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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 ± 7.00 min, 9.85 ± 5.84 min, and 7.00 ± 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. (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. Exception 1. Chronotropic incompetence. No heart rate rise during the tilt testing (i.e. less than 10% from the pre-tilt rate). 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}).

Table 2
Baseline comparison of age, sex, and drug used in HUTT.

Parameter	Total number of subjects (*N*)	Mean (age)	Median (age)	Std. deviation (age)	Minimum (age)	Maximum (age)	Skewness	*P* value by Mann–Whitney test	Power for Mann–Whitney test
Sex									
Female	44	17	15	6.74	8	34	1.01	0.27	0.22
Male	46	18.89	18	7.72	5	33	0.40		
Total	90	17.97	16	7.28	5	34	0.67		
Drug used									
Passive testing	13	19	20	7.41	10	31	0.32	0.91	0.33
ISO	51	16.86	15	7.17	5	34	0.87		
ISDN	26	19.62	17.5	7.28	11	34	0.61		
Total	90	17.97	16	7.28	5	34	0.67		

Table 3 reveals that, of the 90 subjects, 39 were concluded as negative, one subject had postural orthostatic tachycardia, and one more had Pseudo syncope. Remaining 59 had Type 1 (24 subjects), Type 2 (12 subjects), and Type 3 (13 subjects) response.

4.2. Comparison of sensitivity of ISO versus ISDN for HUTT positivity

77 subjects were subjected to either ISO or ISDN. Of 26 subjects of ISDN group, 9 had syncope or presyncope, and in ISO group of 51 subjects, only 20 had syncope and presyncope included in Type 1 or Type 2 or Type 3 responses. The relative risk of positive ISO was 60%, with confidence interval of 0.39–0.93; Fisher's exact test *P* value was 0.03 and Pearson chi-square test *P* value was 0.03, and both were significant (but *P* value by continuity correction was not, i.e. 0.05). Suggesting the use of ISDN leads to higher positive results compared to ISO. The absolute risk difference was 26%, suggesting 26% increase chance of getting positive HUTT with ISDN as compared to ISO; the number needed to treat was 3.82. Specificity and sensitivity of these agents is not mentioned because there is no gold standard test for diagnosing vasovagal syncope. Refer Supplementary Appendix 2 for further details.

4.3. Comparison of frequency of type of responses with respect to passive testing, ISO, and ISDN

49 subjects were HUTT positive, i.e. Type 1, Type 2, or Type 3 responses. Confidence interval was 1.53–2.02. Chi-square test was performed and it showed no significant difference in frequency of types of HUTT positive with respect to passive testing, ISO, and ISDN, i.e. Fisher's exact test *P* value was 0.71 and χ^2 test goodness of fit for the contingency table post hoc Power achieved was 0.82. Refer Supplementary Appendix 3.

4.4. Comparison of time to positive response with respect to ISDN, ISO, and passive testing

Time to response in 49 HUTT-positive patients was studied. Passive testing significantly took more time to produce a positive test as compared to ISDN and ISO. This was tested by an independent *t* test; ISO versus passive test *P* value was 0.007; 95% confidence limit was 1.96–11.34 and effect size by *r* square was 0.009 (small effect). Independent *t* test for passive testing and ISDN revealed the *P* value was 0.001; 95% confidence interval was 4.85–14.15 and *r* square effect size was 0.08 (medium effect). See Tables 4 and 5 and refer Supplementary Appendix 4.

There was no significant difference between ISO and ISDN time to response positive test. Independent *t* test showed *P* value as 0.074; 95% confidence interval was −0.29 to 5.99; post hoc power estimated using G power showed a value of 0.42. (Not sufficient to find a difference, we need a bigger sample.) See Tables 4 and 5 and refer Supplementary Appendix 4.

Table 3
Cross-tabulation of type of response and drug used.

Response type	Drug used			Total
	Passive testing	ISO	ISDN	
Negative	0	30	9	39
Type 1	6	11	7	24
Type 2	4	3	5	12
Type 3	2	6	5	13
POT	0	1	0	1
Pseudosyncope	1	0	0	1
Total	13	51	26	90

5. Discussion

Utility of HUTT has been questioned in recent years; however, it has a profound value in VVS and also in variety of other conditions.[6] In a study by Udani et al., of the HUTT-positive sixteen children, seven were on long-term antiepileptic drugs, but only two had epileptiform abnormalities on their electroencephalogram (EEG).[7]

Apart from this, HUTT utility is also extendable to patients with cardiac syncope, i.e. HOCM,[8] aortic stenosis, and sick sinus syndrome, because syncope in these cases may also be associated with autonomic dysfunction.[9]

In carotid hypersensitivity subjects with syncope, pacing in HUTT-negative subjects resulted in greater clinical benefit than in subjects with HUTT-positive subjects.[10,11] Thus, HUTT has its utility in syncope apart from VVS and this makes the test still a valid one.

