

Sub-Lingual Spray Versus Pearl of TNG as A Provocative Agent for Tilt Table Test

REZA KARBASI-AFSHAR¹, AMIN SABURI², AYAT SHAHMARI³, AREZOO KHOSRAVI⁴

ABSTRACT

Objective: The aim of this study was to determine the false positive ratio of Tilt Table Test (TTT) result by using TNG spray (Sub-lingual; SL) as compared to TNG pearl in patients referred to military service.

Material and Methods: This was a prospective study. It was conducted on 110 cases referred for military service, expressed vasovagal symptoms. We divided the subjects into three groups; first Group (60 cases) used TNG pearl for provoking syncope in TTT, Group 2 (50 cases) and Group 3 (control cases) used TNG spray in the same dose (0.4 mg).

Results: In the first step of tilt study, 10%, and 8% of subjects

had fainted on not using provoking drug in cases and controls, respectively. After using the drugs, 36.6%, 96% and 18% showed positive results in pearl, spray and the control groups, respectively ($p < 0.05$).

Conclusion: Rather than pearl group, a 40 minute tilt using TNG spray showed significant higher positive results, which may be incorrectly positive. Using this form of TNG seems not useful for distinguishing and diagnosing vasovagal shocks, especially in subjects referred for military service capacity. For constant evidence, a cross-over clinical trial study is required, involving suspected cases divided into two groups, who both will be examined with spray and pearl.

Key words: Syncope, Tilt table test, Military service, TNG spray

INTRODUCTION

Neuro cardiogenic syncope (fainting) is defined by a sudden transient loss of consciousness and postural tone caused by changes in arterial blood pressure and cerebral hypo-perfusion [1-4]. Symptoms and signs of impending fainting are the signs and symptoms of per-syncope state: pallor, nausea or stomach discomfort, headache, cold or warm feeling, and dizziness, which are often initially interpreted as more ill-defined head lightness or cognitive loss [5-6]. Typical findings of reflex syncope on tilt table test include a rapid decrease in blood pressure and often, a drop in heart rate resulting from inhibition of sympathetic nervous system and activation of the parasympathetic nervous system, which be profound [7-8]. Many studies have been evaluating tilt-table testing. A large literature search addressed the concurrent use of provocative agents such isoproterenol or nitrates [9-12]. In addition, others have examined the optimal duration of tilt table testing in the context of the syncopal population [13, 14].

However, no study has examined the effect of forms of nitrates in result of the tilt study. Nowadays, rate of malingering is high among people who are referred to military services for formal assessment. The aim of this study was to determine the false positive ratio of tilt testing in subjects by using spray form of TNG as compared to pearl form and a control group.

MATERIAL AND METHODS

Study population and inclusion criteria

This prospective cohort study included only patients with pure reflex syncope, without other co-morbidities. Cases were selected among the young male candidates for military services, who were referred to a military medical care unit in Tehran, Iran. We used the census method for sampling. The aim of the TTT was differentiating the reflex syncope from delayed orthostatic hypotension [15]. However, a relatively rapid normal tilt study or a concomitant drop in heart rate can be quite suggestive of "pure" syncope. Since, neither the magnitude of bradycardia nor the definition of "rapid" drop in blood

pressure have been established, we used the time frame of less than 3 minutes, thus, reducing the possibility of misdiagnosing delayed orthostatic hypotension.

Therefore, inclusion criteria included a history of abrupt syncope (loss of consciousness and postural tone). We excluded patients with associated Orthostatic Hypotension (OH), Postural Tachycardia (POTS), and diabetes, known small fibre neuropathy, Parkinson's disease or any disorder known to be associated with a dysautonomia. We divided fainters into Group 1 (TTT with spray) and Group 2 (TTT with pearl), with simple randomization. In addition, we selected a control group from among cases with the similar complaint, but TTT was performed in these cases who were not on any provocation medications. This means that we had 3 groups ; 1- 50 cases who received TNG spray, 2- 60 cases who received TNG pearl, 3- 50 controls who did not receive any medications.

