Reproducibility of Tilt-Table Test Potentiated with Double Dose Sublingual Nitroglycerin in Patients with Suspected Recurrent Syncopal Episodes

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ABSTRACT

Introduction: Tilt-table test (TT) is a noninvasive and safe test used for the diagnosis of patients with syncope. Currently, there are controversies about the diagnostic utility and reproducibility of TT. The reproducibility of TT has been reported within a wide range from 36% to 90% for a positive test and from 85% to 100% for a negative test. The aim of the present study was to investigate the current reproducibility of TT.

Patients and Methods: All consecutive patients who underwent TT with double dose spray nitroglycerin due to suspected reflex syncope between May 2017 and January 2019 at our hospital were evaluated. Patients underwent a second TT within 1-7 days following the initial test.

Results: A total of 135 (76 female, 56.3% and 59 male, 43.7%) patients aged 18-61 (mean (± SD) 32 ± 10.85) years were included in the study. In the first test, 81 (60.0%) patients had a positive response, 51 (37.8%) patients had a negative response, and 3 (2.2%) patients had an exaggerated response. In the repeated test, 75 (55.6%) patients had a positive response, and 60 (44.4%) patients had a negative response. The reproducibility of a positive tilt test was 85.2%, whereas the reproducibility of a negative tilt test was 88.2%. Overall reproducibility was 86.4%.

Conclusion: In selected patients, TT with double dose sublingual spray nitroglycerin has a high reproducibility. Double dose sublingual spray nitroglycerin might be used for potentiating TT with acceptable safety.

Key Words: Syncope; tilt-table test; reproducibility

Tekrarlayan Şüpheli Senkoplu Hastalarda Çift Doz Dilaltı Nitrogliserin ile Yapılan Eğik Masa Testinin Reprodusibilitesi

ÖZET

Giriş: Eğik masa testi senkop şüpheli hastalarda sıkça kullanılan bir testtir. Testin tanısal değeri ve reprodusibilitesi hakkında karşıt görüşler mevcuttur. Çeşitli serilerde pozitif bir testin reprodusibilitesi %36-90, negatif bir testin reprodusibilitesi ise %85-100 arasında bildirilmiştir. Biz bu çalışmada eğik masa testinin güncel reprodusibilitesini araştırmayı hedefledik.

Hastalar ve Yöntem: Hastanemizde Mayıs 2017-Ocak 2019 tarihleri arasında çift doz sublingual sprey nitrogliserin ile test uygulanan tüm ardışık hastalar çalışmaya dahil edilmek üzere değerlendirildi. Çalışmaya katılmayı kabul eden hastalar ilk testten 1-7 gün sonra ikinci bir teste alındılar.

Bulgular: Toplam 135 hasta [76 erkek (%56.3), 59 kadın (%43.7)] çalışmaya dahil edildi. Yaş aralığı 18-61 ve ortalama yaş (± SD) 32 ± 10.85 idi. İlk testte 81 (%60.0) hastada pozitif sonuç, 51 (%37.8) hastada negatif sonuç ve 3 (%2.2) hastada nitrata abartılı yanıt saptandı. İkinci testte ise 75 (%55.6) hastada pozitif, 60 (%44.4) hastada negatif sonuç saptandı. Pozitif reprodusibilite %85.2, negatif reprodusibilite %88.2 ve toplam reprodusibilite %86.4 idi. Dilaltı nitratın yan etkilerine bağlı olarak test hiçbir hastada sonlandırılmadı.

Sonuç: Seçilmiş hastalarda çift doz dilaltı sprey nitrogliserin ile yapılan eğik masa testinin güncel reprodusibilitesi yüksektir ve çift doz nitrogliserin kullanımı güvenilir olabilir.

Anahtar Kelimeler: Senkop; eğik masa testi; reprodusibilite

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INTRODUCTION

Tilt-table test (TT) is a noninvasive and safe test used for the diagnosis of patients with syncope. Although there have been controversies about the diagnostic utility and reproducibility of TT, the European Society of Cardiology Guidelines for the Diagnosis and Management of Syncope recommends performing TT in patients with suspected reflex syncope[1]. A detailed history, careful physical examination including supine and standing blood pressure (BP) measurements, and 12-lead electrocardiography (ECG) as an initial evaluation may provide significant information about a patient with syncope or presyncope.

