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Comparison of Recurrence Rate Based on the Frequency of Preceding Symptoms in Patients With Neurocardiogenic Syncope or Presyncope

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ABSTRACT

Background and Objectives: In patients with neurocardiogenic syncope or presyncope, symptoms developed unpredictably and intermittently. The purpose of this study was to determine whether there was any significant difference in the recurrence rate of symptoms during the follow-up period between patients with many episodes of symptoms and those with fewer episodes of symptoms before diagnosis, as well as to assess the clinical significance of previous episodes of symptoms during treatment. **Subjects and Methods:** A total of 100 patients with neurocardiogenic syncope or presyncope were divided in two groups (high episode group, n=54; low episode group, n=46) according to the frequency of symptoms before the head-up tilt test. We retrospectively analyzed the recurrence of symptoms using telephone interviews and medical record reviews. **Results:** The clinical characteristics were not significantly different between the two groups. However, the recurrence rate was significantly lower in the high episode group than in the low episode group (5.6% vs. 19.6%, p=0.001). In the high episode group, patients treated with medication showed higher recurrence of symptoms than those without medication. In the lower episode group, a similar result was observed. **Conclusion:** The frequency of previous symptoms at the diagnosis of neurocardiogenic syncope or presyncope did not predict the occurrence of symptoms during the follow-up period. Therefore, to continue drug treatment based on the frequency of symptoms in patients with neurocardiogenic syncope or presyncope may not be the best option. **(Korean Circ J 2011;41:434-439)**

KEY WORDS: Neurocardiogenic syncope; Syncope, vasovagal; Recurrence.

Introduction

Neurocardiogenic syncope is the most common cause of syn-

cope, which occurs in response to various stimuli such as prolonged standing, fear, pain and others. These stimuli cause an exaggerated response of the autonomic nervous system. Neurocardiogenic syncope usually develops after prolonged standing and increased sympathetic activity. Under this condition, exaggerated myocardial contraction of left ventricle activates myocardial mechanoreceptors and vagal afferent nerve fibers that lead to sympathetic inhibition and parasympathetic activation. Finally, peripheral vasodilation and bradycardia cause the occurrence of syncope.[1] However, the pathophysiology of neurocardiogenic syncope is not simple and other factors are also involved.[2]

A detailed history taking is the most important diagnostic step in evaluating patients with suspected neurocardiogenic syncope. Head-up tilt test (HUT) is widely used to confirm di-

agnosis in patients with unexplained syncope.[3)4)] The shorter time interval between the last episode and HUT was a predictor of the positive response of HUT in patients with suspected neurocardiogenic syncope or presyncope.[5)] However, there were only a few studies to evaluate the recurrence of symptoms during follow-up in patients with a positive HUT.[6)7)]

Therefore, the purpose of this study was to determine whether there was any significant difference in the recurrence rate of symptoms during follow-up between patients with a high episode of symptoms and those with a low episode of symptoms before diagnosis, as well as to assess the clinical significance of previous episodes of symptoms during treatment.

Subjects and Methods

Study population

One hundred and seventy-six consecutive patients with suspected neurocardiogenic syncope or presyncope, who showed a positive response of HUT, were recruited at Samsung Medical Center, Seoul, Korea, between January 2000 and December 2000. The medical records and HUT case report forms of these 176 consecutive patients were retrospectively reviewed. Of these, 100 patients who agreed to a telephone interview to discuss the recurrence of symptoms following HUT were included in this study. However, 76 patients were excluded from the study because they declined to give a telephone interview. The selected 100 patients with neurocardiogenic syncope or presyncope were divided into two groups based on the frequency of symptoms before HUT. One group was defined as the high episode group (n=54), in which patients experienced five or more episodes of symptoms. The other group was defined as the low episode group (n=46), in which they experienced less than five episodes of symptoms.

