Original Article

Head-Up Tilt Table Testing with Sublingual Isosorbide Dinitrate in the Diagnosis of Vasovagal Syncope in Children

Çocuklarda Vazovagal Senkop Tanısı İçin Dilaltı İzosorbit Dinitrat ile Yapılan Tilt Testi

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Abstract

Objective: To evaluate the effect of sublingual administration of ISDN on the results of the head-up tilt table test (HUTT) in children and adolescents with vasovagal syncope.

Materials and Methods: The study group consisted of 30 children, each with at least one incidence of vasovagal syncope, and the control group had 15 healthy children. The patients were tilted upright at an angle of 60° for 15 minutes. If the test was negative, sublingual ISDN was administered and the test was continued for an additional 15 minutes.

Results: The sensitivity and specificity of the basal test were 30% and 100%, respectively. Although the specificity decreased somewhat (93.3%) after sublingual ISDN, the sensitivity significantly increased to 96.7%. No severe complications were observed after sublingual ISDN administration.

Conclusion: Our results suggested that sublingual ISDN is a useful, effective and safe agent for pharmacologic stimulation and measurement of the HUTT in children. It increased the sensitivity of the test with a slight decrease in specificity.

Keywords: Head-up tilt table test, Isosorbide dinitrate, Children

Özet

Amaç: *Bu çalışmada vazovagal senkoplu çocuk ve adölesanlarda dilaltı izosorbit dinitratın tilt testi sonuçları üzerine olan etkisinin araştırılması amaçlandı.*

Gereç ve Yöntem: *En az bir vazovagal senkop öyküsü olan 30 çocuk çalışma grubunu ve 15 sağlıklı çocuk kontrol grubunu oluşturdu. Hastalar 15 dakika süre ile 60°'lik açıdaki tilt masasında tutulduktan sonra, eğer test negatif ise, dilaltı izosorbit dinitrat (İSDN) (0.1 mg/kg) verilerek 15 dakika daha teste devam edildi.*

Bulgular: *Bazal testin sensitivitesi % 30 ve spesifitesi % 100 olarak bulundu. Dilaltı İSDN verildikten sonra testin spesifitesi bir miktar düşerken (%93,3) sensitivitesi belirgin olarak yükseldi (%96,7). Dilaltı İSDN verildikten sonra ciddi bir komplikasyon gözlenmedi.*

Sonuç: *Sonuç olarak verilerimiz dilaltı İSDN'ın çocuklarda tilt testinde kullanışlı, etkin ve güvenli bir farmakolojik stimulan ajan olduğuna işaret etmektedir.*

Anahtar Kelimeler: *Tilt testi, İzosorbid dinitrat, Çocuklar*

Introduction

Vasovagal syncope is the most common type of syncope in children and adolescents [1-3]. Although clinical history is the gold standard for diagnosis, the head-up tilt table test (HUTT) is widely used in children with unexplained syncopes [4-6]. However, the diagnostic value of the passive period (without provocation) is limited [7,8]. Intravenous isoprotrenol is commonly used as a pharmacologic stimulant to increase the diagnostic yield of the HUTT [9]. However, intravenous isoproterenol is not commercially available in Turkey. In adults, sublingual isosorbide dinitrate (ISDN) has been used as an alternative to intravenous isoproterenol [10-13], however, data on its usefulness in children is limited [1,14,15]. In this study, we evaluated the effect of sublingual administration of ISDN on the results of the HUTT in children and adolescents with vasovagal syncope.

Materials and Methods

The study group consisted of thirty children, each with at least one incidence vasovagal syncope. The histories were suggestive of typical vasovagal syncope. Before performing the HUTT, other causes of syncope were excluded by physical examination, orthostatic blood pressure testing, routine laboratory measurements, and a cardiovascular workup consisting of an electrocardiogram (ECG), echocardiogram, and 24-hour Holter ECG monitoring. Electroencephalogram was performed, if clinically required. Fifteen healthy children from the same age group were included in the control group.

