Predictors of vasovagal syncope recurrence in children and adolescents and value of head-up tilt table test

Çocuk ve ergenlerde senkop yinelemesinin öngördürücüleri ve tilt testinin bu süreçteki rolü

Sibel Tanrıverdi Yılmaz, Köksal Binnetoğlu, Kadir Babaoğlu, Gürkan Altun

Department of Pediatrics, Faculty of Medicine, Kocaeli University, Kocaeli-*Turkey*

ABSTRACT

Objective: The aim of the study was to define predictors of syncope recurrence in children and adolescents with vasovagal syncope and to determine the value of tilt test.

Methods: A retrospective observational study performed of prospective cohort of 150 patients aged between 8-18 years who were referred to our clinic because of fainting or who underwent tilt test with the pre-diagnosis of vasovagal syncope. The progress updated by telephone or face-to-face interview. Unpaired t-test, Mann-Whitney U test used for normal and non-normal distributed variables. Logistic regression analysis was used to determine the predictors of recurrence.

Results: Tilt test was positive in 97 and negative in 53 patients. Forty-eight patients had mixed, 34 had vasodepressor and 15 had cardioinhibitory type syncope. Recurrence found significantly higher in patients who had syncope in the first 20 minutes of the test (p=0.012). The number of the episodes decreased after the test; 3.86±4.75 vs 0.73±0.44, p<0.001). The recurrence was higher in patients who had more than 4 episodes. The recurrence was similar between positive and negative tilt groups. Age of syncope (OR 1.01, 95% CI 1.002, p=0.027) positive family history (OR 4.47, 95% CI 1.071-1.389, p=0.001) and the number of previous syncopal episodes (OR 1.22, 95% CI 1.882-10.623, p=0.003) were identified as risk factors for recurrence of vasovagal syncope.

Conclusion: Age of syncope, positive family history and the number of previous syncopes are the predictors of recurrence of vasovagal syncope in children and adolescents. The number of recurrent episodes decreased after the test independently from Head-up tilt test results.

(Anadolu Kardiyol Derg 2013; 13: 688-94)

Key words: Syncope, tilt test, children, regression analysis, predictive value

ÖZET

Amaç: Bu çalışmada vazovagal senkoplu çocuk ve adölesanlarda senkop yinelemesinin öngördürücülerini saptamak ve tilt testinin bu süreçteki değerini belirlemek amaçlanmıştır.

Yöntemler: Kliniğimize daha önce bayılma nedeniyle başvuran ve senkop nedeni açıklanamayan veya vazovagal senkop düşünülerek tilt testi yapılmış, 8-18 yaş arası 150 hastanın kayıtları ileriye dönük retrospektif gözlemsel olarak değerlendirilerek, son durumları telefon veya yüz yüze görüşülerek güncellendi. Normal ve normal olmayan değişkenler için t-testi ile Mann-Whitney U testi, vazovagal senkop rekürrens öngördürücülerinin saptanması için lojistik regresyon kullanıldı.

Bulgular: Tilt testi yapılan 150 hastanın 97'sinde tilt testi pozitif, 53'ünde negatif bulunmuştur. Tilt testi 48 hastada mikst, 34 hastada vazodepresör ve 15 hastada kardiyo-inhibitör şeklindeydi. Tilt testi 65 hastada pasif, 32 hastada provokatif fazda pozitifleşti. Testin ilk 20 dakikası içinde senkop görülenlerde anlamlı olarak senkop yinelemesinin daha fazla olduğu gözlendi (p=0,012). Tilt testi yapılana kadar tüm hastalarda senkop sayısı ortalama 3,86±4,75 iken test yapıldıktan sonra senkop sayısı ortalama 0,73±0,44 olarak bulundu (p<0,001). Daha önce dörtten fazla senkop geçirenlerde yineleme oranı daha yüksek bulundu. Tilt testi pozitif ve negatif olanlarda yineleme oranları arasında istatistiksel olarak fark saptanmadı. Senkop yaşı (OR 1,01, %95 CI 1,002, p=0,027), pozitif aile öyküsü (OR 4,47, %95 CI 1,071-1,389, p=0,001), daha önceden geçirilmiş senkop atak sayısı (OR 1,22, %95 CI 1,882-10,623, p=0,003), senkop yinelemesinin bağımsız öngördürücüleri olarak saptandı.

