Prognostic Value of Head-Up Tilt Test with Intravenous Beta-Blocker Administration in Assessing the Efficacy of Therapy in Patients with Vasovagal Syncope

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Background: Although beta-blockers are frequently used in order to prevent the recurrence of vasovagal syncope, the efficacy of this treatment is difficult to determine.

Objectives: To determine if the result of a tilt test with an intravenously administered beta-blocker can predict the long-term efficacy of beta-blockade.

Methods: The study group consisted of 62 patients (29 females, mean age 32.8 ± 12.3 years and 33 males, mean age 35.9 ± 18.2 years) with at least two syncopal episodes during 6 months preceding the positive tilt test. After the baseline tilt test, propranolol (0.1 mg/kg BW) was administered intravenously and the tilt test was repeated. Beta-blockade was considered effective if the subsequent tilt test proved negative (complete efficacy) or if the time until the occurrence of syncope at the subsequent tilt test was longer compared to the baseline test (partial efficacy). All the patients were put on continuous propranolol treatment and were followed up for a period of 1 year or until the time when syncope recurred.

Results: Intravenously administered propranolol prevented ($n = 33$) or delayed ($n = 18$) the occurrence of syncope at the tilt test in 51 patients (82%), while it was found ineffective in the remaining 11 patients (18%). During the 8.6 ± 6.7 months (range 1–14) of the follow-up period, the syncope recurred in 20 patients (32%), with 13 patients (25%) in the group where intravenously administered propranolol proved effective versus 7 patients (64%) for whom intravenously administered propranolol did not prevent syncope during the tilt test ($P < 0.015$). The survival analysis with respect to the recurrence of syncope revealed a significant correlation between the results of the tilt test with intravenously administered propranolol and the efficacy of the long-term beta-blocker therapy ($P < 0.003$). There were no significant differences with respect to the predictive value of the tilt test with propranolol between the patients showing complete and partial propranolol efficacy (ns), while significant differences were observed between these two groups on one hand and the patients in whom intravenously administered propranolol was found ineffective on the other ($P < 0.04$ and $P < 0.002$, respectively).

Conclusions: Intravenously administered propranolol prevents tilt-induced syncope in a significant percentage of patients. The results of the tilt tests combined with the administration of propranolol predict the efficacy of a continuous propranolol treatment. Both complete and partial propranolol efficacy at tilt test can successfully identify those patients who will benefit from continuous beta blockade.

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tilt test; vasovagal syncope; beta-blocker

Although the exact mechanism of vasovagal syncope (VVS) has not been fully explained, it is believed that the inactivation of high-pressure receptors in the presence of central hypovolemia and the paradoxical increase of the sensitivity of cardiopulmonary baroreceptors are the major mechanisms of VVS. Tilt tests (TT) have been shown to identify the patients with syncope in whom hy-

potension and/or bradycardia are the most probable causes of losing consciousness.

Until recently, beta-blockers have been the most frequently used pharmacological remedies in patients with reflex syncope. Their usage, though by many practitioners considered controversial, was based on the results of clinical trials, which showed that both spontaneous and TT-induced episodes of

syncope were preceded by an increased level of plasma catecholamine.¹⁻⁴

However, the subsequent studies with long-term follow-up periods did not confirm these findings. Therefore, some investigators attempted to find more accurate methods to determine the long-term efficacy of beta-blockers, with acute beta-blocker testing (ABT) at TT used for this purpose. However, the results of these studies were inconsistent and the value of this approach has not been determined yet.⁵⁻¹⁰

The objective of the present study was to answer the question whether the results of TT performed after the intravenous administration of propranolol can identify the patients with syncope in whom a continuous beta-blocker therapy is effective.

METHODS

Patients

The study group consisted of 62 patients (29 females, mean age 32.8 ± 12.3 years, and 33 males, mean age 35.9 ± 18.2 years) who had at least two syncopal episodes during the 6 months preceding the study and in whom TT caused syncope.