Tilt Protocol:

All patients remained in the supine position for 10 minutes on a motorized tilt-table, with footboard support. The basal values of blood pressure and heart rate were obtained. Then, the table was tilted upright at a 60°angle. As symptoms (syncope or presyncope) developed during head-up tilt, the tilt-table was lowered to the supine position and the test was terminated. If no symptoms occurred during the passive period, sublingual ISDN (0.1 mg/kg) [14] was given at the 15th minute of the test, while the patient was in the upright position. The test was continued for an additional 15 minutes or until symptoms occurred. The blood pressure was measured at 5-minute intervals by a manual sphygmomanometer, and cardiac rhythm was monitored continuously by a three-lead cardiac monitor.

Table 1. HUTT results during the basal test and after sublingual isosorbide dinitrate administration

Group	Basal test			Sublingual ISDN		
	N	Positive	Negative	N	Positive	Negative
Study	30	9 (30%)	21 (70%)	21	20 (95.3%)	1 (4.7%)
Control	15	0 (0%)	15 (100%)	15	1 (6.7%)	14 (93.3%)

ISDN: isosorbide dinitrate

Table 2. Observed hemodynamic responses in children with positive HUTT results (n=29), during the passive period or after sublingual ISDN administration

Response	Basal test (n=9)	Sublingual ISDN (n=20)
Cardioinhibitory	3 (33.3%)	1 (5%)
Vasodepressor	0	2 (10%)
Mixed-type	6 (66.7%)	17 (85%)

ISDN: isosorbide dinitrate

The control group was studied in the same manner. Informed parental consent was obtained from the study and control patients.

If the patient developed presyncope, syncope, a sudden fall in systolic blood pressure (of >25 mm Hg) or a heart rate (of >30 beats/min), the test result was considered positive, and the patient was immediately returned to the supine position. A marked decrease in systolic blood pressure without a significant decrease in heart rate during symptoms was defined as a vasodepressor response. A cardioinhibitory response was characterized by an abrupt decrease in heart rate without a decrease in blood pressure. A mixed-pattern response was defined as a decrease in blood pressure and heart rate [1,14].

Results

The mean age of the patients with syncope was 12.1±2.3 years (range 7-15 years), and 17 (56.7%) of them were female. We identified 12 patients (40%) with one syncope attack, and 18 (60%) had at least two attacks. During the passive period, nine patients (30%) had a positive response to the HUTT at the median 10th minute (range 4-15 minutes) of the test. Of the remaining 21 patients, 20 (95.3%) had a positive response after sublingual ISDN. In these patients, the median time from ISDN administration to symptoms was 7 minutes (range 4-17 minutes). The time until the display of symptoms was shorter with sublingual ISDN, compared with the passive period (7.5±3.1 and 10.2±4.1 minutes, respectively, p=0.04). In each case, the patients believed that the symptoms produced by testing were the same as those that occurred during the clinical episodes of syncope.

The mean age of the control group was 10.6±1.5 years, and seven were female. None of the control patients developed syncope/presyncope during the basal test. Only one of them had a positive response to the HUTT after sublingual ISDN administration (table 1). The types of positive reactions during the HUTT are given in table 2.

Although the most common positive reaction was of the mixed type in both groups, the cardioinhibitory reaction occurred more frequently during the passive period than ISDN. The difference in the frequencies between the types of positive reactions during the passive period and after sublingual ISDN was not significant (2=4.776, p=0.09)

The sensitivity and specificity of the basal test were 30%

and 100%, respectively. Although the specificity somewhat decreased (93.3%) after sublingual ISDN, the sensitivity significantly increased to 96.7% (Table 3).

The mean decrease in heart rate and systolic blood pressure during symptoms were not significantly different between positive responders in the passive period and after sublingual ISDN (p=0.164 and p=0.905, respectively).