Sonuç: Senkop yaşı, pozitif aile öyküsü ve önceden geçirilmiş senkop atak sayısı çocuk ve ergenlerde senkop yinelemesinin bağımsız öngördürücüleridir. Yinelenen senkop sayısının tilt testi sonuçlarından bağımsız olduğu belirlenmiş ve testten sonra atak sayısının azaldığı saptanmıştır.

(Anadolu Kardiyol Derg 2013; 13: 688-94)

Anahtar kelimeler: Senkop, tilt testi, çocuklar, regresyon analizi, öngördürücü değer

Address for Correspondence/Yazışma Adresi: Dr. Köksal Binnetoğlu, Kocaeli Üniversitesi Tıp Fakültesi, Çocuk Kardiyolojisi Bilim Dalı, Umuttepe Kampüsü, İzmit, Kocaeli-*Türkiye* Phone: +90 262 303 80 35 Fax: +90 262 303 80 03 E-mail: koksaldr@yahoo.com

Accepted Date/Kabul Tarihi: 26.02.2013 **Available Online Date/Çevrimiçi Yayın Tarihi:** 28.08.2013

doi:10.5152/akd.2013.194

Introduction

Syncope is defined as transient loss of consciousness and postural tone resulting from an insufficient supply of oxygen to the brain. It may occur at all ages but especially in children and adolescents (1). It is one of major complaint for 1% of all emergency admissions (2) and incidence is reported to be about 125.8 per 100 000 children (3). It is believed that at least 15% of all children will experience a syncopal episode before the end of the second decade (4-6). The incidence is higher in females than for males and a peak incidence in the 15-19 year-old age group (3). Although it is usually a benign disorder, recurrent syncope may be harmful, may lead to trauma or injury and may induce anxiety. There are many causes of syncope, the most common is neurally-mediated syncope (NMS), sometimes defined as vasovagal syncope or reflex syncope or neurocardiogenic syncope (7). A careful history and physical examination, including lying and standing blood pressure (BP) measurement while lying and standing, heart rate (HR) measurements and a routine electrocardiography (ECG) are essential to make an accurate diagnosis (8-11). Although Head-up tilt test (HUTT) is a practical and useful test for the evaluation of syncope (12-14), it is still unclear who are under high risk for recurrent syncope.

The aim of the study was to define predictors of syncope recurrence in children and adolescents with vasovagal syncope.

Methods

Study design

A retrospective observational study performed on prospective cohort of patients.

Study population

The study group contained children and adolescents aged between 8-18 who were referred to our clinic because of recurrent syncope or pre-syncope between the years 2007-2011 prospectively included in the study. The patients who had underlying major structural heart disease, long QT or Brugada syndrome, and who had medication known to affect heart rate or to cause orthostatic hypotension were excluded. The patients were divided into two main groups according to the result of HUTT. Group 1 included HUTT positive and group 2 included HUTT negative patients. Main groups were divided into recurrent and non-recurrent subgroups.

Patients' history before and after HUTT

The records of 150 patients who underwent HUTT with the history of recurrent syncope or pre-syncope since 2007 were scanned retrospectively and the progress of the patients were also updated by telephone or face-to-face interview. The families were informed about the study and consent form was taken from the participating families. The number of syncopal episodes and associated symptoms, prodromes, triggers, previous tests, indications for HUTT, the HUTT itself and clinical outcomes were evaluated by a standard questionnaire. The posture at the time of episode, the presence of trauma and the time of unconsciousness were also recorded. After HUTT, children and their family were educated to record their symptoms and asked to inform our department after a syncopal episode.

Recurrence

Recurrence was defined as the reappearance of vasovagal syncope after HUTT.

Physical and laboratory examination

All patients with syncope and pre-syncope were examined comprehensively to rule out neurologic and cardiovascular diseases. The blood pressure, heart rate and the presence of murmur were recorded.

Whole blood count, renal and liver function tests, 12 lead electrocardiography and if needed electroencephalography were performed in the patients who were referred to our clinic because of recurrent syncope or pre-syncope. Patients with murmur and arrhythmia underwent echocardiography and 24-hour Holter monitoring.

Head-up tilt test protocol

Informed parental consent was obtained for each patient. All patients were asked to stop the administration of drugs that could affect the automatic nerve function for at least 3 days and to fast for 12 hours before the tilt test. The tilt test was preceded by 5 minutes of observation in a supine position, and blood pressure, heart rate, and ECG were recorded before the tilt test. A 60 degree tilt was used for subjects until the syncope develops or for 45 minutes and if no symptoms occurred after this passive phase, 400 µg sublingual nitroglycerin was administrated and monitored for 15 minutes for the development of syncope. Blood pressure, heart rate, and 12-lead ECG were monitored continuously. Children were placed in a supine position as soon as the syncope occurred. First-aid drugs were available at all times. A vasovagal response was considered when hypotension, or bradycardia, or both were observed (15). Asystole was defined as a pause greater than 5 second(s) (16).