Tilt Tests

Tilt tests were performed in accordance with the Westminster protocol, in the morning (between 9 a.m. and 11 a.m.), after night rest. Heart rate was continuously recorded with a Lohmeir M 608 monitoring device, while blood pressure was measured automatically with a sphygmomanometer, at 60-second intervals. After lying for 15 minutes in supine position, the patients were tilted up at 60° until syncope occurred or for 45 minutes when no symptoms of syncope appeared (passive TT). If no syncope was induced during a passive TT, the patients received 250 μ g of sublingual nitroglycerin (NTG) and TT was continued for another 20 minutes or until the syncope occurred.

After a positive baseline TT, the patients were returned to supine position and were given intravenous propranolol (0.1 mg/kg BW). After resting for 15 minutes in supine position, the patients were tilted up again, following the same protocol as the one used for the baseline test.

Propranolol was considered effective when the results of the second TT (after taking the drug) proved negative (complete efficacy) or if the time until the occurrence of syncope at the subsequent

TT was longer compared to the baseline TT (partial efficacy).

The type of syncopal reaction was defined according to the criteria of the Vasovagal Syncope International Study (VASIS).¹¹

Syncope was defined as a transient, self-terminating loss of consciousness and postural tone without the need for pharmacological or electrical intervention.

Long-Term Therapy and Follow-Up

All the patients, whether negative or positive in TT after intravenous propranolol, were treated continuously with oral propranolol for at least 12 months. The dosage of the drug was determined on individual basis, with the patient's heart rate and blood pressure, as measured during the control visits at every 3 weeks, taken into account. The intention was to keep the systolic blood pressure below 115 mmHg and the heart rate below 55 beats/min while at rest. When such parameters were achieved, the follow-up period for a particular patient started.

After 1 year, a questionnaire was sent by mail to the patients, regarding the results of the treatment and the adverse effects, if any. The data were collected in the database (Access 2000, Microsoft Corporation, US).

The follow-up ended when syncope recurred or when the entire follow-up period was completed.

Statistical Analysis

The "Statistica 5.0" package was used for this purpose. The dependent and the independent variables were compared using the Student *t*-test and the Wilcoxon test, respectively. For analyzing other parameters, the chi-square test was applied. The correlations between the variables were assessed using the C-Pearson or the Q-Kendall correlation coefficients. The Kaplan-Meier curves depicting the survival period with no syncope recurrence were compared using the F-Cox test. The sensitivity, the specificity, the positive, and negative predictive accuracy, as well as the diagnostic accuracy were computed according to standard definitions. The *P* value < 0.05 was considered statistically significant.

RESULTS

Out of the 62 patients with positive TT, 35 patients (56%) had mixed-type VVS, 7 patients (12%)

Table 1. Clinical Characteristics of the Studied Patients

Parameter	Group		P
	BBe	BBne	
Age (years)	35.8 ± 16.5	28.5 ± 9.2	ns
Gender (females/males)	21/30	8/3	ns
Number of syncopal episodes during 6 months before the study	3.2 ± 2.3	5.5 ± 9.4	ns
Duration of history of syncope (months)	32.4 ± 44.2 (6–182)	55.9 ± 74.8 (8–240)	ns
Family history of syncope	5 (10%)	1 (9%)	ns
Mitral valve prolapse	10 (19%)	4 (36%)	ns
Chronic stress	16 (31%)	4 (36%)	ns
Injury associated with syncope	18 (35%)	2 (18%)	ns
Type of vasovagal reaction			
Mixed	26 (51%)	9 (81%)	ns
Vasodepressive	7 (14)	0	ns
Cardioinhibitory	18 (35%)	2 (19%)	ns
Asystole ≥3 second	6 (12%)	1 (9%)	ns
Duration of asystole (second)	8.7 ± 5.8	6	ns
Duration of baseline tilt test (minute)	7.4 ± 3.5	6.6 ± 1.9	ns
Duration of tilt test after intravenous propranolol (minute)	8.5 ± 2.1	5.3 ± 1.3	<0.0002
Numbers of passive TT/TT _{NTG}	17/34	3/8	ns