Table 3. Sensitivity and specificity of the HUTT during the passive period and after sublingual ISDN administration

	15 min basal testing %	15 min sublingual ISDN%	Total %
Sensitivity	30	95.3	96.7
Specificity	100	93.3	93.3

ISDN: isosorbide dinitrate

Discussion

Vasovagal syncope is the most common cause of syncope in children and adolescents [16]. Although its diagnosis depends on the clinical history, the HUTT has been applied in the diagnostic evaluation of cardiovascular syncope in children with recurrent syncope [4,17,18]. Varying results of accuracy have been reported, and it is mostly the result of different tilt test protocols [14,19]. Several factors, including age, angle and duration of tilt, time of day and intravenous cannulation can alter the results [20]. Positive diagnostic rates in children vary from 10% to 44% for passive head-up tilt [6,21-24]. Pharmacologic stimulation with intravenous isoproterenol has commonly been used to increase the diagnostic yield of the HUTT. When tilting is augmented by isoproterenol, positive rates increased to 80% [17]. Catecholamine-associated complications, such as ventricular arrhythmias, and a high percentage of false-positive results have indicated the need for an alternative to isoproterenol. In addition, intravenous isoproterenol is not commercially available in our country. Therefore, another option is needed. In adults, sublingual administration of ISDN has been used as an effective alternative to intravenous isoproterenol [10-13], however, the data in children is limited [1,14,15].

Organic nitrates are potent venodilators and are known to cause syncope by venous pooling. Decreased venous return induces cardiac emptying that triggers ventricular mechanoreceptors, resulting in bradycardia and hypotension [25-27].

The first study was done by Dindar et al. (14), who reported on a sublingual isosorbide-augmented (0.1 mg/kg) HUTT in children. They tilted the table to 70° and waited for 45 minutes. In the absence of symptoms, they returned the patient to the supine position, administered ISDN sublingually, waited for 5 minutes and again tilted the table to 70° for an additional 15 minutes. The sensitivity and the specificity of the passive test was found to be 15% and 100%, respectively; these increased to 77.5% and decreased to 91.6%, respectively, after sublingual ISDN administration. They concluded that the isosorbide- augmented HUTT is suitable for routine clinical practice in children.

Vlahos et al. [15] compared the results of sublingual nitroglycerin and intravenous isoproterenol. After a negative, basal HUTT, performed at an 85 tilt-angle for 20 minutes, they administered sublingual nitroglycerin (400 µg) to one group and intravenous isoproterenol to another group of patients, and continued tilting for an additional 20 minutes. The sensitivity for isoproterenol- and nitroglycerin-augmented HUTTs were 78% and 79%, respectively. The specificity values were 100% and 67%, respectively. Although they did not observe serious adverse effects, they reported significantly prolonged vasovagal symptoms after sublingual nitroglycerin. Based on this result and the lower specificity, they did not support the routine use of nitroglycerin in the evaluation of syncope in pediatric age group.

Swissa et al. [1] compared the diagnostic value and safety of sublingual ISDN with intravenous isoproterenol during the HUTT in pediatric patients with suspected neurocardiogenic syncope. The patients stayed on a tilt-table inclined at a 70 angle for 20 minutes. After a negative passive phase, the patients underwent consecutive rounds of the HUTT with 1.25 to 2.5 mg sublingual ISDN or intravenous isoproterenol administrations (1-3 µg/min) for 20 minutes. The sensitivities of the passive test, and the ISDN- and isoproterenol-augmented tests were found to be 17.6%, 24.1% and 55.5%, respectively. In this study, the time for symptoms to develop was shorter with both ISDN and isoproterenol compared with passive period, and the severity of the cardioinhibition response was significantly higher with ISDN compared with the passive period and isoproterenol. Their results indicated that administration of sublingual ISDN was less sensitive and less safe than intravenous isoproterenol in children with suspected vasovagal syncope [1].

In our study, we did not observe any serious adverse effects during the sublingual ISDN-augmented HUTT. When compared to the passive period, sublingual ISDN administration increased the sensitivity of the test from 30% to 96.7%. However, the specificity did not decrease significantly. Our results are apparently higher than that of three other studies [1,14,15], probably due to the tilt protocol. In addition, the type and the dose of nitrate used could have affected the results.

Although we did not evaluate the severity of the symptoms, changes in heart rate and systolic blood pressure were not significantly different during positive reactions with the passive test and after sublingual ISDN. Further, the difference in the frequencies between the types of positive reactions during the passive period and sublingual ISDN treatment was not significant.

In conclusion, our results suggested that sublingual ISDN is a useful, effective and safe agent for pharmacologic stimulation and assessment of the HUTT in children. It increases the sensitivity of the test, with a slight decrease in specificity.

Conflict interest statement The authors declare that they have no conflict of interest to the publication of this article.

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