Original Article

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A RANDOMIZED CONTROLLED CROSS-OVER TRIAL OF STANDARD ITALIAN PROTOCOL VERSUS FRONT-LOADED GLYCERYL TRINITRATE HEAD-UP TILT TEST

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ABSTRACT

Objective: To evaluate the sensitivity, specificity, and accuracy of front loaded glyceryl trinitrate head-up tilt test as a first line investigation.

Study Design: Randomized cross-over trial.

Place and Duration of Study: This study was conducted at electrophysiology department AFIC/NIHD Rawalpindi. Patients presenting with syncope in the month of Dec 2014 were enrolled in the study.

Material and Methods: Forty four consecutive patients between ages 14-70 years presenting to AFIC for investigation of unexplained syncope were enrolled in this study and were randomized to either of a protocol via sealed envelope method. All of the participants were then crossed-over to the opposite protocol at least one week apart.

Results: For protocol A, there were 28 positive responses (63.3%) and 17 (38.6%) for protocol B. There was no statistically significant difference between the outcomes of protocol A and protocol B (p-value 0.001). Protocol B is as specific (93.75%) as standard Italian method but less sensitive (57.14%) than standard Italian protocol. The time at which positive response occurred during the provocation phase of protocol A and B is 7.2 ± 3.6 vs 9.0 ± 3.5 minutes respectively, which is not significantly different (*p* value = 0.177, 95% CI = -1.4 – 0.88).

Conclusion: Although front-loaded glyceryl trinitrate protocol is equal in specificity with the standard Italian protocol, it has a greater number of false-negative results.

Keywords: Syncope, Headup Tilt test, Specificity.

INTRODUCTION

Head-up tilt table testing is widely used in the work up of vasovagal syncope[1-4]. Upright posture is the most physiological orthostatic stressor and Head-up tilt test allows simulation of upright posture in carefully monitored and controlled conditions. Head-up tilt table testing has emerged as an accepted modality for identifying an individual's predisposition to orthostatic intolerance as it is a safe, useful and cost-effective diagnostic tool greatly improving insight in the management of patients with syncope[5-7].

The specificity, sensitivity and reproducibility as well as the safety profile of HUT is well within the accepted range. Although various centers use different protocols[8], the one being practiced at the Armed Forces Institute of Cardiology is "Standard Italian Protocol" which comprises of a 55 minutes duration procedure.

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Some investigators have reported the utility of front loaded head up tilt testing where sublingual glyceryl trinitrate was used before tilting to 700. This procedure gets completed in 25 minutes as compared to 55 minutes for the standard Italian protocol[9]. However the data reported is sporadic. Therefore in order to validate the utility of front loaded glyceryl trinitrate head-up tilt test we have planned this study. The aim of this study is to improve quality of health care services provided at AFIC/NIHD by suggesting a more efficient and less time consuming method for assessing patients with unexplained syncope.

METHODS

Head-Up Tilt Test Protocols

Protocol A: Standard Italian HUTT:

Duration: 55 minutes

Procedure: Patients rested in supine position for 5 minutes (stabilization phase) before tilted to a 70° position for 30 minutes (passive phase) and remained tilted for a further 20 minutes (provocation phase) after administering 500 mcg sublingual glyceryl

trinitrate (Angised® - GSK) till procedure was completed or positivity criteria was reached.

Protocol B: Front loaded glyceryl trinitrate HUTT:

Procedure: Patients rested in supine position for 5 minutes (stabilization phase) and then tilted to 70° position for 20 minutes (provocation phase) after administering 500 mcg sublingual glyceryl trinitrate (Angised® - GSK) till procedure was completed or positivity criteria was reached.

In both cases, surface electrocardiograph at 25 mm/s were continuously monitored as well as beat-to-beat blood pressures using digital sphygmomanometry. Syncope and pre-syncope were established according to European Society of Cardiology (ESC) guidelines[10,11]. Medications were continued during the test protocol. Informed consent was sought for each participant included in study.

Inclusion Criteria

Forty four consecutive patients between ages of 14 – 70 years, with unexplained syncope of two or more episodes, or one episode while driving or disabling pre-syncope referred to the electrophysiology department at AFIC/NIHD were enrolled in this study.