Head-up tilt test

All patients underwent HUT in a fasting state after obtaining informed consent and HUT consisted of two phases. The first phase of HUT was performed while patients were tilted to an angle of 70° for 30 minutes, or until symptoms appeared. If the first phase produced a negative response, the second phase with isoproterenol provocation was performed while maintaining the same degrees of tilting as the first phase for 15 minutes. Isoproterenol was intravenously administered at an initial rate of 1 μg/min. The infusion rate was increased by 1 μg/min every 3 minutes to a maximum of 5 μg/min. Electrocardiography was continuously monitored. The blood pressure of each patient was non-invasively measured beat-to-beat using a Finapres (OhMeda Monitoring System, Englewood, CO, USA) during the HUT.[5)] A positive response of HUT was defined when syncope or presyncope was reproduced in association with hypotension, bradycardia, or both. Positive responses were classified into three types (va-

sodepressive, cardioinhibitory, mixed) according to the criteria provided in the previous study, in which a vasodepressive response was defined as significant systolic blood pressure decrease <80 mmHg. A cardioinhibitory response was defined as abrupt sinus arrest or heart rate decrease (sinus arrest >3 seconds or heart rate <45 beats/min in the first phase, heart rate <60 beats/min in the second phase). A mixed response was defined as significant decrease of systolic blood pressure and heart rate.[8)]

Symptom recurrence during follow-up

We evaluated symptom recurrence by telephone interview as well as by reviewing patient medical records. We defined the recurrence of symptoms as syncope if the patient experienced a syncopal episode during the follow-up period. We also defined the recurrence of symptoms as presyncope if the patients experienced severe prodromal symptoms such as dizziness, weakness, and sweating which disappeared by sitting or acquiring the supine position during the follow-up period.

Statistical analysis

Means were calculated for continuous variables and the frequency was measured for categorical variables. Comparisons were made by Student's t-test for continuous variables, and the chi-square test was used for categorical variables. A p<0.05 was considered statistically significant. Data were analyzed with Statistical Package for the Social Sciences (SPSS), Version 11.0 (SPSS, Inc., Chicago, IL, USA). Multivariate regression analysis was used to identify possible independent variables associated with symptom recurrence during follow-up.

Results

Baseline clinical characteristics of total patients

The mean age was 37±15 years (n=100); 50% were male. The mean episode of syncope was 3.9±6.3. The mean episode of presyncope was 18.4±63.2. 16% were taking drugs to prevent symptoms. 21% had underlying disease. 28% had a physical injury during syncopal episodes (Table 1).

Comparison of clinical characteristics between high and low episode groups

The frequency of symptoms before HUT was very diverse in both groups (Fig. 1). There was no significant difference of clinical characteristics between high and low episode groups. However, syncope and presyncopal episodes were more frequently noted in the high episode group (5.9±7.9 vs 1.5±1.3, 33.3±83.5 vs. 1.0±1.3, p=0.003) (Table 1).

Comparison of parameters during head-up tilt test between high and low episode groups

There was no significant difference observed in the pattern

of positive response of HUT between high and low episode groups. Vasodepressive type was the most common and cardioinhibitory type was the least common in both groups. However, positive response of HUT was more frequently observed at the first phase of HUT in the high episode group (15% vs. 4%, p=0.001) (Table 2).

Symptom recurrence during follow-up

The mean duration of follow-up was 38.4±3.6 months.

Twelve patients (12%) experienced symptoms during follow-up. Three patients were found in the high episode group and all showed a vasodepressive response during HUT. Nine patients were found in the low episode group. Vasodepressive response was noted in four patients, mixed response in four patients, and cardioinhibitory response in one patient during HUT. The recurrence of symptoms was significantly less in patients with high episodes of symptoms than in those with low episodes of symptoms (5.6% vs. 19.6%, p=0.001)

Table 1. Comparison of clinical characteristics between patients with high episode of symptoms and low episode of symptoms