Autonomic test

Subjects were initially asked to lie supine for a period of at least 5 minutes. Thereafter, they were tilted to an angle of 70 degrees by using a tilt table. This was then sustained for a period of 40 minutes or until a syncopal or pre-syncope symptom occurred. Blood pressure and heart rate were recorded by a non-invasive monitor and external electrocardiograph tracing. In negative subjects, test continued with pharmacological provocation (spray or pearl TNG) according to group 1 or 2. (0.4 mg) The patients were questioned for symptoms such as feeling hot, nausea or dizziness. These symptoms were clinically correlated with a diagnosis of reflex syncope and recorded time of onset in each subject [13-17].

Subjects provided informed consents prior to all testing. Blood pressure was also monitored (in the contra lateral arm) using a standard blood pressure monitor over the arm.

Data analysis

SPSS for Windows 15.0 was used for statistical analysis. The descriptive statistics were presented as frequencies and percentages. Kolmogoroff-Smirnov was used for checking normal

distribution in quantitative variables. The differences between two groups for dichotomous variables were examined by Chi-square test and ANOVA test was used for comparing the quantitative variables in a qualitative variable with 3 or more groups. A p-value of <0.5 was accepted as statistically significant.

RESULTS

All cases and controls were males. This was because, our clinic, Baqiyatallah University Hospital, Tehran, IR Iran, is a referral centre for military service personnel who are referred to be screened for cardiovascular diseases. Demographic data have been arranged in [Table/Fig-1] in terms of groups. The mean age between three groups was not statistically significant ($p>0.05$) and it was declared that these groups were matched for this important confounding factor. In the pearl and spray groups, only 10% of subjects had fainted on not using provoking drug, while 8% of subjects had fainted on not using provoking drug among controls. After using drugs, 36.6%, 96% and 18% showed positive results in pearl, spray and control groups, respectively ($p<0.05$) [Table/Fig-2].

	Pearl (First group)	Spray (Second group)	Control
Male ratio	100%	100%	100%
Age (years)	19.1±2.3	18.9±2.2	19.3±1.1
Disease history	0	0	0
Syncopal symptoms	100%	100%	100%

[Table/Fig-1]: Demographic Characteristics

	Pearl (First group ;60 cases)	Spray (Second group; 50 cases)	Control (50 cases)	p-value
Positive Test without drug (passive phase) (%)	6 (10%)	5(10%)	4(8%)	NS
Positive Test with drugs (%)	22 (36.6%)	48 (96%)	9 (18%)*	$p<0.05$

[Table/Fig-2]: Tilt table Tests Findings

* Without any provocative medications

DISCUSSION

This study showed that

- 1) Provocative agents for tilt table test should be revised for percentages of false positive and negative results.
- 2) Kind of administration of provocation agent is important for results of test and this should be considered in treatment strategies.
- 3) Further studies are needed for tilt table test accuracy and kind and dose of these drugs in results of test, especially in legal problems.
- 4) A combination of several reflex and physical factors may induce the event [16-19].

Syncopal prevalence is higher in the younger age group and reflex syncope is the most common cause [7]. The term, 'reflex syncope' refers to a heterogeneous group of functional disturbances characterized by episodic vasodilatation and or bradycardia, leading to loss of blood pressure and cerebral hypo-perfusion [10,15].

A change in posture versus common setting, such as straining, dehydration, emotional or physical distress, etc. may be the most inciting factor [15-19]. In contrast, orthostatic hypotension (defined as reduction of systolic or diastolic blood pressure within 3 minutes of assuming the erect posture) occurs with greater frequency in the population aged 65 years and older [20,21].