Current study results have shown that ISDN has a 26% increased chance of getting positive HUTT as compared to ISO. Similar findings were observed in a meta-analysis conducted by Forleo et al.[12]

Table 4
Time to positive response with respect to passive testing, ISO, and ISDN in minutes.

Drug used	*N*	Minimum	Maximum	Mean	Std. deviation
Passive testing	12	5	27	16.50	7.00
ISO	20	1	20	9.85	5.84
ISDN	17	2	15	7.00	3.35

Table 5
Time to positive response.

Comparison	*P* value	95% confidence interval	Effect size, *r*	Power
Passive testing versus ISDN	0.001	4.85–14.35	0.08	
Passive testing versus ISO	0.007	1.96–11.34	0.009	
ISDN versus ISO	0.074	−0.29 to 5.99		0.42

In this study, there is no difference in the type of responses between the different modalities of HUTT. Although ISO is a sympathomimetic drug, ISDN is a venodilator (both have different mechanisms of precipitation of syncope). Our study did not show any difference in frequency of types of responses, i.e. Type 1 (mixed), Type 2 (cardioinhibitory), and Type 3 (vasodepressor) across passive testing, ISDN, and ISO.

We also compared the time to get a positive response between passive testing, ISDN, and ISO. It was found that ISDN had the lowest mean (7.00 ± 3.35 min), followed by ISO (9.85 ± 5.84 min); longest time to get positive response was with passive testing (16.50 ± 7.00 min). The difference between passive testing compared to ISDN, and passive testing compared to ISO was statistically significant. But, ISDN compared to ISO was statistically not significant see Table 5.

Post hoc power analysis of our study showed a power of 0.44; this means, our sample size was not adequate to find difference between ISDN and ISO. To achieve a power of 0.8, we needed in each group 47 subjects and totally 94 subjects; but our sample was 20 and 17 for ISO and ISDN, respectively. In a study by Zeng et al., they found significant less duration of test time for ISDN as compared to ISO, i.e. 24.84 ± 35.15 versus 35.7 ± 6.28 min [$P < 0.01$].[13] We had excluded the patients above the age of 35 years in the current study, because ISO was less used above the age of 35 years. Our sample size was reduced by excluding those subjects, and so as to recheck the hypothesis, we did nonparametric test on all 198 subjects. This showed the significant P value of 0.02 for difference in time to positive response between ISDN and ISO. Refer Supplementary Appendix 5. Our P value for 94 subjects was 0.07, which is very much near to significant P value, i.e., 0.05. This value of 0.07 means there is 93% chance that ISDN has lesser time to get positive response as compared to ISO. Further, on taking the whole sample of 198 subjects, significant P value was achieved, which is 0.02. Apart from this, as mentioned above in a study, Zeng et al. have found that ISDN has lesser time to positive response in comparison to ISO. So, we believe that, if we had larger sample, we would have got difference between ISO and ISDN time to positive response. Likewise, there may be other unexplored factors that could have contributed for this insignificant finding.

6. Limitation

The limitations of our study are the following. It was a retrospective study. We could not include all patients who were referred for HUTT because ISO was less used in people who were above the age of 35 years, and so they were excluded from our study; this lead to decrease in sample size and reducing the power of our study.

7. Conclusion

Our study showed that the chances of getting positive HUTT by ISDN is 26% more, as compared to ISO, in subjects who failed to develop positive HUTT during passive testing. Although the mechanism of production of syncope by ISO, ISDN, and passive testing are different, our study showed no difference in incidence of type of positive HUTT, i.e. mixed, cardioinhibitory, or vasodepressor response. HUTT is a time-consuming process; time spent to get a positive response by passive testing was highest and statistically significant compared to ISDN and ISO. Even though the mean time for ISDN was lower in comparison to ISO, this finding was not statistically significant. This insignificant finding may be due to the smaller sample size and other factors.

Conflicts of interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ihj.2016.06.007.

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