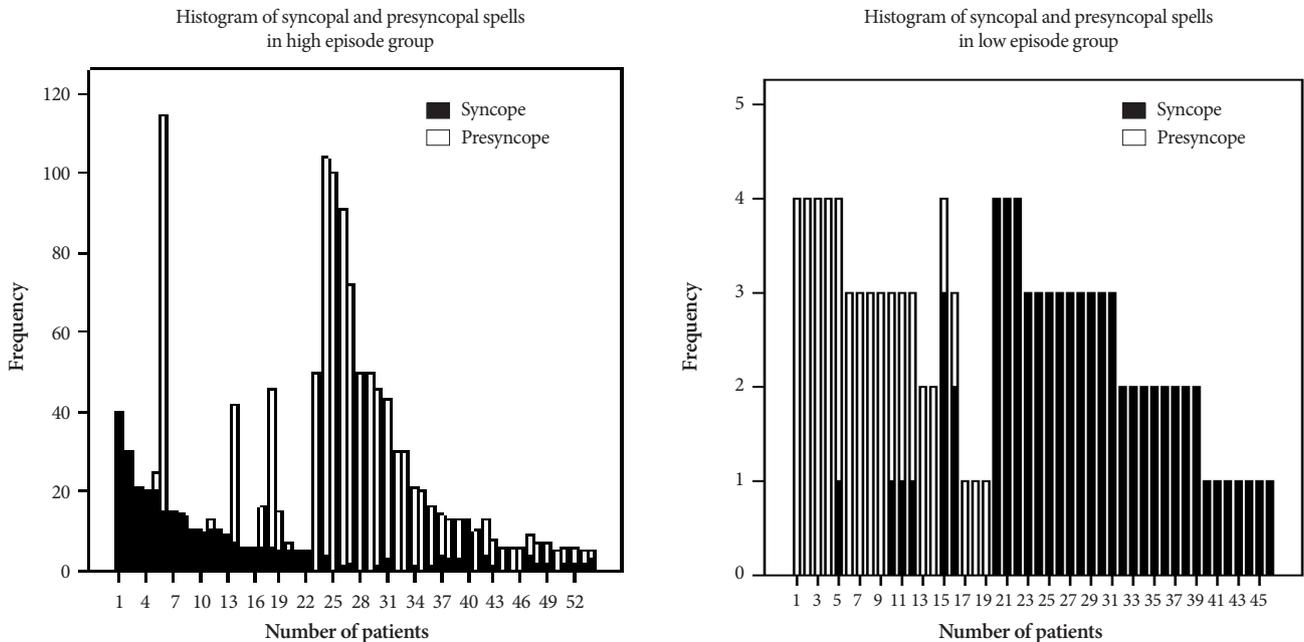| Groups / Variables	High episode group (n=54)	Low episode group (n=46)	p	Total
Age (years)	38±16	40±15	NS	37±15
Male/Female	25/29	25/21	NS	50/50
Syncope/Presyncope	5.9±7.9/33.3±83.5	1.5±1.3/1.0±1.3	0.003	3.9±6.3/18.4±63.2
Medication (%)	10 (18)	6 (13)	NS	16 (16)
Underlying disease (%)	11 (20)	10 (21.7)	NS	21 (21)
Physical injury (%)	16 (30)	12 (26)	NS	28 (28)

Data: mean±SD. NS: not significant

Fig. 1. Histograms of syncopal and presyncopal episodes in both groups.

Table 2. Comparison of parameters during head-up tilt test between patients with high episode of symptoms and low episode of symptoms

Groups / Variables	High episode group (n=54)	Low episode group (n=46)	p
Pattern of positive response (%)			
Vasodepressive type	35 (67)	29 (63)	NS
Cardioinhibitory type	5 (9)	4 (9)	NS
Mixed type	13 (24)	13 (28)	NS
Phase of positive response (%)			
Passive (the first phase)	8 (15)	2 (4)	0.001
Isoproterenol provocation (the second phase)	46 (85)	44 (96)	NS

NS : not significant

(Figs. 2 and 3).

