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DIAGNOSTIC VALUE OF SUBLINGUAL NITROGLYCERIN TILT TEST: COMPARISON WITH THE STANDARD ISOPROTERENOL TILT TEST

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ABSTRACT

Sublingual nitroglycerin (TNG) has been introduced as a promising provocative agent for tilt table testing, but it has not been compared directly with the standard isoproterenol (ISO) infusion test previously. We tried to assess the diagnostic value and safety of TNG tilt testing as compared with ISO infusion in patients with unexplained syncope.

TNG and ISO tilt tests were performed in two successive days on a random basis for both cases and controls. 65 consecutive patients with unexplained syncope after thorough work-up and 20 healthy volunteers were recruited into the study. Positive responses were observed in 20 patients (31%) during the passive phase, 25 (55% of cases or 38% of total) during the TNG phase and 26 (58% or 40% of total) during the ISO phase. In the control group, positive responses during the passive, TNG and ISO phases occurred in 1,1 and 2 cases, respectively. The sensitivity and specificity of the tests can be summarized as 69% and 90% respectively for the TNG test versus 71% and 85% respectively for the ISO test. Owing to discordant responses in 75% of the cases, the sequential use of the tests (if one is negative) would increase the sensitivity to 89% while decreasing the specificity slightly (to 80%). Side effects were also less frequent with TNG. We conclude that sublingual TNG testing is an effective and safe alternative to the ISO infusion test and can be used as a complementary test.

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Keywords: Syncope, Tilt table test, Isoproterenol, Nitroglycerin.

INTRODUCTION

Tilt table testing (TTT) is a widely accepted tool for confirmation of the clinical diagnosis of neurocardiogenic or vasovagal syncope.[1] Several adjunctive pharmacologic agents have been proposed to increase the sensitivity of the test,[2-5] with varying results,[6,7] but isoproterenol (ISO) infusion has remained as the most popular one.[1,8,9] ISO infusion, however, is rather cumbersome, undesirable in many patients with organic heart disease,[10] and with relatively frequent side effects.[11] Sublingual nitroglycerin (TNG) seems to be a promising provocative agent, but it

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has not been previously compared directly with the standard protocols. The present study was designed to compare the diagnostic value and tolerability of sublingual nitroglycerin (TNG) tilt testing and ISO infusion in the same group of patients.

PATIENTS AND METHODS

Patients

Sixty-five consecutive patients (40% men; age 17-56 years, mean 34±11.2) with unexplained syncope were included. The number of episodes of syncope varied from 1 to 20 episodes (mean 3.3±3.8 episodes). No abnormalities were found after a careful physical examination, routine lab tests, 12 lead electrocardiography, echocardiography and 24h Holter recording. Other investigations including stress tests, electrophysiologic studies, angiography or brain CT scan were performed if clinically indicated.

Control group

Control subjects were 20 healthy volunteers (50% men; age 17-56 years, mean 29±9.5). They had no history of syncope or presyncope and no evidence of any abnormalities on physical examination, electrocardiography and echocardiography.

TTT Protocol

An informed consent was obtained from all patients and control subjects. Both ISO and TNG protocols were performed in every patient and control subject on two successive days, in a random order. Tests were performed in the morning after an overnight fast. Nobody took any medications. The room was quiet with dim lights. An electronically controlled table with foot board support and restraining belts at chest level was used. The electrocardiogram was continuously recorded and blood pressure was recorded by a non-invasive sphygmomanometer every 3 minutes or sooner if needed.

Passive phase: After 15 minutes of rest in the supine position, the table was tilted to 70° and the tilt was sustained for up to 45 minutes. Pharmacologic provocation was then started as described below if a positive response was not encountered.

***TNG phase*:** Patients received 400 µg of sublingual TNG and continued to be tilted at 70° for a maximum of 20 minutes.

ISO phase: ISO infusion was started at 1µg/min in the supine position and the [illegible] minutes. If a positive response was not seen, the dose was increased by 1µg/min at 10 minute stages, up to a maximum of 4 µg/min or until the heart rate increased to over 150 beats per minute.

Definitions

Syncope: Transient loss of consciousness with spontaneous recovery.

Presyncope: A state of intense dizziness associated with one or more symptoms of decreased vision, slow response to verbal stimuli, partial loss of tone, nausea or vomiting.

Positive response: Development of symptom(s) of presyncope or syncope accompanied by a rapid (within 5 min) fall in systolic blood pressure by more than 50% of the baseline or to less than 60 mmHg, and/or a fall in heart rate (HR) by more than 30% from the peak HR or to less than 50 bpm.

Type of response

Responses were classified as type I or mixed (hypotension or bradycardia develops but ventricular rate does not fall to less than 40 bpm for over 10 seconds and without asystole of over 3 seconds), type II or cardioinhibitory (hypotension with a ventricular rate of less than 40 for greater than 10 seconds or asystole for over 3 seconds) and type III or vasodepressor (hypotension develops but rate does not fall over 10% from the peak).

