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Vasovagal Syncope: A Prospective, Randomized, Crossover Evaluation of the Effect of Propranolol, Nadolol and Placebo on Syncope Recurrence and Patients' Well-Being

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OBJECTIVES We sought to assess the relative therapeutic efficacy of propranolol, nadolol and placebo in recurrent vasovagal syncope (VVS).

BACKGROUND Central and peripheral mechanisms have been implicated in the pathogenesis of VVS. Propranolol, nadolol and placebo have different sites of action on central and/or peripheral mechanisms. It has not yet been clarified whether one of the aforementioned treatments is more efficient than the others in reducing clinical episodes and exerting a beneficial effect on patients' well-being.

METHODS We studied 30 consecutive patients with recurrent VVS and a positive head-up tilt test. All were serially and randomly assigned to propranolol, nadolol or placebo. Therapy with each drug lasted three months. On the day of drug crossover, patients reported the total number of syncopal and presyncopal attacks during the previous period. They also gave a general assessment of their quality of life, taking into account: 1) symptom recurrence; 2) drug side effects; and 3) their personal well-being during therapy (scale 0 to 4: 0 = very bad/discontinuation; 1 = bad; 2 = good; 3 = very good; 4 = excellent). At the end of the nine-month follow-up period, they reported whether they preferred a specific treatment over the others.

RESULTS Spontaneous syncopal and presyncopal episode recurrence during each three-month follow-up period was reduced by all drugs tested (analysis of variance [ANOVA]: chi-square = 67.4, $p < 0.0001$ for syncopal attacks; chi-square = 60.1, $p < 0.0001$ for presyncopal attacks) No differences were observed in the recurrence of syncope and presyncope among the three drugs. All drugs improved the patients' well-being (ANOVA: chi-square = 61.9, $p < 0.0001$).

CONCLUSIONS Propranolol, nadolol and placebo are equally effective treatments in VVS, as demonstrated by a reduction in the recurrence of syncope and presyncope, as well as an improvement in the patients' well-being. (J Am Coll Cardiol 2002;40:499–504) © 2002 by the American College of Cardiology Foundation

Vasovagal syncope (VVS) is a common disorder of autonomic cardiovascular regulation. It is generally considered to result from a paradoxical reflex initiated when ventricular preload is reduced by excessive venous pooling. Central mechanisms are also important (1–3). The drug class most widely used for VVS is beta-blockers (4–13). These drugs exert their effects by multiple mechanisms. Some of them are mediated through peripheral pathways, whereas others are mediated through central nervous system pathways; for example, propranolol, which enters the blood-brain barrier, has been shown to act not only by blocking $beta_1$- and $beta_2$-adrenergic receptors, but also by decreasing serotonin levels in cerebrospinal fluid (14), and it is believed that its antihypertensive properties are partially exerted by blocking central nervous system pathways (15,16). In VVS, it has never been systematically tested whether a high brain penetration by a lipid-soluble, noncardioselective beta-blocker, such as propranolol, might add to the therapeutic efficacy of beta-blockade, relative to that obtained with nadolol, a beta-blocker with properties similar to propranolol in all aspects, except lipid solubility (nadolol does not enter the blood-brain barrier). It should be noted that, up to now, only a few randomized, placebo-controlled studies have assessed the efficacy of beta-blockers in VVS (17–19). No randomized, blinded, crossover study has been conducted to confirm the efficacy of lipophilic beta-blockers versus hydrophilic beta-blockers versus placebo. The value of a placebo arm in such a study is important, as it addresses the clinical importance of cortical brain inputs in the pathogenesis of VVS. In addition, the patients' well-being during therapy for this syndrome, which most of the time is not life-threatening, has been a rather underestimated issue (20). The aim of this study was to test in patients with recurrent VVS whether one of the treatments—propranolol, nadolol or placebo—is more efficient than the others in terms of reducing syncopal and presyncopal attacks, as well as exerting a beneficial effect on the patients' well being.