Exclusion Criteria

Patients with known cerebrovascular disease, structural heart disease (left ventricular outflow obstruction, critical mitral stenosis, proximal coronary artery stenosis) previous adverse reaction to nitrates, or inability to attend the second tilt test because of other commitments[1,2].

Test interruptions

The test was interrupted when the protocol was completed in the absence of symptoms, or if there was occurrence of syncope, progressive (>5 min) symptomatic orthostatic hypotension, and/or bradycardia[8]. The test was also terminated on development of any adverse event, arrhythmia or if requested by participant.

Ramdomization technique

A random number table generated by computer was used to allocate study participants to either protocol A or B and the decided protocol was assigned via sealed envelopes. All the participants were crossed-over to the opposite protocol with a gap of at least one week, at the same time of the day.

Table-2: Clinical characteristics of study subjects (n=44).

Age (years)	
Mean ± SD	43 ± 18.7 yrs
Median	38 years
Range	13 – 75 years
Height (cm)	
Mean ± SD	167.6 ± 8.2 cm
Median	170 cm
Range	132 – 176 cm
Weight (kg)	
Mean ± SD	70.29±11.9 kg
Median	74 kg
Range	30 – 85 kg
Gender (%)	
Males	81.8%
Females	18.2%
Co-morbidities (%)	
IHD	6.8%
Hypertension	27.3%
Diabetes Mellitus	9.1%
Asthma	5%
Smoking Status (%)	
Smokers	5%
Non-smokers	95%
Cardiovascular drugs (%)	30%

Statistical analysis

The data were entered in IBM SPSS Statistics software (version 19). Continuous data was expressed as median and mean along with standard deviation values. Proportions were expressed as percentages with confidence intervals of 95%. Different groups of continuous variables were compared by using paired-sample student's t-test while categorical variable groups were compared via non-parametric chi-square and McNemar's test. Sensitivity, specificity, and predictive values were calculated in usual manner and a *p*-value of 0.05 is considered significant. (Table-1)

RESULTS

Forty four patients with history of unexplained syncope visited AFIC in the month of December 2014 for whom Head-up Tilt Test

was advised and were enrolled in the present randomized controlled trial after obtaining informed consent. Clinical characteristics of the patients are summarized in table-2. No control group was required because study subjects acted as their own controls by cross-over technique.

For protocol A, there were 28 positive responses (63.3%), out of which 26 (92.8%) were mixed (type 1) responses while 2 (7.14%) were cardioinhibitory (type 3) in nature; and 16 (36.3%) study subjects completed the test procedure of 55 minutes without onset of any symptom or hemodynamic change. Only 17 (38.6%) positive responses were observed in

Table 1: 2 x 2 contingency table for protocol A and B.

		Protocol A		Total
		Positive	Negative	
Protocol B	Positive	16	1	17
	Negative	12	15	27
Total		28	16	44

Table-3: Comparison of Head-up Tilt Test Protocol A and Protocol B (Chi-square & Paired-t test results).

	Protocol A	Protocol B	*p* – values
Number of cases	40	40	
Duration of procedure	55 mins	25 mins	
Negative responses	36.3% (16)	61.3% (27)	0.0001
Positive Responses	63.7% (28)	38.6% (17)	0.0001
Type 1 – Mixed	26	15	
Type 2- Cardio inhibitory response	2	2	
Type 3 – Vaso depressive response	0	0	
Most frequently encountered symptoms at test interruption			
Asymptomatic	6	1	
Diziness	14	13	
Heart sinking	5	0	
Blackout	1	3	
Syncope	2	0	
Time at positive response during provocation phase			(paired t-test)
Mean ± SD	7.2 ± 3.6 mins	9.0 ± 3.5 mins	*p* value = 0.177 95% CI = -1.4 - 0.88
Time to complete test with a positive outcome			
Mean ± SD	37.7 ± 3.7 mins	9.4 ± 3.7 mins	(paired t-test)
Median	36 mins	8 mins	*p* = 0.0001
Range	34 – 48 mins	2 – 16 mins	95% CI = 25 - 30
Blood pressure at time of positive response			
Systolic BP (mmHg)	69.4 ± 1.2	70.8 ± 2.9	(paired t-test)
Mean ± SD	69	70	*p* = 0.55
Median	66 – 71	22 – 56	CI = -2 – 1.1
Range			
Diastolic BP (mmHg)	30.8 ± 8.04	29.7 ± 7.17	(paired t-test)
Mean ± SD	30	32	*p* = 0.69
Median	22 - 56	22 - 45	CI = -4.5 – 6
Range			
Heart rate at time of positive response (bpm)	66.4 ± 2.5	65.7 ± 4.3	(paired t-test) *p* = 0.18 CI = -2.4 – 11