The syncopal phase was classified according to a modification of the original VASIS classification (17).

Type 1 mixed. Heart rate falls at the time of syncope, but the ventricular rate does not fall to less than 40 beats /min, or falls to less than 40 beats/min for less than 10 second with or without asystole of less than 3 second. Blood pressure falls before the heart rate falls.

Type 2A, cardioinhibition without asystole. Heart rate falls to a ventricular rate less than 40 beats/min for more than 10 s, but asystole of more than 3 s does not occur. Blood pressure falls before the heart rate falls.

Type 2B, cardioinhibition with asystole. Asystole occurs for more than 3 s. Heart rate fall coincides with or precedes blood pressure fall.

Type 3 vasodepressor. Heart rate does not fall more than 10%, from its peak, at the time of syncope.

Statistical analysis

For statistical analysis, SPSS software (SPSS Inc. SPSS version 13.0., Chicago, Illinois, USA) was used. Statistical analysis was used to characterize children with positive and negative tilt responses, children with recurrence of syncope. Continuous variables are given as mean±SD; categorical variables were defined as percentage. Differences for continuous variables between normally distributed groups were examined for statistical significance with a two-sample t-test and with the Mann-Whitney U test for non-normal distributed variables. Chi-square test used for the categorical variables. Forward stepwise logistic regression analysis (odds ratio, 95% CI and p value) was used to determine the predictors of recurrence of vasovagal syncope. The two tailed p value≤ 0.05 was considered statistically significant.

Results

The features of study group

The study included 150 patients (100 female-50 male) who underwent HUTT because of repeating syncope and pre-syncope aged between 8-18 years. The average age of first syncope was mean 12.3±3.1 years. The average follow-up period ranged between 3-78 months (mean 23±14 months). The average number of previous syncope was 3.8±4.7 in the application (Table 1). 69.3% of patients had syncope while standing and 33% of them had syncope while exercising. Dizziness (41%) and blurred vision (21%) were the most frequent prodromal symptoms.

Physical examination and laboratory findings

Thirteen patients (8.7%) had the diagnosis of neurologic disorders such as epilepsy, hyperactivity and migraine. Minor cardiac pathologies such bicuspid aorta, mild aortic stenosis, mild mitral regurgitation, mitral valve prolapse were detected in 21 patients (14%) which were thought not to cause syncope or presyncope.

HUTT results

The patients were divided into two groups according to the result of HUTT. Group 1 included 97 (64.6%) HUTT positive and group 2 included 53 (34.6%) HUTT negative patients. The mean occurrence time of syncope during HUTT was 13.1±10.2 minutes. HUTT was positive in the 70% of females. But it was positive in the 54% of males (p<0.005). The number of previous syncopal episodes were similar in both subgroups. The features of patients who underwent HUTT are shown in Table 2.

Recurrence (number of episodes after HUTT)

Twenty-seven of 100 female patients and 13 of 50 male patients had recurrent syncopal episode (p=0.89). The recurrence rate was higher in older patients (p=0.028). In addition, recurrence rate was found higher in smoking patients and in patients who had previous family story (p=0.043 and 0.001). One hundred and eight patients had less than 3 previous syncopal episodes and 42 patients had more than 4 previous syncopal episodes. The recurrence rate was found higher in the patients who had more than 4 previous syncopal episode (p<0.001). The effect of HUTT on recurrence was evaluated and we found that the number of previous syncopal episodes till HUTT was performed was mean 3.86±4.75 but after HUTT it decreased to 0.73±0.44 (p<0.001). Twenty-four of

Table 1. The clinical features of the patients

Clinical features	
Gender, M/F, n (%)	100(66.7)/50(33.3)
Age at initial syncope[1], years	11.6±3
Age at HUTT, years	12.3±3.1
Syncope episode[1], n	3.8±4.7
Duration of symptoms[1], months	8.5±10.6
Follow-up[1], months	23±14
Pre-syncope only, n, M/F	17 (8/9)
Triggering factors, n (%)	125 (83)
Prodromal symptoms, n	150
Trauma, n (%)	24 (16)
Convulsion, n (%)	11 (7.3)