Reproducibility may be defined as a variation in measurements made under different conditions. Different conditions may be due to different measurement methods or instruments being used, measurements performed by different observers, or measurements conducted over time[2]. The reproducibility of TT has been reported within a wide range from 36% to 90% for a positive test and from 85% to 100% for a negative test[3-7]. The wide range for the positive test result may be due to patients included, protocol of the test, or time interval between repeated tests. The reproducibility of TT is significant with respect to diagnostic accuracy concerns. Both physicians and patients seek a reliable test that can provide information about the reason of the syncope. Although the reproducibility of TT is questionable, we believe that the accumulating knowledge about transient loss of consciousness may enable physicians to select proper patients before ordering a TT, and this may result in a high reproducibility of the test. In the present study, we aimed to investigate the contemporary reproducibility of TT in a patient group with suspected recent reflex syncope who underwent TT potentiated with double dose (800 μg) sublingual nitroglycerin after a comprehensive initial diagnostic evaluation and within a short time interval between repeated tests.

PATIENTS and METHODS

All patients presenting to our cardiology department with transient loss of consciousness are evaluated as follows. The initial assessment includes a detailed history, a careful physical examination including supine and standing BP measurements, and 12-lead ECG and transthoracic echocardiography (TTE). If the diagnosis is not clear with the initial assessment, further tests are performed. These include 24-hour rhythm Holter, carotid ultrasound, carotid sinus massage in patients aged > 40 years, neurology consultation, and TT. A 24-hour rhythm Holter before TT was routinely performed for all patients.

All consecutive patients who underwent TT due to suspected reflex syncope between May 2017 and January 2019 at our hospital were evaluated. Patients aged ≥ 18 years and those who provided written informed consent were included in the study. All patients had normal ECG and normal TTE. Patients who were referred to TT due to only one syncope or presyncope episode were excluded from the study. Patients who underwent the first TT after 30 days of the last syncope episode and those receiving vasoactive medication were also excluded.

All tests were performed between 10:00 am and 12:00 am at our laboratory. The laboratory room is quiet, dim, and at a comfortable temperature. Patients underwent the test after at least 4 h of fasting. Nicotine, caffeine, and alcohol were omitted for 24 h prior to testing. At the beginning of each procedure, the demographic and clinical data of the patient were recorded, as well as the test indication. TT protocol was as follows: first, the patient is placed supine on a tilt-table and secured with protective straps to avoid falls. The patient rests supine for 10 min. Thereafter, the table is elevated up to 70°. If there is no syncope within 20 min, it was followed by a pharmacological phase lasting 15 min after the administration of sublingual nitroglycerin 800 μg in aerosol[8]. Tilting was maintained until a positive result was obtained, intolerance due to other causes was detected, or the protocol was concluded (a total of 45 min). The ECG was monitored continuously during the procedure. BP was measured noninvasively with an automatic sphygmomanometer every 3 min or more frequently if symptoms or bradycardia appeared. To exclude carotid sinus hypersensitivity, carotid sinus massage is performed both in the supine position and in the early phase of the supine position. The test was performed by an experienced nurse with a cardiologist on call.

A positive response TT for vasovagal response was defined as Type 1, mixed; Type 2, cardioinhibitory; and Type 3, vasodepressor (Table 1)[9]. An exaggerated response to nitrates was defined as a gradual development of symptoms, consequence of progressive (occurring > 5 min) decrease in BP along with only a slight reduction (< 30%), or no change in heart rate[10].

The study was approved by the local ethics committee in accordance with the Declaration of Helsinki. Informed consent was obtained from all the patients.

Statistical Analysis

Data of the study were analyzed by using statistical package for the social sciences (SPSS) statistics for windows, version 22.0 (IBM Corp., Armonk, NY). Descriptive statistics are expressed as frequency, average with standard deviation, and median with minimum and maximum values. Chi-square test was used to compare categorical variables. Student's t-test in binary groups is used if the parametric test condition is provided in the measurement values, and Mann-Whitney U test is used if it is not provided. In more than two measurement

Table 1. Classification of positive responses to tilt-table test

Type 1-mixed

Heart rate decreases at the time of syncope, but the ventricular rate does not decrease to < 40 beats/min^{-1} for > 10 s with or without asystole of < 3 s. Blood pressure decreases before heart rate decreases.