It seems that a 40 minute tilt table test using sub-lingual spray form of nitrate (0.4 mg) may be associated with false positive results. This means that, if the patients of other groups are exposed to TNG spray, they may show a positive test results, although for approving this hypothesis, a cross over clinical trial study involving suspected cases divided into two groups, who both will be examined with spray and pearl, is required. This high positive result in spray group can be due to rapid absorption of TNG spray via sublingual mucosa. Thus, this form of nitroglycerin should not be used for diagnosis of neuro-cardiogenic syncope. Pearl form of this agent showed better results and it can be used for this property. Using this form of TNG seems to be not useful for distinguishing and diagnosing vasovagal shocks, especially in subjects referred for military service capacity.

"The sensitivity of passive tilt table testing had been variously reported to be 19% to 69% [22-24]." Some medications such as TNG and Isoprenaline were suggested for provocation of vasovagal symptoms in TTT [24]. TNG is recommended for TTT due to its safety and availability [25].

A TTT is routinely started with a passive phase to declare the possibility of symptoms without pharmacological interventions. Then, drugs are prescribed to accelerate the appearing symptoms. In our study, the result of this phase was similar in three groups and this can be due to similarity in properties of cases.

A higher rate of positivity of TTT has been reported with more aggressive protocols, shorter interval between the last episode and the test, younger age, increasing severity of syncopal attacks, and female sex. Most of these factors were controlled in our study and the differences in our results may have occurred because of the differences between drugs [24].

Nevertheless, there are some study limitations which restricted this research from being concluded definitely. We excluded all the patients who had known cause of dysautonomias, in an attempt to select a very pure population of patients with reflex syncope only. As a result, these findings do not apply to patients with dysautonomias who happen to faint, but only to patients who experience syncope in the absence of an underlying autonomic disorder. Finally, since we do not perform tilt table tests for longer than 40 minutes, we do not know how many additional patients would have fainted in longer time frames without use of provocation agents. We performed TTT on each group one time, although it is better to perform this test with two forms of TNG and then compare both results. This is the main limitation which restricted this research from calculating false positives for each form of TNG.

ACKNOWLEDGEMENT

We would like to thank all participants for their cooperation.

REFERENCES

- [1] Folino AF. Cerebral autoregulation in neurally mediated syncope: victim or executioner? *Heart*. 2006;92(6):724-06.
- [2] Folino AF, Russo G, Porta A, Buja G, Cerutti S, Illiceto S. Modulations of autonomic activity leading to tilt-mediated syncope. *Int J Cardiol*. 2007;120(1):102-07.
- [3] Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, et al. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J*. 2009;30(21):2631-71.
- [4] van Dijk JG, Sheldon R. Is there any point to vasovagal syncope? *Clin Auton Res*. 2008;18(4):167-09.
- [5] Alsheklee A, Guerch M, Ridha F, McNeeley K, Chelmsky TC. Postural tachycardia syndrome with asystole on head-up tilt. *Clin Auton Res*. 2008;18(1):36-09.
- [6] Freeman R. A treatment for neurally mediated syncope? (Don't) hold your breath. *Ann Neurol*. 2008;63(3):265-07.
- [7] Colman N, Nahm K, Ganzeboom KS, Shen WK, Reitsma J, Linzer M, et al. Epidemiology of reflex syncope. *Clin Auton Res*. 2004;14 Suppl 1:9-17.
- [8] Sutton R, Bloomfield DM. Indications, methodology, and classification of results of tilt-table testing. *Am J Cardiol*. 1999;84(8A):10Q-9Q.
- [9] Parry SW, Tan MP. An approach to the evaluation and management of syncope in adults. *BMJ*. 2010;340:c880.