Comparison of recurrence of symptoms between patients with and without medication during follow-up

Of 54 patients with high episodes of symptoms, 10 patients were on medication to prevent symptom recurrence. Two of 10 patients (20%) experienced symptom recurrence. Forty four patients did not take any medication to prevent symptom and 1 of these (2.3%) had symptom recurrence. Therefore,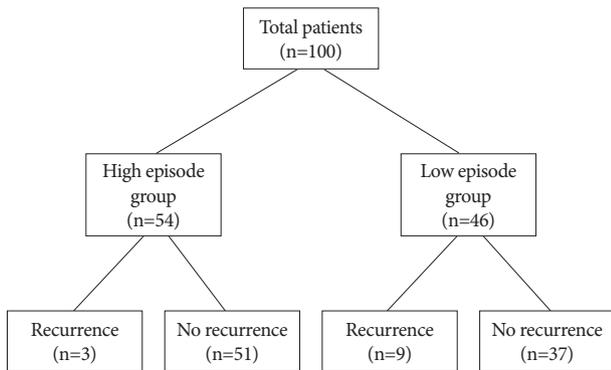 the recurrence of symptom was more frequently noted in patients with medication than those without medication (p=0.014) (Fig. 4). Of 46 patients with low episodes of symptoms, six patients were on medication to prevent symptom recurrence. Two these (33.3%) experienced symptom recurrence, whereas 40 patients did not take any medication to prevent symptom. Seven of the 40 patients (17.5%) had symptom recurrence. Therefore, the recurrence of symptoms was more frequently observed in patients with medication than those without medication (p=0.01) (Fig. 4).

Clinical predictors of the recurrence of symptoms

By multivariate logistic regression analysis, significant predictors of the recurrence of symptoms were symptom frequency and medication (Table 3).

Discussion

Neurocardiogenic syncope is the most common cause of syncope. Symptom recurrence is unpredictable however and sometimes a long, symptom free period is observed.

Several studies evaluated the rate of symptom recurrence in patients with neurocardiogenic syncope during the follow-up period. However, a significant difference in the recurrence rate among the studies was observed. Ruiz et al.[6] reported that the recurrence rate was 8.9% in patients with neurocardiogenic syncope, who experienced more than one episode of syncope and did not take any medication to prevent symptom. Brignole et al.[9] stated that the recurrence rate was 27%

Fig. 2. Recurrence of symptoms in patients with high and low episodes of symptom during follow-up.
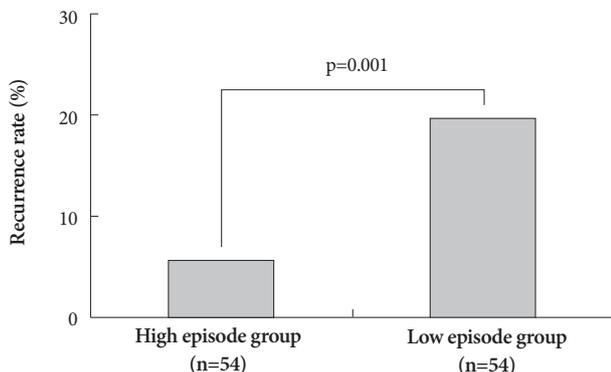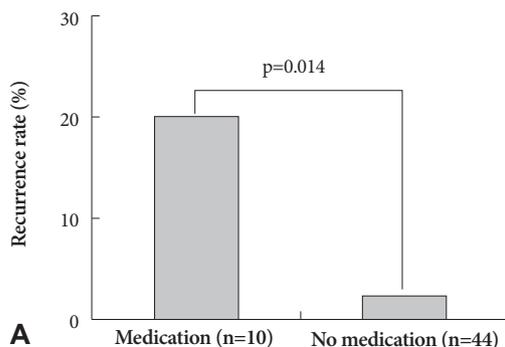
Fig. 3. Comparison of recurrence rate between the high episode group and low episode group. The recurrence of symptoms was significantly less in the high episode group than in the low episode group (5.6% vs. 19.6%, p=0.001).