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Abbreviations and Acronyms
ANOVA = analysis of variance
ECG = electrocardiogram/electrocardiographic
VVS = vasovagal syncope

METHODS

Study group. Thirty consecutive patients with recurrent VVS were studied (13 men and 17 women; mean [±SE] age 41 ± 3 years). Inclusion criteria comprised a typical history of recurrent VVS (at least two syncopal episodes within the preceding three months) and a positive diagnostic head-up tilt test response on the day the patients were enrolled. All patients had a clinical cardiologic examination within normal limits and a normal 12-lead electrocardiogram (ECG). As appropriate, patients also had a negative neurologic, echocardiographic and cardiac electrophysiologic study, as well as an exercise ECG negative for ischemia. Patients with a definitive history or clinical suspicion of autonomic failure (i.e., diabetes mellitus or renal impairment), arterial hypertension, chronic obstructive airway disease or peripheral vascular disease were not included in the study. The mean duration of symptoms before study inclusion was 72 ± 50 months, and the mean number of syncopal and presyncopal episodes during the three months preceding study inclusion was 3.4 ± 0.4 and 9.1 ± 1.1, respectively.

Tilt test protocol. Tilt tests were performed between 9 and 11 AM after fasting since midnight, in a quiet room. A venous cannula was inserted into an antecubital vein, and all subjects rested in the supine position for 30 min. They were connected to a continuous ECG monitor and an automatic arterial blood pressure sphygmomanometer. After baseline measures of heart rate and arterial blood pressure were obtained, all subjects were tilted head-up at 60° on an electrically driven table with a foot-plate support, according to the protocol previously described (21). The development of syncope or presyncope, associated with systolic arterial hypotension (<80 mm Hg), with or without bradycardia or asystole, was considered a positive response. The subtypes of VVS were classified according to the criteria proposed by the Vasovagal Syncope International Study (22) investigators. If a positive response occurred during the initial upright tilt, the patients were returned to the supine position and the test was terminated. If 30 min of the passive tilt test was completed without a positive response, the patients were returned to the supine position for 10 min, and then the upright tilt was repeated for 15 min, with intravenous infusion of isoproterenol (initial infusion rate of 2 μg/min, increased by 1 μg/min each minute until the heart rate reached 130 beats/min or until a maximal infusion rate of 5 μg/min).

Study protocol. Patients were reassured about the benign nature of their syndrome. They gave written, informed consent to enter the study. The study protocol was approved by the institutional ethics committee. Patients were randomized to one of the six serial drug combinations (propranolol/nadolol/placebo; propranolol/placebo/nadolol; nadolol/propranolol/placebo; nadolol/placebo/propranolol; placebo/propranolol/nadolol; or placebo/nadolol/propranolol). Propranolol was given at a dose of 20 to 40 mg three times a day; nadolol at 40 to 80 mg/day; and placebo drug at 1 capsule per day. For each patient, the beta-blocker was administered at the maximally tolerated dose. The subjects were informed that the number of daily doses of each drug has nothing to do with its efficacy, but is purely a matter of pharmacokinetics. Therapy with each drug lasted three months. At the end of each three-month interval, the patients were asked: 1) to report the total number of syncopal and presyncopal episodes during this period; and 2) to give a general assessment of their quality of life, as modified by each drug, taking into account symptom recurrence, drug side effects and their personal well-being during therapy (scale 0 to 4: 0 = very bad/discontinuation; 1 = bad; 2 = good; 3 = very good; 4 = excellent). A repeated tilt test was performed at the end of each three-month period. After each tilt test, drug crossover was performed. Patients had no knowledge of the treatment assigned. At the end of the nine-month follow-up period, they were asked to report whether they preferred a specific treatment over the others.

Statistical analysis. Data were analyzed by nonparametric, repeated measures analysis of variance (ANOVA) (Friedman test, STATISTICA, version 6.0). The chi-square test with Yate's correction was used as a test of significance for categorical frequency data. A p value of <0.05 was considered statistically significant.