Type 2-cardioinhibitory

A. Cardioinhibition without asystole: heart rate decreases to a ventricular rate < 40 beats/min^{-1} for > 10 s, but asystole of > 3 s does not occur before heart rate decreases.

B. Cardioinhibition with asystole: asystole occurs for > 3 s. Blood pressure decreases with or occurs before heart rate decreases.

Type 3-vasodepressor

Heart rate does not decrease > 10% from its peak at the time of syncope.

Exception 1. Chronotropic incompetence: no heart rate increase during the tilt testing (i.e., < 10% from the pre-tilt rate).

Exception 2. Excessive heart rate increase: an excessive heart rate both at the onset of the position and throughout its duration before syncope (i.e., > 130 beats/min^{-1}).

groups, Kruskal-Wallis variance analysis was used because the groups have non-normal distribution. Shapiro-Wilk test was used to analyze the distribution of normality. A p value < 0.05 was considered statistically significant.

RESULTS

Basal Characteristics and Initial Test Results

A total of 135 (76 female, 56.3% and 59 male, 43.7%) patients were included in the present study. The age of the patients was 18-61 [mean (± SD) 32 ± 10.85] years. The mean number of syncopal episodes per patient (± SD) was 7.76 ± 6.08 (minimum 2 and maximum 40). The reported mean duration of symptoms (± SD) was 14.56 ± 1.24 (median 10, minimum 1, and maximum 70) months. In the first test, 81 (60.0%) patients had a positive response, 51 (37.8%) patients had a negative response, and 3 (2.2%) patients had an exaggerated response. No significant difference in the outcome of the initial test was observed with respect to gender (p= 0.55) and age (p= 0.72). The number of reported syncopal episodes was higher in patients with a positive initial test than in those with a negative initial test (9.79 ± 6.99 and 4.76 ± 2.05, respectively, p< 0.001). The reported duration of symptoms was higher in patients with a positive initial test than in those with a negative initial test (17.88 ± 6.07 and 9.75 ± 3.16, respectively, p= 0.002).

Second Test Results

The mean (± SD) time interval between the initial test and the repeated test was 3 ± 1.6 (minimum 1 and maximum 7) days, and time interval did not differ between patients with a positive initial test and those with a negative initial test (p> 0.05). Of the 135 patients, 75 (55.6%) had a positive response, and 60 (44.4%) had a negative response at the repeated test. The number of reported syncopal episodes and duration of symptoms were higher in patients with a positive second test than in those with a negative second test (9.61 ± 7.20 and 5.25 ± 3.03, p< 0.001 and 17.19 ± 1.79 and 11.27 ± 1.58, p= 0.03, respectively). The number of patients with recurrent positive response was 69, with recurrent negative response 45, initially positive and negative at the repeated test was 12, and initially negative and positive at the repeated test 6. The relationship between demographic and clinical characteristics and results of tests is shown in Table 2. Of the three patients with an exaggerated response initially, all had a negative response at the repeated test. The reproducibility of a positive tilt test was 85.2%, whereas the reproducibility of a negative tilt test was 88.2%. Overall reproducibility was 86.4% (Table 3).

Sublingual nitroglycerin was administered to 68 patients in the first test and 90 patients in the repeated test. No test was terminated due to nitroglycerin side effects. In the first test, 20 (29.4%) patients reported headache, and 5 (7.4%) patients reported nausea. In the second test, 26 (28.9%) patients reported headache, and 8 (8.9%) patients reported nausea.

DISCUSSION

The present study presents a high reproducibility for TT potentiated with double dose sublingual nitroglycerin that repeated within a short period following the initial test in patients with suspected recent recurrent vasovagal syncope. The reproducibility was high for positive result, as well negative result. Our study differs from other studies due to potentiation with higher dose nitroglycerin, higher number of patients, and recent last syncope episode. Moreover, our patients were carefully assessed with respect to other reasons for loss of consciousness before ordering TT.