RESULTS

Positive responses are summarized in Table I. During the initial passive phase, 20 patients (31%) showed positive responses. With pharmacologic provocation, positive responses to TNG and ISO occurred in another 25 (55% of cases or 38% of total) and 26 (58% of cases or 40% of total) patients, respectively. Therefore the total positive rate of TNG and ISO tests can be considered to be 69% and 71%, respectively.

The types of responses are summarized in Table II. In the control group, positive responses occurred during the passive phase in one case, during the ISO phase in two and during the TNG phase in one case. A concordant response to ISO and TNG tests was observed in 13 cases (25%) only, while 38 cases (75%) showed positive responses with one or the other test.

Thus, the sensitivity and specificity of the tests can be summarized as 71% and 85% for the ISO test and 69% and 90% for the TNG test, respectively. Owing to discordant responses, if the two tests are used sequentially (when one is negative), the sensitivity would rise to 89% while specificity would decrease slightly to 80%.

The mean time to positive responses was not significantly different between TNG and ISO phases (11.2±3.7 min versus 11.0±3.9 min, respectively), but

Table I. Summary of positive responses.

	Passive Phase	ISO Phase	TNG Phase
Cases (65)			
Positive Responses Time to Response	20 (31%) 15.5±7.3 min.	26 (40%) 11.0±3.9 min.	25 (38%) 11.2±3.7 min.
Controls (20)			
Positive Responses Time to Response	1 (5%) 12 min.	2 (10%) 15.4±2.5 min.	1 (5%) 10 min.

ISO= Isoproterenol, TNG= Nitroglycerin.

Table II. Types of responses.

	Type 1	Type 2	Type 3
Positive Phase	13 (65%)	6 (30%)	1 (5%)
ISO Phase	20 (77%)	4 (15%)	2 (8%)
TNG Phase	13 (52%)	9 (36%)	3 (12%)

ISO= Isoproterenol, TNG= Nitroglycerin.

was shorter than that of the passive phase (15.5±7.3 min).

Side effects

Few significant side effects were encountered with both protocols. With ISO, they included self-terminating episodes of supraventricular tachycardia (2 patients, one control), chest pain (one patient), headache (2 patients, one control) and nausea (3 patients, 2 controls). With TNG, one patient and one control subject suffered from headache. Also, many patients felt an unpleasant sensation with ISO, but tolerated TNG well.

DISCUSSION

Vasovagal syncope is thought to be the most common cause of syncope. Concerning this disorder, clinical history may be unreliable due to the possible absence of typical precipitating factors and prodromal symptoms.

The sensitivity of passive TTT has been variously reported as 19 to 69%[4,12,13] but is mostly poor. Isoproterenol has been known to increase the sensitivity while decreasing the specificity of the test,[13,14] but it requires an infusion system and is unpleasant to many patients, with relatively frequent side effects.[11]

The TNG tilt test, first introduced by Raviele et al.[15] is a promising agent because it does not require to be infused and seems to be safer than ISO. In this study we compared both tests in the same group of patients and similar sensitivities were obtained for TNG and ISO protocols (71% versus 64% respectively) with a somewhat better specificity for the TNG test (90% versus 85%). Side effects were also less frequent with the TNG test.

Our rate of positive responses during all three phases was somewhat lower than some earlier studies. The rate of posi

aggressive protocols, increasing severity of syncopal attacks, a shorter interval between the last episode and the test, younger age and female sex.[13,14,16] We could not identify any differences regarding the above parameters between our study and those with a higher rate of positive responses, but racial factors cannot be excluded.

As noted previously[17,18] discordant responses were seen in three-fourths of the patients (75%). This discrepancy is suggestive of the presence of different pathophysiological subsets of patients with vasovagal syncope, provoked by different triggers. Alternatively, the reproducibility of the test can be involved, which requires to be studied further. Nevertheless, when one test is negative, the rate of positive responses can be increased by performing the other test, without significant loss of specificity.

Limitations

As noted by others[8] the definition of neurocardiogenic syncope is a clinical one and no "gold standard" exists.

Thus the definitions of sensitivity and specificity would be arbitrary. Day to day variability of the responses cannot be ruled out, even though the order of performance of the tests was selected randomly. Our control subjects had a younger mean age but this is likely to decrease the specificity, not to increase it, as positive responses are more prevalent in younger people.[12]

CONCLUSION

The TNG tilt test is a more tolerable and equally sensitive alternative to ISO tilt testing. It can be used as the first line provocative agent in TTT, as a complementary test in those with negative ISO tilt, or as an alternative to ISO in those with a contraindication to catecholaminergic drugs.

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