Table 1. Rest Heart Rate and Number and Type of Positive Tilt Test Responses at Diagnosis and After Each Drug Treatment

	Baseline	Propranolol	Nadolol	Placebo
Rest heart rate (beats/min)*	65 ± 3	47 ± 2	45 ± 2	60 ± 3
Positive tilt test (n)	30/30	5/30	4/30	10/30
Type of syncope (n)				
Mixed	14	5	3	7
Cardioinhibitory	11	0	1	1
Vasodepressive	5	0	0	2
No. of positive tilt tests with isoproterenol infusion	13	4	4	9

*Mean value ± SE.

RESULTS

One patient discontinued propranolol because of fatigue. The rest heart rate, number and type of positive tilt test responses at diagnosis and after each drug treatment are shown in Table 1. The rest heart rate, assessed at the end of each three-month period, was reduced to the same extent by propranolol and nadolol administration. During placebo administration, a trend toward increased positive, repeated

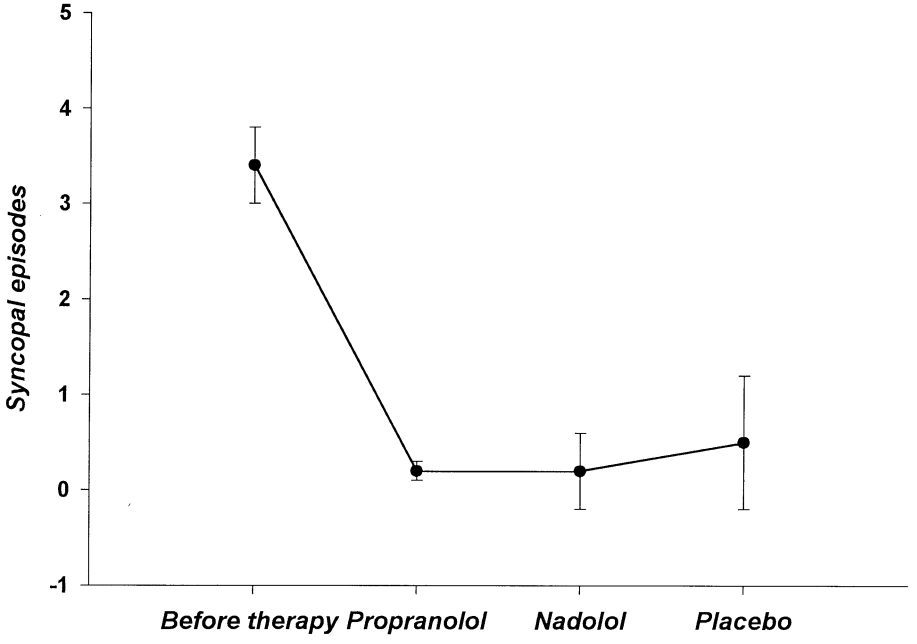

Figure 1. Mean (±SE) number of syncopal episodes before and during therapy with propranolol, nadolol and placebo.

tilt test results was observed, as compared with the other two drugs tested ($p = 0.1$ vs. nadolol and $p = 0.2$ vs. propranolol), but did not reach statistical significance.

Spontaneous syncope and presyncope during follow-up. Spontaneous syncopal and presyncopal episode recurrence during each three-month follow-up period was reduced by all drugs tested (ANOVA: chi-square = 67.4, $p < 0.0001$ for syncopal attacks; chi-square = 60.1, $p < 0.0001$ for presyncopal attacks). The study patients' mean ± SE numbers of syncopal and presyncopal episodes are shown schematically in Figures 1 and 2. No difference was observed between the drugs regarding the frequency of syncopal and presyncopal episodes.