Data are presented as number (percentage) or mean±SD
[1]Age- The time of initial syncope, Duration of symptoms- The time from the initial syncope till HUTT was performed (month), Follow-up period- Time from HUTT till the time of interview(month), syncope episode-The number of episodes before HUTT.
F - female, HUTT - head-up tilt test, M - male

Table 2. The features of the patients who underwent HUTT

Variables	HUTT positive (n=97)	HUTT negative (n=53)	*p
Sex, F/M	70/27	30/23	0.050
Age, years	11.5±2.9	11.7±3.3	0.710
Number of previous syncope, n	3.9±5.1	3.7±3.9	0.786
Duration of symptoms, months	8.5±11.4	8.5±9.1	0.993
Only pre-syncope, n (%)	12 (12.3)	5 (9.4)	0.123
Trauma during syncope, n (%)	14 (14.4)	10 (18.8)	0.479
Convulsion during syncope, n (%)	6 (6.1)	5 (9.4)	0.462
Heart rate at rest, beat/minute	92±15	90.8±16.4	0.475
Systolic blood pressure at rest, mmHg	104.4±13.2	106.2±10.8	0.562
Smoking/alcohol, n (%)	6 (6.1)	3 (5.6)	0.897

Data are presented as number (percentage) or mean±SD
*unpaired t-test and Chi-square test
F - female, HUTT - head-up tilt test, M - male

Table 3. Comparison of clinical characteristics in recurrent and non-recurrent groups

Variables	Recurrent group (n=40)	Non-recurrent group (n=110)	*p
Sex, F/M, n	27 / 13	73 / 37	0.896
Age at initial syncope, years	12.5±2.9	11.3±3	0.028
Age at HUTT, years	13.4±2.7	11.9±2.8	0.205
Previous syncopal episode, n	6.3±7.6	2.9±2.6	<0.001
Duration of symptoms, months	10.7±11.3	7.7±10.2	0.126
Follow-up period, months	26.5±14.1	22.3±13.9	0.121
Family story, n (%)	28 (70)	44 (40)	0.001
Trauma during syncope, n (%)	9 (22.5)	15 (13.6)	0.190
Smoking, n (%)	5 (12.5)	4 (3.6)	0.043

Data are presented as number (percentage) or mean±SD
*unpaired t-test and Chi-square test
F - female, HUTT - head-up tilt test, M - male

Table 4. The electrocardiographic features of recurrent and non- recurrent groups

Variables	Recurrent group (n=40)	Non recurrent group (n=110)	*p
Heart rate, beat/minute	84±12	82.1±11.3	0.390
PR distance, msec	123.6±18.9	128.5±19.1	0.169
QRS duration, msec	77.45±9.42	75.25±16.01	0.416
P dispersion, msec	34.1±9.1	35.5±8.5	0.427
QTc dispersion, msec	22.73±12.9	19.3±10.3	0.103

Data are presented as mean±SD
*unpaired t-test

150 patients had previous history of trauma during syncope but only 9 of them had recurrent syncope. So recurrence rate was not statistically significant in trauma positive and trauma negative patients (p=0.190) (Table 3).

The electrocardiographic parameters found similar in recurrent and non-recurrent group. There was not statistically difference between both recurrent and non-recurrent group (Table 4).

Recurrent syncope was observed in 16 HUTT- negative patients (30.2%) and 24 HUTT-positive (24.7%) patients (p=0.47). The mean recurrence time of syncope during HUTT was 13.19±10.2 minutes. In HUTT positive group, 65 patients had syncope in passive phase and 32 had in provocative phase of HUTT. In group 1, 15 patients had cardioinhibitor, 34 had vasodepressor and 48 had mixed type vasovagal syncope. Although the recurrence rate was found somewhat higher in patients who had syncope in active phase or in the first 20 minutes of passive phase of HUTT, logistic regression analysis showed no statistically significance (Table 5).

We used forward stepwise logistic regression analysis to determine the predictors of recurrence of vasovagal syncope. We entered gender, age of syncope, HUTT result, QTC and P dispersion, the time of positivity of HUTT, the number of syncope and family history of heart disease as independent variable. Only age of syncope (OR 1.01, 95% CI 1.002, p=0.027) positive family history (OR 4.47, 95% CI 1.071-1.389, p=0.001) and the number of previous syncopal episodes (OR 1.22, 95% CI 1.882-10.623, p=0.003) were identified as risk factors for recurrence of vasovagal syncope (Table 6).

