP [mmHg] Mean ± SD	70.64 ± 13.39	38.82 ± 8.86	<0.001

DBP, diastolic blood pressure; HR, heart rate; Max, maximal; Min, minimal; Min; minute; SBP, systolic blood pressure; SD, Standard deviation.

Table [4]: Hemodynamics at the time of syncope among patients with positive response.

Hemodynamics		Patients [n=38]
Heart rate [beat/min]	Mean ± SD	74.41 ± 30.83
	Range	28 – 139
Systolic blood pressure [mmHg]	Mean ± SD	65.2 ± 11
	Range	43 – 90
Diastolic blood pressure [mmHg]	Mean ± SD	38.56 ± 7.98
	Range	23 – 60

SD, Standard deviation

Table [5]: Comparison between male and female regarding result of tilt table test and type distribution

		Males [n = 29]	Females [n = 31]	P-value
TTT result n [%]	Negative	12 [41.3 %]	10 [32.2 %]	0.464
	Positive	17 [58.7 %]	21 [67.8 %]	
Type of positive response n [%]	I [Mixed]	4 [13.7 %]	8 [25.8 %]	0.727
	IIa [Cardioinhibitory without asystole]	1 [3.4 %]	1 [3.2 %]	
	IIb [Cardioinhibitory with asystole]	2 [6.4 %]	1 [3.2 %]	
	III [Vasodepressor]	10 [34.3 %]	11 [35.4 %]	

Table [6]: Comparison between patients with positive and negative response comorbidities and medications

		Negative [n = 22]	Positive [n = 38]	P-value
Comorbidities n [%]	Smoking	8 [36.4 %]	11 [28.9 %]	0.552
	Diabetes mellitus	5 [22.7 %]	8 [21.1 %]	0.879
	Hypertension	5 [22.7 %]	5 [22.7 %]	0.338
Medications n [%]	ACE-I	1 [4.5 %]	4 [10.5 %]	0.419
	BB	2 [9.1 %]	5 [13.2 %]	0.636
	CCB	1 [4.5 %]	3 [7.9 %]	0.616

ACE-I, angiotensin converting enzyme inhibitors; BB, beta blockers; CCB, calcium channel blockers

Table [7]: Comparison between different types of positive response as regard comorbidities and medications

		Type I ^a [n=12]	Type IIa ^b [n=2]	Type IIb ^c [n=3]	Type III ^d [n=21]	P-value
Comorbidities n [%]	Smoking	2 [16.7%]	1 [50%]	2 [66.7%]	6 [28.6%]	0.336
	DM	2 [16.7 %]	1 [50%]	1 [33.3%]	4 [19.1%]	0.689
	HTN	1 [8.3%]	0	1 [33.3%]	3 [14.3%]	0.651
Medications n [%]	ACE-I	1 [8.3%]	0	0	3 [14.3%]	0.810
	BB	1 [8.3%]	0	1 [33.3%]	3 [14.3%]	0.651
	CCB	0	0	1 [33.3%]	2 [9.5%]	0.267

ACE-I, angiotensin converting enzyme inhibitors; BB, beta blockers; CCB, calcium channel blockers; DM, diabetes mellitus; HTN, hypertension; ^a Mixed type. ^b Cardioinhibitory without asystole type. ^c Cardioinhibitory with asystole type.

^d Vasodepressor type.

DISCUSSION

Tilt table test is a tool used to evaluate the syncope; this study was designed to evaluate the effect of provocation by sublingual nitroglycerine on the result of tilt test after negative long passive duration. We found high TTT reproducibility with provocation by sublingual isosorbide dinitrate in our carefully selected suspected syncope patients. Our study revealed that 38 patients [63.3%] turned from negative response during passive test to positive response after provocation by sublingual nitroglycerine. Also, there was significant increase in heart rate with significant decrease in blood pressure. In patients with positive response, syncope is preceded by initial significant increase in heart rate and decrease blood pressure, then at time of syncope blood pressure decreased to the lowest blood pressure with a decrease in heart rate in most of them.

It may be explained as followed, initially in all patients, nitroglycerine causes venous dilation and mild arterial dilation which leads to decreased systolic and diastolic blood pressure, decreased blood pressure and decreased venous return effect of nitroglycerine with orthostatic stress increase sympathetic tone which causes an increase in heart rate and ventricular contraction. Then in individuals with positive response this action sets off the Bezold-Jarish reflex via mechanoreceptors, which decreases the excitability of the sympathetic nerves and increases the excitability of the parasympathetic nerves, resulting in a decrease in heart rate, more decrease in blood pressure and occurrence of neurally mediated syncope.

In a study done by **Xu et al.** [14] 4873 patients with reflex syncope underwent tilt table test after provocation by sublingual nitroglycerine, this study results concluded that patients who had syncope showed increased heart rate during tilting then decreased at the time of syncope associated with decreased blood pressure which agreed with our results.