Clinical episodes and repeated tilt test results. Interestingly enough, significant reductions in syncopal and presyncopal episodes were observed not only in patients whose tilt test became negative with each treatment, but also in those who had positive repeated tilt test results with propranolol (ANOVA: chi-square = 5.0, $p < 0.02$ for syncopal episodes; chi-square = 5.0, $p < 0.02$ for presyncopal attacks), nadolol (ANOVA: chi-square = 4.0, $p < 0.04$ for syncopal; chi-square = 4.0, $p < 0.04$ for presyn-

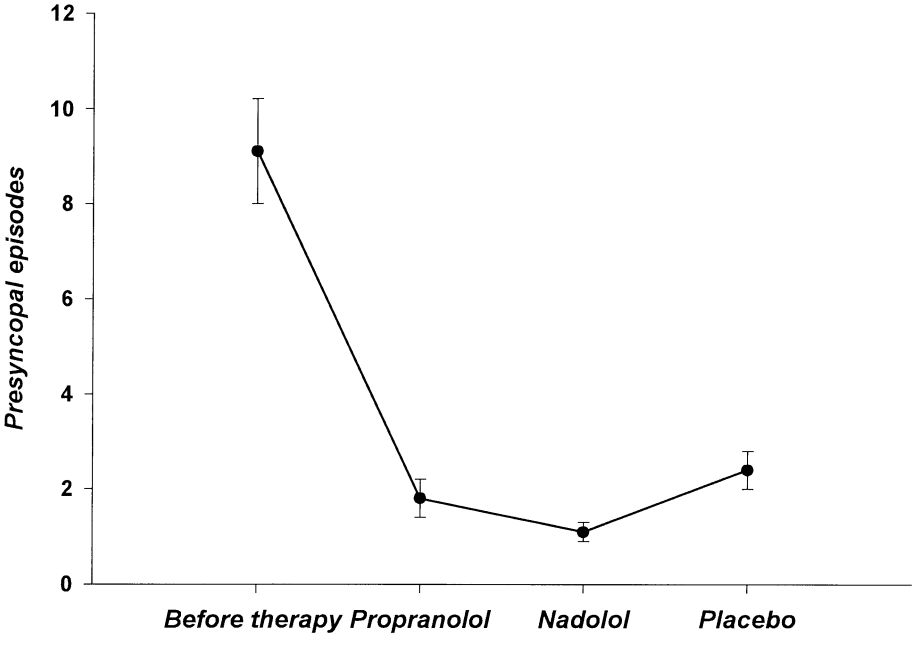

Figure 2. Mean (±SE) number of presyncopal episodes before and during therapy with propranolol, nadolol and placebo.