Beta-blocker effective (BBe) and ineffective (BBne) group.

showed vasodepressive and 20 patients (32%) cardioinhibitory type of VVS. In 20 patients (32%), syncope occurred at the passive TT, while in the remaining 42 patients (68%) syncope during TT_{NTG}. Intravenously administered propranolol prevented or delayed syncope during the second TT in 51 patients (82%) (BBe, beta-blocker effective group), while 11 patients (18%) had TT-induced syncope despite the infusion of propranolol (BBne, beta-blocker ineffective group). In 33 patients (65%) in BBe group propranolol prevented syncope, while in the remaining 18 subjects (35%) it delayed the time when syncope occurred ($P < 0.05$).

There was no significant difference with respect to age between the patients in whom syncope was induced during the passive TT and those who fainted during the TT_{NTG} (34.9 ± 15.7 years vs 33.5 ± 16.1 years, ns). The clinical characteristics of the patients investigated are presented in Table 1.

During the 8.6 ± 6.7 (range 1–14) months of the follow-up period, 20 patients (32%) had a recurrence of syncope: 13 (25%) patients from BBe group (propranolol prevented/delayed syncope at second TT) and 7 patients (64%) patients from BBne group (syncope at second TT despite administration of propranolol) ($P < 0.015$) (Fig. 1). The mean daily dose during the continuous propranolol oral treatment was 39.5 ± 8.2 mg (range 20–120 mg) in BBe

Figure 1. A scheme of the test with specification of a number and percentage of results obtained in its successive phases.

Figure 2. Kaplan-Meier analysis showing a probability of event-free survival in study group patients. Beta-blocker partially (BBpe) and completely (BBce) effective; Beta-blocker effective (BBe) and ineffective (BBne) group.

group and 35.2 ± 7.3 mg (range 30–100) in BBne group (ns).

Figure 2 shows the Kaplan-Meier curves depicting the probability of survival without syncope recurrence. These curves show a statistically significant correlation between the results of the TT performed after propranolol and the effects of the continuous propranolol therapy ($P < 0.003$). The patients with a negative TT after the infusion of propranolol (BBe group) had better outcomes than those in whom the second TT was positive. After the second month of treatment, the risk of syncope recurrence was 15% lower in the patients with negative TT than in those for whom the second TT proved positive. After the 11th month of the follow-up period, this difference reached a plateau of 30%.

There were no differences in the outcome between the patients with complete and those with partial propranolol efficacy at the second TT (ns), while for both these subgroups the outcome observed was significantly better than for the patients in BBne group (syncope at second TT despite administration of propranolol) ($P < 0.04$ and $P < 0.002$, respectively) (Fig. 3). The sensitivity, the

specificity, the positive, and negative prognostic value, as well as the diagnostic accuracy of TT with propranolol in predicting the risk of syncope recurrence are presented in Table 2.

The patients with a positive TT after propranolol presented a higher number of previous syncopal episodes and a shorter time lapse after the occurrence of the first syncopal episode than those with a negative second TT. The subjective assessment of the efficacy of the treatment also revealed a significant correlation between the effectiveness of the continuous propranolol therapy and the result of the second TT ($P < 0.015$).

Propranolol-induced side effects occurred in 11 patients (22%)–16 patients (26%) from BBe group (propranolol prevented/delayed syncope at second TT) and 5 patients (45%) from BBne group (syncope at second TT despite administration of propranolol) (ns). The most frequent symptoms included vertigo (5%), nausea (10%), abdominal pain (6%), or depression (12%). These symptoms were mild and none of the patients discontinued the medication. The results of the long-term follow-up are presented in Table 3.