case of the shorter protocol B, where 15 (88.2%) and 2 (11.7%) responses were of mixed (type 1) and cardioinhibitory (type 3) nature, respectively; and 27 (61.3%) study participants completed the test procedure of 25 minutes without onset of any symptoms.

By comparing both protocols no statistically significant difference has been observed in the outcomes of protocol A and protocol B (*p*-value = 0.02). The shorter protocol B is 57.14% sensitive and 93.75% specific while its positive predictive value is 94.11% and its negative predictive value is 55.5%. Outcomes of protocol A and B are summarized in table-3.

The most frequently encountered symptom at positive test interruption was dizziness in both protocols. There was a strong statistical difference between the time required to achieve a positive outcome result (*p* value = 0.0001, 95% CI = 25 - 30) , and was observed to be 37.7 ± 3.7 minutes vs 9.4 ± 3.7 minutes for protocol A and B, respectively. No statistically significant difference was noted in the time at which positive response occurred during the provocation phase (*p* value = 0.177, 95% CI = -1.4 – 0.88) , and was observed to be 7.2 ± 3.6 minutes vs 9.0 ± 3.5 minutes for protocol A and B, respectively. Similarly no statistically significant difference was found between systolic/diastolic blood pressures and heart rates (*p* = 0.55, 95% CI = -2 – 1.1; *p* = 0.69, 95% CI = -4.5 – 6; P = 0.18, 95% CI = -2.4 – 11) of patients when they acquired positive symptoms during head-up tilt test.

DISCUSSION

Front loaded glyceryl trinitrate Head-up tilt test is a shorter protocol which requires almost half of the time to perform the test as compared to the standard Italian protocol. It is more specific (93.75%) but less sensitive (57.14%)[12,13]. According to our initial results it can be concluded that front loaded glyceryl trinitrate head-up tilt test is more specific to rule out vasovagal syncope and for establishing a positive diagnosis. A much shorter time is required for procedure completion[12-14]. The test was well tolerated by all study participants of all age groups with no serious side effects[8].

The pattern of hemodynamic responses was almost similar for both protocol A and B with the majority of responses falling in the mixed (type-1) category[12], contrary to many other studies reporting excessive incidence of cardioinhibitory (type-2) and vasodepressive (type 3) responses[13,14] This difference may be due to limited sample size.

No statistically significant difference was reported by Zeng et al in the distribution of outcomes between the two protocols with overall concordance of 86.5%[15]. Similar sort of results were reported by Parry et al where the two protocols were not significantly different from one another. Contrary to our observations, Parry et al observed higher incidence of false positive responses with the shorter head up tilt test[12]. This may be due to a difference in glyceryl trinitrate dose and mode of administration, as sublingual spray is more frequently used than sublingual tablet. In a study conducted by Fitzpatrick, a significant increase in the number of false negative results with shorter tilt periods has been noted[19]. Similarly we have also observed a lesser number of positive responses in the shorter front loaded glyceryl trinitrate head-up tilt test (38.8% vs 63.3%), with more chances of detecting false negative cases; however specificity rates are the same as the standard Italian protocol[2,14,16,17].

In this study we have used 500 mcg sublingual tablet of glyceryl trinitrate (Angised® - GSK) which was safe and well tolerated. The time at which positive symptoms occurred after sublingual administration of glyceryl trinitrate was 7.2 ± 3.6 minutes and 9.0 ± 3.5 minutes for protocol A and B respectively[18]. Contrary to our results, the reported time at which positive symptoms took place is slightly less in some other studies[12,15].

CONCLUSION

Although front-loaded glyceryl trinitrate protocol is equal in specificity with the standard Italian protocol, it has a greater number of false-negative results. Hence a study with larger sample size is recommended in future.