Table 5. Comparison of recurrent and non-recurrent groups according to HUTT

Variables	Recurrent group (n=40)	Non recurrent group (n=110)	*p
HUTT result, n (%)			
- HUTT negative (n=53)	16 (40)	37 (33.6)	0.471
- HUTT positive (n=97)	24 (60)	73 (66.3)	
HUTT stage, n (%)			
- Positive in provocative phase (n=32)	10 (25)	22 (20)	0.297
- Positive in passive phase (n=65)	14 (35)	51 (46.3)	
Type of syncope, n (%)			
- Cardioinhibitor (15%)	3 (7.5)	12 (10.9)	0.557
- Vasodepressor (35%)	11 (27.5)	23 (20.9)	
- Mixed (50%)	10 (25)	38 (34.5)	
Syncope time in HUTT, n (%)			
- 0-20 minutes	14 (58.3%)	34 (46.6%)	0.033
- 21-45 minutes	0	17 (23.3%)	
- >45 minutes	10 (41.7%)	22 (30.1%)	

Data are presented as as number (percentage).
*Chi-square test.
HUTT - head-up tilt test

Table 6. Logistic regression analysis of risk factors for recurrent syncope

Risk factors	OR	95% CI	p
Age	1.01	1.002-1.026	0.027
Family story	4.47	1.071-1.389	0.001
The number of previous syncopal episodes at the admission	1.22	1.882-10.623	0.003

CI - confidence interval of 95%, OR - Estimated relative risk showed by odds ratio

Discussion

HUTT is being increasingly used in the evaluation of syncope in children, and it is still unclear which children are at high risk of recurrent syncope. Risk factors for recurrence have not been well-characterized, but a history of previous syncopal episodes and the number of episodes indicate a greater risk of recurrence. Logistic regression analysis of our study showed that only age of syncope, positive family history and the number of syncope were identified as risk factors for recurrence of vasovagal syncope.

Syncope is a common clinical problem mostly encountered in adolescents. It is observed in 15 of every 100 children before the end of adolescence. The most frequent age that the syncope occurs is between 15-19 years (18, 19). There is not a consensus about the pathophysiology and accurate treatment of syncope. The most common pattern of unexplained syncope in children is vasovagal syncope (3). The imbalance of the autonomic nervous system is thought to be most important cause of vasovagal syncope. Qingyou et al. (20) reported that the majority of patients with vasovagal syncope were over 12 years of age and in whom HUTT was mostly positive. The mean age of our study group was 12±3 years.

The initiative signs before the syncope are dizziness, drowsiness, pallor, sweating, nausea, hyperventilation, cold and moist skin and epigastric tenderness (21). About 63.3% of our patients stated that they were starving before the syncopal episodes; 20% of them had nausea, sweating, blurred vision, and 40% had dizziness. One of the most important features of vasovagal syncope is the development of syncope while standing and 104 of 150 patients had syncope while standing. Fear, excitement, sight of blood and hot bath were the other triggering factors of syncope in our patients.

In one of every three children who are examined because of syncope had a positive relative history with syncope or pre-syncope suggests that familial factors is important in the pathophysiology (22-24). Mathias et al. (25) reported that 28% of patients with syncope had a positive family history, and this ratio rose to 51% in patients with HUTT-proven vasovagal syncope. Also in our study the recurrence rate was found higher in patients with positive family history (p=0.001).

The diagnosis of vasovagal syncope is established by history, physical examination and the exclusion of other etiologies. Amirati et al. (26) stated that the cause of syncope could not be determined by routine tests in 49.6% of patients. The HUTT offers a simple, noninvasive diagnostic tool for evaluation of syncope in children (27). HUTT was introduced into clinical evaluation of patients with syncope of unknown origin by Kenny et al. (28) in 1986. This test enables the reproduction of a neutrally- mediated reflex in laboratory settings. Blood pooling and decrease in venous return due to orthostatic stress and immobilization trigger the reflex. The final effect, hypotension and usually concomitant HR slowing, is related to impaired vasoconstrictor capability followed by sympathetic withdrawal and vagal hyperactivity. The clinical situation corresponding to HUTT is reflex syncope triggered by prolonged standing. Although this test can also be positive in patients with other forms of reflex syncope and in patients with sick sinus syndrome, it has a diagnostic value in vasovagal syncope (29). HUTT is not usually needed in patients whose reflex syncope is already diagnosed by clinical history and in patients with single or rare syncope unless special situations (e.g. injury, anxiety, occupational implications such as aircraft pilots, etc.) (29). Several studies report that girls are more prone to syncope than males (30) and in our study the 66.7% of the patients with syncope or pre-syncope were female.

