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Original Article

# Isoprenaline versus nitroglycerine in head-up tilt test☆

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ABSTRACT

*Background:* HUTT test is used in evaluation of syncope. Isoprenaline and isosorbide dinitrate are used to increase the sensitivity of the test. These drugs act by different mechanisms. We aimed to compare the results of isoprenaline with isosorbide dinitrate.

*Methods and results:* We studied 198 subjects referred for HUTT to our institute; those above the age of 35 years were not included in our study, because isoprenaline was not used commonly above this age; thus, only 90 subjects were analyzed.

We found that isosorbide dinitrate resulted in more HUTT-positive results than isoprenaline by absolute risk difference of 26%; relative risk for positive isoprenaline was 60%, confidence interval 0.38–0.93, and *P* value of 0.03. There was no difference in frequency of types of responses, i.e. Type 1, Type 2, and Type 3 between passive testing, isosorbide dinitrate, and isoprenaline, confidence interval 1.53–2.02, and *P* value 0.71. Time to get positive response was highest for passive testing followed by ISO and ISDN; the mean was $16.85 \pm 7.00$ min, $9.85 \pm 5.84$ min, and $7.00 \pm 3.35$ min, respectively. Statistically, ISDN versus ISO time to get positive response was not significant; *P* value was 0.074 and 95% confidence interval was −0.28 to 5.98.

*Conclusions:* Isosorbide dinitrate yields more positive HUTT than isoprenaline. The frequencies of type of responses are not different between passive testing, isosorbide dinitrate, and isoprenaline. There is no difference in time taken for positive response between isosorbide dinitrate and isoprenaline. In comparison to isosorbide dinitrate and isoprenaline, passive testing showed longest time for positive response.



## 1. Introduction

Syncope is defined in European Guidelines for the diagnosis and management of syncope (version 2009) as transient loss of conciseness (T-LOC) due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery.[1]

Vasovagal syncope (VVS) is one of the commonest types of syncope. In a study published in NEJM, vasovagal was present in (21.2%), cardiac in (9.5%), and orthostatic in (9.4%); for 36.6%, the cause was unknown.[2] Diagnosis of vasovagal syncope is sometimes challenging. VVS is associated with hypotension and bradycardia. The exact mechanism of VVS is still an enigma. Postulated mechanisms state that, following prolonged standing, there is pooling of blood in lower part of the body leading to central hypovolumia; this leads to stimulation of baroreceptors in carotids, and increasing the sympathetic stimulation, heart is made to contract vigorously. This vigorous contraction stimulates mechanoreceptors, paradoxically leading to withdrawal of sympathetic drive and increasing parasympathetic output; this leads to hypotension and bradycardia, respectively, leading to syncope.[3]

Head-up tilt test (HUTT) is used for diagnosis of syncope. This test consists of brief periods of 5–20 min supine phase followed by a passive tilt phase 20–40 min at 50–70°. If the patient does not develop symptoms during passive tilt, various techniques are used to potentiate the test. These techniques are as follows: administering drugs like isoprenaline (ISO), nitroglycerine (NTG), isosorbide dinitrate (ISDN), or adenosine, or resorting to nonpharmacological techniques like applying suction to lower part of the body.

In HUTT, ISO and ISDN are commonly employed to potentiate the test results. These two agents act by different mechanisms. ISO increases sympathetic stimulation leading to increased chronotrope, and inotropy on heart mimicking increased

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sympathetic stimulation seen before the VVS, where as ISDN a venodilator increases the pooling of blood in venous system thus causing central hypovolumia seen in VVS.[4]

## 2. Aims and objectives

1. We aimed to find out whether there is any difference between ISDN versus ISO in terms of getting a positive versus a negative test.
2. As mechanisms of action of ISO and ISDN are different, we aimed to find out whether the frequency of types of responses, see Table 1, produced by passive testing, ISO, and ISDN are similar or dissimilar.

Procedure time of HUTT is long; so, we aimed to find out between ISO and ISDN which consumes lesser time to get positive results. We also compared time taken by passive testing versus both drugs.

## 3. Methodology

This was a retrospective study. From the year 2009 to 2011, patients referred to HUTT at our institute were analyzed for this study. Totally, we found 198 subjects with age range from 5 to 84 years, but only subjects lesser than 35 years were included in the study, because above the age of 35 years ISDN was used more commonly as compared to ISO. So, we did not include them initially in our study. Hence, the number of subjects included in this study was 90. But for the purpose of increasing the power of study, we did few statistical tests in all 198 subjects. However, conclusions are only drawn from the subjects who are less than 35 years.