Conflict of Interest

This study has no conflict of interest to declare by any author.

REFERENCES

1. Kenny RA, O'Shea D, Parry SW. The Newcastle protocols for head-up tilt table testing in the diagnosis of vasovagal syncope, carotid sinus hypersensitivity, and related disorders.Heart 2000; 83: 564–9.
2. Benditt DG, Ferguson DW, Grubb BP et al. Tilt table testing for assessing syncope. J Am Coll Cardiol 1996; 28: 263–75.
3. Parry SW, Kenny RA. Tilt table testing in the diagnosis of unexplained syncope. QJM 1999; 92: 623–9.
4. Brignole M, Alboni P, Benditt DG et al. Guidelines on management (diagnosis and treatment) of syncope. Eur Heart J 2001; 22: 1256–306.
5. Lamarre-Cliche M, Cusson J. The fainting patient: value of the head-upright tilt-table test in adult patients with orthostatic intolerance. CMAJ 2001;164:372–6.
6. Udani V, Bavdekar M, Karia S. Head-up tilt test in the diagnosis of neurocardiogenic syncope in childhood and adolescence. Neurol India 2004;52:185–7.
7. Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: a useful test for evaluating unexplained syncope. Lancet 1986;1:1352–5.
8. Bartoletti A, Alboni P, Ammirati F, Brignole M, Del Rosso A, Foglia Manzillo G et al. 'The Italian Protocol': a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. Europace. 2000 Oct;2(4):339-42.
9. Graham LA, Kenny RA, Gray JC. Comparison of provocative test for unexplained syncope: isoprenaline and glyceryl trinitrate for diagnosing vasovagal syncope. Eur Heart J 2001; 22: 497–503.
10. McIntosh S, Lawson J, da Costa D et al. Use of sublingual glyceryl trinitrate during head-up tilt as a provocative test for vasovagal responses in elderly patients with unexplained syncope. Cardiol Elder 1996; 4: 33–7.
11. Brignole M, Alboni P, Benditt DG et al. Guidelines on management (diagnosis and treatment) of syjncope. Eur Heart J 2001; 22: 1256–306.
12. Parry SW, Gray JC, Newton JL, Reeve P, Shea DO, Kenny RA. 'Front-loaded' head-up tilt table testing: validation of a rapid first line nitrate-provoked tilt protocol for the diagnosis of vasovagal syncope. Age and ageing. 2008; 37: 411–415
13. Kurbaan AS, Franzen AC, Williams T et al. Usefulness of tilt test-induced patterns of heart rate and blood pressure using a two-stage protocol with glyceryl trinitrate provocation in patients with syncope of unknown origin. Am J Cardiol 1999; 84: 665–70.
14. Alasti M, Nikoo MH, Jadbabaei MH, Seyedian M, Payami B, Taghavianpour S. Randomized Prospective Comparison of Two Protocols for Head-up Tilt Testing in Patients with Normal Heart and Recurrent Unexplained Syncope. Indian Pacing and Electrophysiology Journal. 2013; 13(6): 203-211
15. Zeng C, Liu G, Yang C, Sun W, Wang Y, He D. Evaluation of a single stage nitroglycerin tilt table test for diagnosis of neurally mediated syncope. PACE. 2001; 24(10): 1494-99
16. Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009). The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). Developed in collaboration with, European Heart Rhythm Association, Heart Failure Association, and Heart Rhythm Society. European Heart Journal 2009; 30: 2631–2671.
17. Del Rosso A, Ungar A, Bartolli P, Cellai T, Mussi C, Marchianni N. Usefulness and safety of shortened head-up tilt testing Potentiated with sublingual glycerl trinitrate in older patients with recurrent unexplained syncope. J Am Geriatr Soc. 2002; 50:1324–8.
18. Aerts AJJ, Dendale P. Nitrate Stimulated Tilt Table Testing: A Review of the Literature. PACE. 2003; 26: 1528-1537
19. Fitzpatrick AP, Theodorakis G, Vardas P. Methodology of head upright tilt table testing in patients with unexplained syncope. J Am Coll Cardiol. 1991; 17:125–130.