HUTT positive patients have syncope mostly early in the morning (31). Kula et al. (32) evaluated the QTc dispersion in patients with vasovagal syncope. In this study QTc dispersion was significantly higher early morning and late night in HUTT-positive group compared with HUT-negative group. In our study QTc dispersion wasn't significantly different in HUTT- positive and HUTT- negative patients.

The response to HUTT may be variable. Raviele et al. (33) reported that cardioinhibitory type was more frequent in young patients, but mixed and vasodepressive types were frequent in older patients. But in our study most of the HUTT positive patients were mixed type.

Some studies report epilepsy-like tonic-clonic convulsions during vasovagal syncope. Grubb et al. (34) performed HUTT for 15 patients with treatment- resistant convulsions and showed the diffuse slowdown pattern in EEG in 5 patients but not any epileptiform activity. This may suggest that HUTT may be used to distinguish epilepsy from syncope induced convulsion.

The recurrence rates of syncope is reported to be approximately 35% within 3 years and 82% of them occurs in the first 2 years (35). Sheldon et al. (36) and Koukam et al. (37) reported that the most powerful predictor of syncope recurrence was the total number of historical syncopal spells free from the results of HUTT. The results of our study are compatible with previous reports. As mentioned in previous studies, positive HUTT must not be suggested as an appropriate prognostic indicator but the number of the frequency of recent episodes should be considered as more valuable predictor of recurrence (38). But in contrast, the study of Salim et al. (39) showed that the recurrence rate was higher in HUTT positive patients than in HUTT negative patients. In a study with 190 adult patients, the recurrence rate was found higher in whom arterial baroreflex sensitivity was shown to be decreased within the first minutes of HUTT. This suggests that this parameter should be used as an independent predictor (40). Baron-Esquivias et al. (41) reported that 5 previous episodes were the best predictor of recurrence. Recurrence rate was lower in those patients with <5 (25.1%) than in those patients with ≥5 previous episodes. In that study patients with <5 previous episodes had a syncope-free survival time of 54.1 months (95% CI 49.4-59), but it dropped to 39.6 months (95% CI 32-47) in those patients with ≥5 previous episodes. In our study, the overall recurrence rate for vasovagal syncope has been estimated at 30 percent.

In study of Alehan et al. (42) the reproducibility of HUTT in children was evaluated. In this study the positive HUTT was reproduced in 29 of the 39 patients (74.4%), the negative HUTT was reproduced in 16 of 19 patients (84.2%). The overall reproducibility of a positive or negative HUTT was found 77.6% (45/58). This reproducibility of positive tests could be modified by the so-called 'tilt training effect' described as a therapeutic option in adults and adolescents (43, 44). Our results support these findings. Because, we observed that the number of episodes were shown to be decreased after HUTT.

Study limitations

HUTT is still the gold standard test for vasovagal syncope. But there is not another test to compare the results of HUTT. The other limitation is that we didn't evaluate the reproducibility of HUTT. The recurrence rate of syncopes was determined by face-to face or by telephone interview.

Conclusion

In conclusion our study stated that only age of syncope, family history and the number of syncope were identified as risk factors for recurrence of vasovagal syncope. Interestingly the number of episodes shown to be decreased after HUTT and this may suggest the therapeutic feature of HUTT.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - K.BA., K.Bİ.; Design - S.T.Y.; Supervision - K.BA., S.T.Y.; Resource - S.T.Y., G.A.; Material- G.A.; Data collection&/or Processing - S.T.Y., K.Bİ., G.A.; Analysis &/or interpretation - K.BA., S.T.Y.; Literature search - K.Bİ., G.A.; Writing - S.T.Y., K.BA.; Critical review - K.Bİ., G.A., K.BA.