The data were collected from these 90 subjects, who had undergone tilt procedure, and the protocol of tilt has been described below. Following this, we have compared the sensitivity of ISO and ISDN in the evaluation of syncope in terms of the following: (1) positive versus a negative test, (2) frequency of types of responses by passive testing, ISO, and ISDN, and (3) time taken by passive testing versus both drugs.

### 3.1. Tilt protocol

Patients were tested in the morning with overnight fast. The test was performed in a quiet room with dim light. Resuscitation equipment with trained nurse and resident doctor was always present while performing the test. The manual sphygmomanometer BP recording was used for recording blood pressure once in every 2 min, from the beginning to end of the test. ECG was monitored continuously from beginning to end of test. IV canula was placed with normal saline on flow. Patients were advised to lay supine for 20 min; following this, passive tilt at 70° was done for 20 min. In those who did not develop presyncope or syncope during passive tilt, intravenous ISO (1–3 μg/min) for 20 min or sublingual 1.25–2.5 mg isosorbide dinitrate (ISDN) every 5 min for 20 min was given.

The test was concluded as positive if the patient along with presyncope or syncope developed fall in systolic BP more than 25% or/and drop in heart rate more than 30 beats $min^{-1}$. The patient was then brought back to supine position immediately. Positive test results were grouped into three types: Type 1 means a partial decrease in heart rate and fall in BP. Type 2 means a decrease in heart rate and fall in BP. Type 3, also called vasodepressor syncope, consisted of fall in BP but without a decrease in heart rate.[5] (See Table 1.)

Once the relevant data were collected, it was subjected to appropriate statistical analysis, which has been described below.

### 3.2. Data analysis

SPSS version 17 was used to analyze data; G-Power was used to assess the power of our sample. To prevent Type 1 error, alpha value (*P* value) was set to less than 0.05. We tried to prevent type 2 errors by setting beta value at 0.80, but our post hoc power was not achieved in some tests, and they are reported in appropriate places.

Categorical variables were analyzed by contingency table, relative risk, absolute risk difference, number needed to treat, and chi-square tests. Means were expressed as mean ± standard deviations. Numerical variables were analyzed by nonparametric Mann–Whitney test if the *P* value of normality of distribution by Shapiro–Wilk was significant, i.e. less than 0.05. If Shapiro–Wilk test showed the *P* value not less than 0.05, then independent *t* test was performed. Levene's test for equality of variances was considered while reporting independent *t* test results from SPSS output. Effect sizes were reported by *r* square value, considered small for 0.01, medium for 0.9, and large if 0.25.

## 4. Results

### 4.1. Baseline characteristics of our sample

A total of 90 subjects were included in this study. The age range was from 5 years to 35 years. Mean age was 17.97 ± 7.27 years. Passive testing, ISO, and ISDN respectively, had a mean of 19 ± 7.41 years, 16.86 ± 7.19 years, and 19.62 ± 7.29 years, and numbers of subjects in each of these groups were 13, 51, and 26, respectively. Age-wise skewness of the whole sample was 0.67, and for ISO group, ISDN, and passive testing group they were 0.8, 0.6, and 0.3, respectively. Mann–Whitney test was performed to check for significant difference between ISO and ISDN group with respect to age, and it was found to be not significant (two-tailed *P* value was 0.91).

Further, out of 90 subjects, there were 46 males and 44 females. Age versus sex comparison by Mann–Whitney test showed no significant difference, i.e. two-tailed *P* value was 0.27. So at baseline, groups were comparable with respect to age, sex, and drug used. (See Table 2 and refer Supplementary Appendix 1.)

**Table 1**
Classification of HUTT-positive response.[5]

| | |
|---|---|
| Type 1 Mixed | Heart rate falls at the time of syncope but the ventricular rate does not fall to less than 40 beats $min^{-1}$ or falls to less than 40 beats $min^{-1}$ for less than 10 s with or without asystole of less than 3 s. Blood pressure falls before the heart rate falls. |
| Type 2 Cardioinhibitory | (A) Cardioinhibition without asystole. Heart rate falls to a ventricular rate less than 40 beats $min^{-1}$ for more than 10 s but asystole of more than 3 s does not occur. Blood pressure falls before the heart rate falls.<br>(B) Cardioinhibition with asystole. Asystole occurs for more than 3 s. Blood pressure falls with or occurs before the heart rate fall. |
| Type 3 Vasodepressor | Heart rate does not fall more than 10% from its peak at the time of syncope.<br>Exception 1. Chronotropic incompetence. No heart rate rise during the tilt testing (i.e. less than 10% from the pre-tilt rate).<br>Exception 2. Excessive heart rate rise. An excessive heart rate rise both at the onset of the upright position and throughout its duration before syncope (i.e. greater than 130 beats $min^{-1}$). |

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