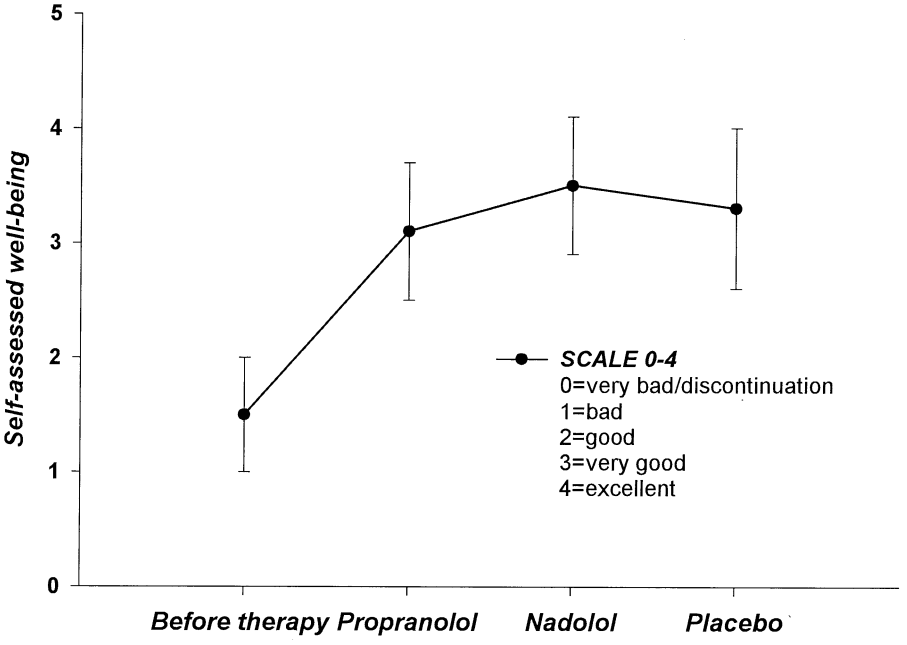

Figure 3. Patients' self-assessed well-being before and during therapy with propranolol, nadolol and placebo.

copal episodes) and placebo treatment (ANOVA: chi-square = 5.4, $p < 0.02$ for syncopal episodes; chi-square = 10.0, $p < 0.001$ for presyncopal episodes). Based on this, repeated tilt test results were not representative of the patients' clinical improvement.

Drug side effects and patients' well-being. All drugs improved the patients' well-being (ANOVA: chi-square = 61.9, $p < 0.0001$). The mean ± SE values of the personal well-being score before therapy and during therapy with each drug are presented schematically in Figure 3. During propranolol treatment, five patients were not fully satisfied due to central side effects (fatigue), whereas three reported a feeling of "no drug" treatment while taking the placebo. One patient discontinued propranolol. Four patients reported to prefer nadolol treatment over the others, two preferred placebo and three preferred propranolol. The majority of them (70%) were equally satisfied with the three drugs tested, regarding not only their therapeutic efficacy but also the lack of clinically important side effects and a general self-assessment of well-being during therapy.

DISCUSSION

Main findings. In the present study, we found that lipophilic beta-blockers, hydrophilic beta-blockers and placebo drug are equally effective in treating patients with recurrent VVS. All cause a significant decrease in syncopal and presyncopal episodes and an improvement in the patients' well-being, although occasional personal preferences have been reported.

Therapy. Recurrent VVS can be a severely disabling disorder. Therapy of this syndrome has largely been empiric, based on the mechanisms that are currently believed to be the cause of vasovagal fainting. Although central as well as peripheral mechanisms are important in vasovagal pathogenesis, their relative contribution has not been fully elucidated.

Our present observation—that is, crossing the blood-brain barrier by beta-blockers does not add to their therapeutic efficacy—is in keeping with previous experimental reports in rats, in which the vasovagal reaction could be blocked by beta-blockers, independent of the drug's ability to penetrate the central nervous system (23). A similar therapeutic efficacy between lipid- and water-soluble components tested might be due to the fact that central mechanisms acted upon by propranolol do not add significantly to the therapeutic potential of beta-blockers in VVS. Hence, it seems that the peripheral mechanisms acted upon by nadolol, as well as by propranolol, are more clinically important than the central mechanisms influenced by propranolol alone.

Although beta-blockers have been the most widely used drug class in the treatment of VVS, up to now, to the best of our knowledge, only three randomized placebo-controlled studies assessing the therapeutic efficacy of a hydrophilic, cardioselective beta-blocker (atenolol) have been published. In the first study (17), patients with VVS were randomized to six-week treatment with atenolol, scopolamine, clonidine and placebo. Atenolol was not superior to the placebo treatment in preventing VVS during repeated tilt testing; moreover, a comparison of the time to syncope in positive tilt tests during treatment with atenolol or placebo showed that syncope occurred earlier with atenolol. In the second study (18), patients with VVS were randomized to atenolol or placebo, and a repeated tilt test was performed one month later. A significantly higher response rate was found in the atenolol group. A similar

trend regarding repeated tilt test results was observed in our study patients. Nevertheless, the clinical response to treatment was the same between beta-blockade and placebo treatment. The clinical response to treatment seems to be more important than repeated tilt test results, because the value of the head-up tilt test for assessing therapeutic interventions has already been questioned by previous investigators (12,24–27). Our study patients with positive repeated tilt test results (under each drug treatment tested) also showed important clinical improvement. The results of the third published randomized, controlled study are also in keeping with our findings: Madrid et al. (19) recently found that the recurrence of neurocardiogenic syncope in patients treated with atenolol is similar to that of patients treated with placebo.