- [10] Petersen ME, Williams TR, Gordon C, Chamberlain-Webber R, Sutton R. The normal response to prolonged passive head up tilt testing. *Heart*. 2000;84(5):509-14.
- [11] Stewart JM. Postural tachycardia syndrome and reflex syncope: similarities and differences. *J Paediatr*. 2009;154(4):481-5.
- [12] Ojha A, McNeeley K, Heller E, Alshekhlee A, Chelimsky G, Chelimsky TC. Orthostatic syndromes differ in syncope frequency. *Am J Med*. 2010;123(3):245-09.
- [13] Parry SW, Kenny RA. The management of vasovagal syncope. *QJM*. 1999;92(12):697-05.
- [14] Saul JP. Syncope: etiology, management, and when to refer. *JSC Med Assoc*. 1999;95(10):385-07.
- [15] Gibbons CH, Freeman R. Delayed orthostatic hypotension: a frequent cause of orthostatic intolerance. *Neurology*. 2006;67(1):28-32.
- [16] Driscoll DJ, Jacobsen SJ, Porter CJ, Wollan PC. Syncope in children and adolescents. *J Am Coll Cardiol*. 1997;29(5):1039-45.
- [17] Ganzeboom KS, Colman N, Reitsma JB, Shen WK, Wieling W. Prevalence and triggers of syncope in medical students. *Am J Cardiol*. 2003;91(8):1006-8, A8.
- [18] Lombroso CT, Lerman P. Breathholding spells (cyanotic and pallid infantile syncope). *Paediatrics*. 1967;39(4):563-81.
- [19] Wieling W, Ganzeboom KS, Krediet CT, Grundmeijer HG, Wilde AA, van Dijk JG. Initial diagnostic strategy in the case of transient losses of consciousness: the importance of the medical history. *Ned Tijdschr Geneesk*. 2003;147(18):849-54.
- [20] Wieling W, Schatz IJ. The consensus statement on the definition of orthostatic hypotension: a revisit after 13 years. *J Hypertens*. 2009;27(5):935-08.
- [21] Gehrking JA, Hines SM, Benrud-Larson LM, Opher-Gehrking TL, Low PA. What is the minimum duration of head-up tilt necessary to detect orthostatic hypotension? *Clin Auton Res*. 2005;15(2):71-05.
- [22] Pongiglione G, Fish F, Starsburger JF, et al. Heart rate and blood pressure response to upright tilt in young patients with unexplained syncope. *J Am Coll Cardiol*. 1990;16:165-70.
- [23] Fitzpatrick AP, Epstein LM, Lesh MD, et al. Effect of patient characteristics on the yield of prolonged baseline head-up tilt testing and the additional yield of drug provocation. *Heart*. 1996;76:406-11.
- [24] Oraii S, Maleki M, Minoii M, Kafaii P. Comparing two different protocols for tilt table testing: sublingual glyceryl trinitrate versus isoprenaline infusion. *Heart*. 1999 Jun;81(6):603-05.
- [25] Raviele A, Gasparini G, Dipede F, et al. Nitroglycerin infusion during upright tilt: a new test for the diagnosis of vasovagal syncope. *Am Heart J*. 1994;127:103-11.

PARTICULARS OF CONTRIBUTORS:

1. Faculty of Medicine & Cardiovascular Research Center, Department of Cardiovascular Diseases, Baqiyatallah University of Medical Sciences, Tehran, Iran.
2. Atherosclerosis and Coronary Artery Research Centre, Birjand University of Medical Sciences, Birjand, Iran.
3. Department of Cardiovascular Diseases, Baqiyatallah University of Medical Sciences, Tehran, Iran.
4. Cardiologist, Department of Cardiovascular Diseases, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Mollasadra St, Vanak Sq, Tehran, Iran.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Arezoo Khosravi,
 Cardiologist, Department of Cardiovascular Diseases, Faculty of Medicine,
 Baqiyatallah University of Medical Sciences, Mollasadra St, Vanak Sq, Tehran, Iran.
 Phone: +982188600067, E-mail: md.researcher@yahoo.com

Date of Submission: **Dec 20, 2012**Date of Peer Review: **May 07, 2013**Date of Acceptance: **Aug 12, 2013**Date of Publishing: **Oct 05, 2013****FINANCIAL OR OTHER COMPETING INTERESTS:** None.