The main finding of our study is that the overall reproducibility of TT is high with double dose sublingual spray nitroglycerin in patients with recent recurrent syncopal episodes. The reproducibility of a test is significant because it represents the usefulness of the test. The nature of vasovagal syncope is

Table 2. Relationship between demographic and clinical characteristics and results of tests

	Positive/Positive (n= 69)	Negative/Negative (n= 45)	Positive/Negative (n= 12)	Negative/Positive (n= 6)	p
Age, year	32.96 ± 11.51	32.89 ± 10.20	32.42 ± 11.57	24.33 ± 7.28	0.30
Male/female	29/40	23/22	4/8	1/5	0.40
Syncope episodes					
Mean	9.91 ± 7.42	4.58 ± 2.02	9.08 ± 3.82	6.17 ± 1.83	< 0.001
Median	8	4	9.5	6.5	
Duration of symptoms, month					
Mean	17.52 ± 15.97	9.27 ± 1.49	19.92 ± 17.21	13.33 ± 9.02	0.009
Median	12	8	12.5	10.5	
Time interval between tests, day					
Mean	3.25 ± 1.71	3.11 ± 1.35	2.67 ± 1.61	4.50 ± 1.64	0.14
Median	3	3 2	5		

Table 3. Reproducibility of tilt-table test

	Repeated test Positive, n	Repeated test Negative, n	Reproducibility %
Initial test positive, n	69	12	85.2
Initial test negative, n	6	45	88.2

complex, and the timing of syncopal episodes is not predictable. Patients with vasovagal syncope may have significant fluctuations in parasympathetic activity resulting in unpredictable syncopal episodes[11]. Therefore, it is difficult to obtain 100% reproducibility for TT. Sagrista-Sauleda et al. conducted a study in which they performed three consecutive tests in 127 patients with a normal ECG and no structural heart disease[12]. The reproducibility of the positive result in the second test was 65% and decreased to 51% in the third test. They reported that the reproducibility of the negative result is 80%, and that there is no significant difference according to the time interval between the tests. On the other hand, they found that the time interval between the tests has an impact on positive results.

In previous a study, the overall reproducibility of TT with sublingual nitrate was reported to be 77%[13]. However, the time interval between repeated tests was 1-28 days in that study, and the dose of sublingual spray nitroglycerin was 400 μg. In our study, the time interval between repeated tests was short (mean ± SD 3 ± 1.6 days), and 800 µg sublingual nitroglycerin was administered to increase the sensitivity and reproducibility of TT. However, we did not aim to investigate the effects of different sublingual nitroglycerin dosages on the reproducibility of TT. In a study conducted in elderly patients with sublingual nitroglycerin dosages of 250 μg, 375 μg, and 500 μg, there was no significant positive test result according to nitroglycerin dosages[14]. However, no studies investigated the effect of ≥ 800 μg sublingual nitrate dosages on the results of TT.

Nitrates are often used to enhance the sensitivity of the test and shorten its duration with an acceptable specificity. Moreover, nitrates are safe, well tolerated, and easy to use[15-17]. Several protocols are being used, with different nitrate formulations, preparations, and dosages. Although none of the protocols have been shown to be superior to others, sublingual spray nitroglycerin has the advantage of not to be affected from dryness of the mouth. Graham et al.[18] reported that a protocol with 800 µg sublingual nitroglycerin is safe. In their study, no patients had adverse events resulting in the termination of glyceryl trinitrate head-up tilt. One control had nausea resulting in the termination of glyceryl trinitrate tilt. Headache was reported by 17 (30%) patients and two controls, but was not severe enough to preclude completion of the test protocol. In our study, double dose sublingual spray was safe, and no patients were terminated from the test due to side effects. The frequency of side effects, such as headache and nausea, was similar to the previous study.

We consider that our study has two important limitations. First, we did not test different dosages of sublingual nitroglycerin. Further studies are needed to investigate the effects of different dosages on reproducibility. Second, despite the time interval between tests was short, it was not constant. Since the time interval between tests may influence the reproducibility of positive results, a study with constant time interval may reveal more accurate results.

CONCLUSION

In selected patients, TT with double dose sublingual spray nitroglycerin has a high reproducibility. Double dose sublingual spray nitroglycerin might be used for potentiating TT with acceptable safety.

CONFLICT of INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: ÇÇ
Analysis/Interpretation: ÇÇ
Data Acquisition: ÇÇ
Writting: ÇÇ
Critical Revision: ÇÇ
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