Table 3. Predictors of recurrence of symptoms in multivariate logistic regression analysis

Predictor variables	OR	95% confidence interval
Sex	0.398	0.098-1.614
Age	1.000	0.955-1.047
Frequency*	0.201	0.045-0.892
Underlying disease	0.782	0.130-4.713
Medication†	5.877	1.051-32.855
Physical injury	0.462	0.079-2.704

*p=0.035, †p=0.044. OR: odds ratio in multiple logistic regression
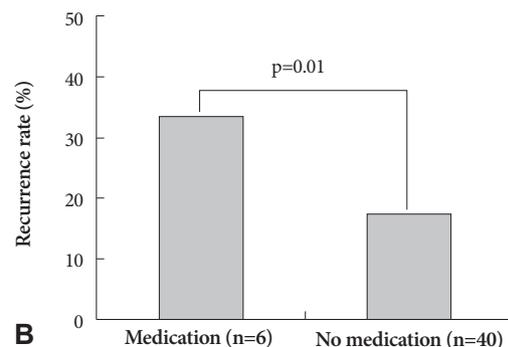
Fig. 4. Comparison of recurrence rate based on drug treatment in patients with high episode (A) and low episode (B) of symptoms. The recurrence of symptoms was more frequently observed in patients with medication than in those without medication in both groups (p=0.01).

or 20% in 30 patients on placebo or atenolol, respectively. Sheldon et al.[7] reported that there was 28% of symptom recurrence in 101 patients without medication during 3 year follow-up. Natale et al.[10] reported different recurrence rates according to treatment. The recurrence rate was 6% in patients who were treated on drugs guided by repeat HUT, 36% in patients with empirical drug treatment, and 67% in patients without drug treatment. Cox et al.[11] reported that the recurrence rate was 42% in patients who stopped drugs, which was effective on repeat HUT. Ahn et al.[12] reported that the recurrence rate was 7.1% in patients who were treated on drugs guided by repeat HUT, 16.7% in patients with empirical drug treatment, and 22.4% in patients who stopped drug during follow-up.

In our study, the recurrence rate was 12% in 100 patients during 38.4±3.6 months. Interestingly, we found that the recurrence rate was lower in high episode group compared to the low episode group (5.6% vs. 19.6%) following HUT. In contrast to our report, Sheldon et al.[7] stated that symptom recurrence was related to the frequency of symptom episodes before HUT. Kouakam et al.[13] and Barón-Esquivias et al.[14] also reported similar results and proposed that the frequency of symptoms before HUT as a predictor of symptom recurrence during follow-up. We also evaluated a predictor of symptom recurrence by multivariate logistic regression analysis. Significant predictors of the recurrence of symptoms were symptom frequency and medication. The different results obtained by us may be related to differences in the inclusion criteria of patients, HUT protocol, and the definition of symptom recurrence.

In the past, many physicians prescribed many different types of medication including β-blocker, theophylline, serotonin-reuptake inhibitor, α-blocker, and other drugs to patients with neurocardiogenic syncope or presyncope based on their symptom frequency. However, prospective randomized trials did not show any beneficial effect of those drugs except midodrine.[15-20]

In our study, we started medication to prevent symptoms if patients complained of frequent symptoms. β-blocker was used as an initial drug to prevent symptoms. If patients still experienced symptoms, β-blocker was stopped and other medications such as theophylline, midodrine, fluoxetine were used as second drugs. If patients showed a positive response at the first phase of HUT, β-blocker was not used as the initial drug to prevent symptoms. Other drugs such as theophylline, midodrine, and fluoxetine were used as the initial drugs to prevent symptoms. Interestingly, the recurrence of symptoms was more frequently noted in patients with medication than those without medication regardless of high and low episode groups. This finding in our study might be related to several factors such as frequent episodes of symptoms in treated groups and disappointing results of drug efficacy. Recent European Society of Cardiology guidelines emphasizes patient education, avoidance of triggers, and prompt position change at the prodromal symptoms rather than prescribing medications.[21]

Study limitation

This study was retrospective in design and seventy six of the total 176 consecutive patients were excluded from the analysis because they did not participate in a telephone interview during the follow-up period. The study population included both patients with neurocardiogenic syncope and presyncope. We also used a different HUT protocol to confirm neurocardiogeic syncope or presyncope. Taken together, these factors might affect the results of our study.

Conclusion

In our study, the frequency of previous symptoms at the diagnosis of neurocardiogenic syncope or presyncope did note predict the occurrence of symptoms during the follow-up period. Therefore, it is inadvisable to continue drug treatment based on the frequency of symptoms in patients with neurocardiogenic syncope or presyncope.

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