Goabas et al. [15] agreed with our results in an Egyptian study on 60 patients of syncope of unknown origin who underwent tilt table test after negative long passive test [45 minutes], then provocation stage by sublingual dinitrate 78% of patients had a positive response.

In a study by **Glockler et al.** [16] on 261 patients with syncope of unknown origin, and

negative short passive test [20 minutes] then after provocation by sublingual nitroglycerine spray 0.4 mg, 76.6% of patients had positive response. Also, **Russo et al.** [17] 1135 patients with clinical suspicion of vasovagal syncope investigated by tilt table test with negative short passive test [20 minutes] then after provocation by sublingual nitroglycerine spray 0.3 mg, 63.1 % of patients had positive response. Additionally, **Bilagi et al.** [18] revealed that after short negative passive test [20 minutes] and provocation by sublingual isosorbide dinitrate, 65.3% of patients had syncope.

These studies were consistent with our study that sublingual nitroglycerine has positive impact on the result of tilt table test in patients with unexplained syncope. Also, studies with short passive phase revealed that percentage of patients with positive response after provocation close to our results, which means that long duration of passive tilt table test does not affect the results of provocation test with providing reliable clinical information, so we recommend using the short passive test to save time of the test for the patient and operator and for better tolerability.

Our study showed that the most common type of response was vasodepressor type in 35 % of patients. In agreement with our results, **Goabas et al.** [15] reported that the most common type of response was vasodepressor response [type III] in 39.1 % of patients. On the other hand, **Glockler et al.** [16] and **Bilagi et al.** [18] reported that the most common type of response was mixed response [type I].

As mentioned above, Egyptian study by **Goabas et al.** [15] agreed with our result regarding the type of positive response in contrast to other international studies results, this can be explained by the bad rehydration habits among Egyptians, long standing, crowding, long duration of work, hot weather or by small number of patients.

Our study revealed range between 4.5 and 16 minutes with most of positive response between 6 to 10 minutes which means that 15 minutes as a duration of provocation stage with sublingual dinitrate is enough to reproduce syncope in patients with neurally mediated syncope with accepted sensitivity and specificity, **Bilagi et al.** [18] reported Most positive responses were concentrated in the 5 to 9 min during pharmacological phase by ISDN.

On the other hand, **Glockler *et al.*** [16] disagreed with our results; they had a shorter median time to response which was 3 minutes after provocation by Nitroglycerine sublingual spray. with most of positive responses between 3 and 5 minutes. This can be explained by the fact that aerosol formulations of nitroglycerin have a better bioavailability and more homogenous absorption since they do not depend on the patient's capability for salivation and mastication, which can be compromised, especially in elderly persons. It is possible that these characteristics, in conjunction with the higher dose that was produced by the aerosol, shortened the amount of time required for the test to become positive.

Our study showed there is no significant link between tilt table test results and comorbidities nor medication use, so TTT can be performed regardless of individual comorbidities and medication use, providing valid clinical information, and neither syncope nor TTT response were related to either comorbidity nor medication. In agreement with our results a study by **Mishra *et al.*** [19] on 44 patients with neuro mediated syncope with sublingual nitroglycerine provocation revealed that no statically significant difference between positive and negative patients regarding comorbidities and medication use with p-values for hypertension = 0.058, diabetes = 0.088, angiotensin converting enzyme inhibitors use = 0.375, beta blocker = 0.932 and calcium channel blocker = 0.086. Therefore, the TTT can be performed irrespective of the patient comorbidities and medication use, providing reliable clinical information.

Our study revealed that there was no significant link between gender and TTT results nor type of positive response, so TTT can be performed regardless patient gender. In accordance with the current study, **Pietrucha *et al.*** [20] analyzed the results of TTT in patients with syncope in relation to their gender and used protocol of TTT, they concluded that there was no significant relationship between gender and the result of TTT with [P = 0.17] in nitroglycerine protocol [the same as our protocol] and [P = 0.58] in Italian protocol [short passive protocol]. Also, there were no significant relationship between gender and type of response during tilt test with [P = 0.072] in nitroglycerine protocol and [P = 0.079] in Italian protocol.

Limitation: The current study was limited by small sample size, the lack for control group, being a single center study. Further studies with larger sample size and longer follow-up are needed to confirm our results.

Conclusion: The current study revealed that the sublingual nitroglycerine has positive impact on the result of tilt table test in patients with unexplained syncope. Sublingual nitroglycerine provocation resulted in significant initial increase in heart rate and significant reduction in blood pressure in both patients with positive and negative test results with decreased heart rate and more reduction in blood pressure in patients with positive response. The long duration of passive tilt table test does not affect the result of provocation test, so we recommend using the short passive test to reduce time of the test and for better tolerability. Gender didn't affect the result of tilt table test nor type of positive response. comorbidities and medications use didn't affect the result of tilt table test nor type of positive response.

Financial and non-financial relations and activities of interest: None

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