References

1. O'Laughlin MP. Syncope. In: Garson A, Bricker JT, McNamara DG, ed. The Science and Practice of Pediatric Cardiology. Philadelphia: Lea&Febiger, 1990.p.1929-45.
2. Pratt JL, Fleisher GR. Syncope in children and adolescents. Pediatr Emerg Care 1989; 5: 80-2. [CrossRef]
3. Driscoll DJ, Jacobsen SJ, Porter CJ, Wollan PC. Syncope in children and adolescents. J Am Coll Cardiol 1997; 29: 1039-45. [CrossRef]
4. Ruckman RN. Cardiac causes of syncope. Pediatr Rev 1987; 9: 101-8. [CrossRef]
5. Strasberg B, Sagie A, Rechavia E, Sclarovsky S, Agmon J. The noninvasive evaluation of syncope of suspected cardiovascular origin. Am Heart J 1989; 117: 160-3. [CrossRef]
6. Scott WA. Evaluating the child with syncope. Pediatr Ann 1991; 20: 350-9.
7. Dietz S, Murfitt J, Florence L, Thakker P, Whitehouse WP. Head-up tilt testing in children and young people: a retrospective observational study. J Paediatr Child Health 2011; 47: 292-8. [CrossRef]
8. Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, et al. Task Force on Syncope, European Society of Cardiology. Part 2. Diagnostic tests and treatment: summary of recommendations. Europace 2001; 3: 261-8. [CrossRef]
9. Linzer M, Yang EH, Estes NA 3rd, Wang P, Vorperian VR, Kapoor WN. Diagnosing syncope. Part 1: Value of history, physical examination, and electrocardiography. Clinical Efficacy Assessment Project of the American College of Physicians. Ann Intern Med 1997; 126: 989-96. [CrossRef]
10. Kapoor WN. Syncope. N Engl J Med 2000; 343: 1856-62. [CrossRef]
11. Colman N, Nahm K, van Dijk JG, Reitsma JB, Wieling W, Kaufmann H. Diagnostic value of history taking in reflex syncope. Clin Auton Res 2004; 14: 37-44. [CrossRef]
12. Lerman-Sagie T, Rechavia E, Strasberg B, Sagie A, Blieden L, Mimouni M. Head-up tilt for the evaluation of syncope of unknown origin in children. J Pediatr 1991; 118: 676-9. [CrossRef]
13. Grubb BP, Temesy-Armos P, Moore J, Wolfe D, Hahn H, Elliott L. The use of head-upright tilt table testing in the evaluation and management of syncope in children and adolescents. Pacing Clin Electrophysiol 1992; 15: 742-8. [CrossRef]
14. Thilenius OG, Quinones JA, Husayni TS, Novak J. Tilt test for diagnosis of unexplained syncope in pediatric patients. Pediatrics 1991; 87: 334-8.
15. Sutton R, Petersen M, Brignole M, Raviele A, Menozzi C, Giani P. Proposed classification for tilt induced vasovagal syncope. Eur J Cardiac Pacing Electrophysiol 1992; 2: 180-3.
16. Lacroix D, Kouakam C, Klug D, Guédon-Moreau L, Vaksmann G, Kacet S, et al. Asystolic cardiac arrest during head-up tilt test: incidence and therapeutic implications. Pacing Clin Electrophysiol 1997; 20: 2746-54. [CrossRef]
17. Brignole M, Menozzi C, Del Rosso A, Costa S, Gaggioli G, Bottoni Net al. New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. Vasovagal Syncope International Study Europace 2000; 2: 66-76.
18. Bignole M, Alboni P, Benditt T, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, et al. Guidelines on management (diagnosis and treatment) of syncope. Eur Heart J. 2001; 22: 1256-306. [CrossRef]
19. Carlioz R, Graux P, Haye J, Letourneau T, Guyomar Y, Hubert E, et al. Prospective evaluation of high dose or low dose isoproterenol upright tilt protocol for unexplained syncope in young adults. Am Heart J 1997; 133: 346-52. [CrossRef]
20. Qingyou Z, Junbao D, Jianjun C, Wanzhen L. Association of clinical characteristics of unexplained syncope with the outcome of head-up tilt tests in children. Pediatr Cardiol 2004; 25: 360-4. [CrossRef]
21. Wolfe DA, Grubb BP, Kimmel SR. Head-upright tilt test: A new method of evaluating syncope. Am Fam Physician 1993; 47: 149-59.
22. Márquez MF, Urias KI, Hermosillo AG, Jardón JL, Iturralde P, Colín L, et al. Familial vasovagal syncope. Europace 2005; 7: 472-4. [CrossRef]
23. Cooper CJ, Ridker P, Shea J, Creager MA. Familial occurrence of neurocardiogenic syncope. N Engl J Med 1994; 331: 205. [CrossRef]
24. Lewis SL, O'Toole M. Familial occurrence of neurocardiogenic syncope. N Engl J Med 1994; 331: 1529. [CrossRef]
25. Mathias CJ, Deguchi K, Bleasdale-Barr K, Kimber JR. Frequency of family history in vasovagal syncope. Lancet 1998; 352: 33-4. [CrossRef]
26. Ammirati F, Clivicchi F, Biffi A, Magris B, Pandozi C, Santini M. Head-up tilt testing potentiated with low dose sublingual isosorbide dinitrate: a simplified time- saving approach for the evaluation of unexplained syncope. Am Heart J 1998; 135: 671-7. [CrossRef]
27. Lerman-Sagie T, Rechavia E, Strasberg B, Sagie A, Blieden L, Mimouni M. Head-up tilt for the evaluation of syncope of unknown origin in children. J Pediatr 1991; 118: 676-9. [CrossRef]
28. Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: a useful test for investigating unexplained syncope. Lancet 1986; 1: 1352-5. [CrossRef]
29. Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, et al. Task Force for the Diagnosis and Management of Syncope; European Society of Cardiology (ESC); European Heart Rhythm Association (EHRA); Heart Failure Association (HFA); Heart Rhythm Society (HRS). Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 2009; 30: 2631-71. [CrossRef]

