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ORIGINAL ARTICLE

Comparison of Efficacy, Pattern of Response, Occurrence of Arrhythmias, and the Tolerability of Nitroglycerine and Isoprenaline as Provocative Drugs During Head-Up Tilt Test

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Background Various protocols exist for performing head-up tilt test (HUTT). Serious ventricular arrhythmias have been reported during HUTT using Isoprenaline (ISO) provocation and their incidence with sublingual Nitroglycerine provocation is unknown. This study aims to assess the efficacy, pattern of response, tolerability, and frequency of arrhythmias during head-up tilt test with sublingual Nitroglycerine (NTG) provocation compared to ISO) provocation.

Methods This is a retrospective observational study.

Result From 2007 to 2015, a total of 816 patients (68% men, median age 49 IQR 25.75–65 years) underwent head-up tilt testing using sublingual NTG provocation whereas ISO was used in 189 patients (66.1% men, median age 48 IQR 36–60 years). A positive response was more frequently observed in the NTG group than the ISO group (48.4% vs 35.9%, p=0.002), with more frequent type II b (cardio-inhibition with >3 sec asystole) and type III (vasodepressor) responses ([15. 9% vs 4.1%, p=0.001] and 0% vs 29.4%, p=0.004) respectively. Bradyarrhythmias occurring always as a part of a positive HUTT response were the commonest arrhythmias (29% in NTG group vs 25.4% in ISO group, p=0.31). Tachyarrhythmias (or premature beats) were more frequent in the ISO group (12.7% vs 7.9%, p=<0.005). The use of NTG was significantly associated with a positive response (OR 1.775, 95% CI 1.269–2.483, p=0.001), whereas the use of ISO predicted the occurrence of premature beats/tachyarrhythmias (OR 3.06, 95% CI 2.195–4.267, p<0.005). Intolerance needing termination of the test was significantly more frequent in the ISO group than NTG group (1.6% vs 0.12%, p= 0.02).

Conclusion Head-up tilt test with NTG provocation has a higher yield of a positive response, lower incidence of unwanted arrhythmias and better tolerability compared to ISO. The occurrence of VASIS type II b and type III response was more with Nitroglycerine than Isoprenaline.

Keywords Arrhythmias • Head-Up Tilt Test • Isoprenaline • Nitroglycerine

Abbreviations: HUTT, Head up tilt test; ISO, Isoprenaline; NTG, Nitroglycerine

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Introduction

Syncope, which is defined as transient loss of consciousness with spontaneous recovery, is a common cause of emergency room visits and hospitalisation [1,2]. Appropriate evaluation of syncope is essential to identify the various causes of syncope and to differentiate benign from the more serious cause. Head-up tilt test (HUTT) has been widely used in the evaluation of patients with suspected neuro cardiogenic syncope. During HUTT, various protocols for pharmacologic provocation using Isoprenaline (ISO), adenosine, or Nitroglycerine (NTG) have been used to increase the sensitivity [3–5]. In the absence of pharmacological provocation, no complications were reported and the test was considered safe [6]. However, studies using ISO provocation have reported frequent arrhythmias, including ventricular tachycardia and ventricular fibrillation [7]. Initially intravenous NTG, and subsequently sublingual NTG has been used as an alternative to ISO for provocation, with similar sensitivity and specificity but better tolerability [8,9]. The incidence of significant arrhythmias during HUTT with sublingual NTG provocation is unknown and it is not evident whether the frequency of arrhythmias with NTG provocation is similar to the ISO provocation. The purpose of this study was to compare the frequency of test positivity, the pattern of the response, incidence of arrhythmic events during HUTT with sublingual NTG versus ISO provocation in patients with suspected neuro cardiogenic syncope.

Methods

This is a retrospective study of subjects with a history of syncope, who had undergone HUTT with NTG or ISO provocation, at Sri Jayadeva Institute of Cardiovascular Sciences and Research from the January 2007 to April 2015. Cardiology Fellows, and electrophysiology Residents, under the guidance of the staff electrophysiologist, evaluated all patients at the syncope clinic, using a standard protocol. All patients underwent a detailed clinical evaluation including clinical history, thorough physical examination, 12-lead electrocardiogram, 2D echocardiogram and a mandatory 24-hour Holter recording. Those patients with a history suggestive of neuro cardiogenic syncope with normal Holter recordings were subjected to HUTT. The present cohort consisted of patients who had: a) history suggestive of syncope; b) had no structural heart disease on echocardiogram; c) no evidence of any significant (>30 seconds) of atrial or ventricular tachyarrhythmia or significant pauses of >2.5 seconds on Holter; and d) who had undergone HUTT with sublingual NTG or ISO as provocation. However, if the patient had structural heart disease, or possibility/confirmation of coronary artery disease (effort angina, regional wall motion abnormalities in the echocardiogram, positive treadmill test, or angiographic documentation of CAD) only NTG was used for provocation, and such patients were excluded from this study. In other patients, the choice of NTG or ISO was based on the preference of the physician attending the test.

The Head-Up Tilt Test

Head up tilt test with sublingual NTG (400 mcg) or ISO (up to 3 mcg/min infusion) was performed following the European Society of Cardiology (ESC) guidelines [10]. In brief, the procedure was performed in the morning, after overnight fast in a quiet, in a slightly darkened room specially designated for HUTT. The room was equipped with a crash cart and all resuscitative equipment including a defibrillator. No other investigations were undertaken on the same day. All cardioactive and vasoactive drugs were stopped for four half-lives before the study. Head-up tilt test was performed under the supervision of a cardiology resident doctor, or electrophysiology Fellow along with a staff nurse. The tilt test was performed by means of an electronically controlled tilt table with a footboard for weight bearing. Patients were assisted to lie down on the tilt table, and restraining belts were placed at chest and thigh levels. A 20-gauge intravenous cannula was placed in the upper limb vein and the patient was allowed to rest for 30 minutes in supine position. Blood pressure was measured using a noninvasive automated blood pressure monitor, heart rate, and rhythm was continuously monitored using three limb leads. A three-lead ECG monitor was used for monitoring and a single lead strip recorder recording lead II was programmed to perform recordings every five minutes on a strip recorder. The strip recorder was programmed to be automatically activated if the heart rate dropped to <40 bpm or >100 bpm, or manually triggered if there was an arrhythmia was noted by the attending doctor or staff nurse. Blood pressure and heart rate were also recorded if symptoms or arrhythmias developed. All suspected arrhythmia recordings from the strip recorder were crossed checked, and classified by the attending staff electrophysiologist. The test was performed in two consecutive phases. During the first phase, participants were tilted to an angle of 70^{o}, for up to 45 minutes without medication (control phase). If syncope did not develop, participants received 400 micrograms of sublingual NTG spray during the second phase and continued to be tilted at the same angle for a further 20 minutes (pharmacologic phase). In the ISO group, the drug was infused at an incremental rate from 1 up to 3 mg/min in order to increase average heart rate by about 25% over baseline, administered without returning the patient to the supine position. The endpoints of the test were a positive response or completion of the protocol. If syncope occurred during the test, the tilt table was rapidly lowered to the supine position and the study was terminated.

Definitions

Syncope was defined as sudden transient loss of consciousness with an inability to maintain postural tone and with spontaneous recovery. Pre-syncope was defined as the complex of premonitory signs and symptoms of imminent syncope (i.e., severe lightheadedness, severe weakness, transient greying of vision, or hearing loss) with difficulty in maintaining postural tone. The syncopal phase was classified

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