Figure 3. Distribution of true (TP) and false (FP) positive results, true (TN) and false (FN) negative results and number of patients after application of 1- and 2-variable efficacy criteria of ABT in estimation of long-term VVS treatment efficacy. Beta-blocker effective (BBe) and ineffective (BBne) in long-term follow-up. Criteria of the therapeutic effectiveness of ABT: 1-variable—BB complete effective; 2-variable criterion—BB complete and partially effective.

DISCUSSION

Recurrent episodes of VVS often cause physical and mental deterioration. In most patients medical therapy is empirical, with pathophysiological mechanisms of reflex syncope taken into account. The data showing that intravenous beta blockade prevents TT-induced hypotension and/or bradycardia strongly suggest that increased adrenergic activity is a triggering mechanism for VVS.

Although beta blockers are widely used in the prevention of VVS, there are no data to evidence the prognostic value of various methods of eval-

uation with respect to the long-term efficacy of a beta blocker. The reason behind this is the difficulty in conducting controlled clinical trials, as well as the lack of knowledge in the natural history of syncope.^{12–15} Also, the definition of the efficacy of various treatment options has not been precisely determined so far.¹⁶

The question arises whether a TT preceded by a beta-blocker infusion can be considered a reliable indicator of the long-term efficacy of this medication. The results of the investigations in which this issue was addressed seem encouraging enough. Natale et al.¹⁷ studied 112 patients with a history of syncope and a positive TT, who were put through the second TT with intravenous infusion of esmolol and were subsequently treated with oral metoprolol of a daily dose ranging from 50 to 100 mg. Out of the 36 patients who had recurrent syncope during the 2.7 ± 1.2 year follow-up period, 32 had positive TT with esmolol. Similar results were presented by Cox et al.,¹⁸ who observed syncope recurrence during a 28 ± 11 month follow-up in only 12 of the 118 patients with a negative TT preceded by an intravenous infusion of propranolol.

As we demonstrated earlier (by using indirect methods), both partial and complete efficacy of intravenous beta blocker administered just before TT shows similar values.¹⁹ The results of the present

Table 2. Values of Standard Prognostic Indices Obtained After Application of 1- and 2-Variable Efficacy Criteria of ABT in Estimation of the Efficacy of Long-Term VVS Therapy

Prognostic Indices	Efficacy Criterion	
	1-variable	2-variable
Sensitivity (%)	70	35
Specificity (%)	64	90
Positive predictive value (%)	48	64
Negative predictive value (%)	82	75
Diagnostic accuracy (%)	66	73

1-variable criterion—total beta-blocker efficacy; 2-variable criterion—complete and partial beta-blocker efficacy.

Table 3. Results of the Long-Term Follow-Up

Parameter	Group		P
	BBe	BBne	
Patients with syncope recurrences	13 (25%)	7 (64%)	<0.015
Total number of syncope recurrences	28	14	ns
Mean number of syncopal episodes per patient	2.15 ± 0.9	2 ± 0.8	ns
Time to first recurrence of syncope (months)	6.7 ± 3.1 (1–11)	2.4 ± 1.3 (1–4)	<0.003
Duration of follow-up (months)	9.4 ± 7 (1–14)	4.8 ± 3.8 (1–13)	<0.05
Daily dose of propranolol (mg)	39.5 ± 8.2 (20–120)	35.2 ± 7.3 (30–100)	ns
Side effects	11 (22%)	5 (45%)	ns
Subjective assessment of efficacy of treatment			
Complete	26 (51%)	2 (18%)	<0.03
Partial	22 (43%)	4 (36%)	ns
Ineffective	3 (6%)	5 (46%)	<0.0007

Beta-blocker effective (BBe) and ineffective (BBne) group.

study reconfirmed our initial findings. Complete efficacy was achieved in only 33 patients (53%), which in statistical terms is a result lower than those reported by others. However, in most investigations TT was combined with administration of isoproterenol, hence the efficacy of beta blocker might have been overestimated due to the agonist-antagonist reaction.^{10,18,20} This view was indirectly confirmed by Cox et al.,¹⁸ who reported the efficacy of intravenous propranolol administered prior to TT in only 9 patients (43%) with TT-induced syncope at the baseline test.