30. Strieper MJ, Campbell RM. Efficacy of alpha adrenergic agonist therapy prevention of pediatric neurocardiogenic syncope. J Am Cardiol 1993; 22: 594-7. [CrossRef]
31. Kula S, Olguntürk R, Tunaoğlu FS, Saygılı A. Distribution of syncopal episodes in children and adolescents with neurally mediated cardiac syncope through the day. Europace 2005; 7: 634-7. [CrossRef]
32. Kula S, Olguntürk R, Tunaoğlu FS, Canter B. Circadian variation of QTc dispersion in children with vasovagal syncope. Int J Cardiol 2004; 97: 407-10. [CrossRef]
33. Raviele A, Brignole M, Sutton R, Alboni P, Giani P, Menozzi C, et al. Effect of etilefrine in preventing syncopal recurrence in patients with vasovagal syncope. a double-blind, randomized, placebo-controlled trial. The Vasovagal Syncope International Study. Circulation 1999; 99: 1452-7. [CrossRef]
34. Grubb BP. Pathophysiology and differential diagnosis of neurocardiogenic syncope. Am J Cardiol 1999; 84: 30-90. [CrossRef]
35. Kapoor WN, Peterson J, Wieand HS, Karpf M. Diagnostic and prognostic implication of recurrences in patients with syncope. Am J Med 1987; 83: 700-8. [CrossRef]
36. Sheldon R, Rose S, Flanagan P, Koshman ML, Killam S. Risk factors for syncope recurrence after a positive tilt-table test in patients with syncope. Circulation 1996 1; 93: 973-81. [CrossRef]
37. Kouakam C, Vaksmann G, Pachy E, Lacroix D, Rey C, Kacet S. Long-term follow-up of children and adolescents with syncope; predictor of syncope recurrence. Eur Heart J 2001; 22: 1618-25. [CrossRef]
38. Domenichini G, Diemberger I, Biffi M, Martignani C, Valzania C, Bertini M, et al. Long term follow-up of patients with syncope evaluated by head-up tilt test. Ann Noninvasive Electrocardiol 2010; 15: 101-6. [CrossRef]
39. Salim MA, Ware LE, Barnard M, Alpert BS, DiSessa TG. Syncope recurrence in children: relation to tilt-test results. Pediatrics 1998; 102: 924-6. [CrossRef]
40. Iacoviello M, Forleo C, Guida P, Sorrentino S, D'Andria V, Rodio M, et al. Independent role of reduced arterial baroreflex sensitivity during head-up tilt testing in predicting vasovagal syncope recurrence. Europace 2010; 12: 1149-55. [CrossRef]
41. Barón-Esquivias G, Errázquin F, Pedrote A, Cayuela A, Gómez S, Aguilera A, et al. Long-term outcome of patients with vasovagal syncope. Am Heart J 2004; 147: 883-9 [CrossRef]
42. Alehan D, Üner A, Ayabakan C, Özer S, Özme S. Reproducibility of the head-up tilt test results in children with vasovagal syncope. Int J Cardiol 2003; 88:19-25. [CrossRef]
43. Ector H, Reybrouck T, Heidbüchel H, Gewillig M, Van de Werf F. Tilt training: a new treatment for recurrent neurocardiogenic syncope and severe orthostatic intolerance. Pacing Clin Electrophysiol 1998; 21: 193-6. [CrossRef]
44. Di Girolamo E, Di Iorio C, Leonzio L, Sabatini P, Barsotti A. Usefulness of a tilt training program for the prevention of refractory neurocardiogenic syncope in adolescents: A controlled study. Circulation 1999; 100: 1798-801. [CrossRef]