The value of a placebo arm in a study testing the therapeutic efficacy in VVS can assess the contribution of the brain cortex in the pathogenesis of VVS. It is important to note that most previous placebo-controlled studies of VVS (17,19,28–34) also found that placebo treatment is equally effective as the other treatments tested. Its effectiveness may be due to the fact that cortical inputs may interface into the hypothalamus and other places in the brain to either potentiate or eliminate an afferent cardiac or noncardiac input. Cortical inputs may also replace or mimic cardiac or peripheral afferent signals and thus introduce or not introduce a vagal reaction. In this respect, reassuring the patient about the benign nature of the syndrome and placebo administration seems to be helpful in reducing episodes. It is possible that simply reassuring patients may be of important clinical value, but this has not yet been systematically tested. So far, the importance of the central nervous system has been traditionally associated with the so-called "central" type of neurally mediated syncope (linked to strong emotional stimulation, such as that occurring in patients with blood or injury phobia) (1,35), but not with the "postural" type (associated with standing) of neurally mediated syncope. As we have observed, it is possible that the role of the central nervous system, as acted upon by placebo administration (and possibly by reassuring the patient), is more important than previously thought. An interesting nonpharmacologic therapy for neurocardiogenic syncope—tilt training—has been proposed (36,37). The investigators report that one of the possible mechanisms of symptom improvement may be related to a powerful, positive psychological impact on patients who often suffer a severe psychological burden. Another important issue in VVS is that patients with multiple vasovagal episodes are more likely to have psychiatric disorders, such as somatization, panic, generalized anxiety and depression (38), which can sometimes be undiagnosed. It is possible that in some patients with VVS, a sporadic first syncopal episode (otherwise not requiring diagnostic or therapeutic intervention) may lead to recurrences through psychological/psychopathologic mechanisms, usually accentuated by psychosocial factors (39). Whatever the case, it has been clear from this study's results that the brain cortex plays an important role in the integration of the vasovagal reflex, and this finding warrants further investigation.

Quality of life and drug treatment for VVS. A rather underestimated issue in vasovagal syndrome treatment, which most of the times is not life-threatening, regards these patients' well-being during therapy. In this study, the majority of patients were equally satisfied with the three drugs tested, pertaining to not only the drugs' therapeutic efficacy and lack of side effects but also the patients' personal well-being. It was interesting to note that, although all treatments improved their well-being, some patients were not satisfied with propranolol treatment due to central side effects, whereas a relatively small number of patients had a feeling of "no drug" treatment with placebo. Hence, it seems that certain patients need individualized therapy. This is in keeping with the current concepts about VVS, which seem to be the final clinical expression of different multiple conditions that are still poorly characterized (1). In this respect, quality-of-life issues should be taken into account to individually optimize treatment.

Study limitations. The patients' assessment periods were relatively short (three months). However, a balance was achieved by the high rate of symptoms before study inclusion. Despite the small number of study patients, a massive reduction in symptoms was observed during follow-up, offering available discriminative power to the test used for statistical evaluation. The present study did not systematically assess quality of life. In the future, more sophisticated measures of this should be used.

CONCLUSIONS

Lipophilic and hydrophilic beta-blockers and placebo are equally effective treatments in VVS, as demonstrated by the reduction in the recurrence of syncope and presyncope, as well as by improvement in the patients' well-being. The results of the present study favor the view that: 1) lipophilia and, hence, central nervous system action, do not add to the therapeutic efficacy of beta-blockade; and 2) cortical regions acted upon by placebo (and possibly by patient reassurement) are important in the integration of the vasovagal reflex. Individualized selection of the ideal drug, as assessed by a combination of its efficacy, lack of side effects and the patient's well-being, is sometimes warranted.

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