A few studies reported that both the positive and the negative prognostic values of TT with intravenous beta blocker were low and did not exceed 20 and 53%, respectively.²¹ However, our results are more encouraging—out of the 20 patients who had syncope recurrence, 7/11 (64%) showed positive TT after intravenous propranolol and only in 13/51 (25%) the results of the test were negative. Thus, the positive and the negative predictive values in our study were rather high—64% and 75%, which suggests clinical usefulness of this method of risk stratification.

We believe that the decision whether to start the pharmacological treatment in patients with VVS should be based not only on the well-established clinical criteria but also on the parameters reflecting the subjective opinions of the patients treated. Patients' expectations include not only the benefits resulting from the therapy but also the risk associated with the treatment. The ability to precisely define the complaints made by a patient and the possibility to adequately control his/her well-being are also crucial for the final effects of the therapy.

Our study shows that these factors need to be included in the methodological considerations in order to avoid a discrepancy between the patients' opinions on the efficacy of the treatment on one hand and such objective endpoints as the time lapse between starting the treatment and the first recurrence of syncope on the other.

Our special focus was on precise and individualized determination of the dosage of oral propranolol applied in the continuous therapy. We believe that our approach resulted in administering rather low doses of the drug, which suggests that a widely used empirical approach is less accurate.

The main limitation of our study is the fact that there was no placebo group involved. Therefore, the objective efficacy of the treatment tested is difficult to assess because, in theory at least, one may anticipate that the efficacy of a beta-blocker in preventing syncope recurrences is not different from that of a placebo. Under such circumstances the therapeutic success could be regarded as illusive or reduced by the adverse effects of beta-blockers. However, the methodology used in our study should limit these reservations. Firstly, the possibility that beta-blockers markedly increase the risk of VVS was not confirmed by the changes in the hemodynamical parameters measured at the initial stage of TT. The patients with dysautonomic reactions or orthostatic hypotension—two conditions that may be worsened by a beta-blocker therapy, were not included in the study. Secondly, the hypothesis that the efficacy of beta-blockers is not different from that of a placebo is not in line with the findings of the present study, which evidenced

strong correlation between the results of TT with propranolol and the long-term effects of a continuous oral therapy. Although our study cannot definitely answer this question due to the lack of a placebo group, Cox et al.¹⁸ documented a significantly lower efficacy of a placebo, when compared to a continuous beta blockade in the prevention of syncope recurrences.

A factor that may limit the prognostic value of TT with propranolol is the lack of correlation between the intravenous and the continuous oral doses of propranolol. Thus, in practice, the efficacy of a precisely established intravenous dose of propranolol is confronted with the long-term efficacy of an oral dose, which is determined on the basis on absolutely empirical grounds.

Another limitation of our study is a low rate of reproducibility of TT, which according to various authors, ranges between 65 and 90%.²²

The results of our study suggest that the long-term efficacy of a continuous beta-blocker treatment may be predicted by the results of TT with intravenously administered propranolol. We also showed that both partial and complete acute efficacies of intravenous propranolol are equally valuable. The high predictive value of TT with propranolol, as demonstrated in our study, was mainly due to the reduction of the number of false positive results, which was achieved through defining partial response to intravenous propranolol as a parameter identifying the patients with no syncopal recurrences while put on continuous propranolol treatment. However, it should be remembered that the patients with complete acute efficacy of intravenous propranolol showed the highest rate of benefit from the continuous treatment.

The use of NTG did not significantly affect the results, which proves that TT_{NTG} is a reliable tool for making prognoses for the patients with syncope treated with a beta blocker.

CONCLUSIONS

Intravenous propranolol prevents tilt-induced syncope in a significant percentage of patients. The results of the tilt tests combined with the administration of propranolol predict the efficacy of a continuous propranolol treatment. Both complete and partial propranolol efficacy at tilt tests can successfully identify those patients who will benefit from continuous beta blockade.

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