JACC Vol. 25, No. 1
January 1995:65–9

Limitations of Head-Up Tilt Test for Evaluating the Efficacy of Therapeutic Interventions in Patients With Vasovagal Syncope: Results of a Controlled Study of Etilefrine Versus Placebo

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Objectives. **This study assessed the efficacy of oral etilefrine (10 mg three times a day) in preventing a positive response to head-up tilt testing.**

Background. **Previous reports have suggested that oral etilefrine can be effective either in preventing a positive response to head-up tilt testing or in reducing syncopal recurrences in patients with vasovagal syncope. Up to now most studies assessing drug therapy in these patients have been uncontrolled.**

Methods. **This was a randomized double-blind crossover study of etilefrine versus placebo in 30 consecutive patients with syncope and a baseline positive head-up tilt test. After the first test, patients had no treatment for 3 days and were randomized to receive etilefrine or placebo for 4 additional days. They underwent tilt testing under treatment and again after 3 days of washout; they then received the alternative treatment for 4 days, and a third test was performed.**

Results. **Head-up tilt test results were negative in 13 (43%) patients with etilefrine and 15 (50%) with placebo (p = NS). Therefore, the statistical power of the study was only 10%. The rate of positive responses decreased with repeated testing irrespective of the assigned treatment: A positive response was obtained during the second head-up tilt test in 20 patients (10 with placebo, 10 with etilefrine) but in only 12 during the third (7 with etilefrine, 5 with placebo) ($p < 0.05$).**

Conclusions. **Oral etilefrine (10 mg three times a day) was not superior to placebo in preventing a positive response to head-up tilt testing. Despite a low statistical power, the high rate of negative response with placebo (50%) suggests that controlled trials are needed to assess the real efficacy of any treatment in patients with vasovagal syncope.**

(J Am Coll Cardiol 1995;25:65–9)

In 1986 Kenny et al. (1) first described the clinical usefulness of head-up tilt testing for the diagnosis of vasovagal syncope. Since then, head-up tilt testing has been used extensively by many investigators. In recent years, head-up tilt testing has been used not only to diagnose vasovagal syncope (2–6), but also to assess the clinical efficacy of therapeutic interventions, such as drugs (7–15) or pacemakers (16–21). Its use in evaluating therapeutic interventions has at least two limitations. First, the reproducibility of the test is not well characterized because of the great variability in the methodology of the different studies addressing this issue, especially in the time interval between the baseline and the repeated tests, which has varied from 10 min to 6 weeks (22–26). Second, the meaning of negative head-up tilt test results under treatment in patients with previous positive results has not been established because most studies have been uncontrolled.

The initial aim of our study was to assess the efficacy of oral etilefrine in preventing a positive response to head-up tilt testing. Despite reports (23,25,26) that suggested that the reproducibility of a positive response was high, we considered that only a controlled study would suffice. For this reason we designed a double-blind randomized crossover study with oral etilefrine versus placebo in patients with syncope of unknown origin and a positive response to head-up tilt testing. Our findings raised the issue of whether repeated head-up tilt tests have limitations for assessing therapy for vasovagal syncope.

In the present study we discuss the therapeutic value of etilefrine in vasovagal syncope and the limitations of head-up tilt testing in assessing therapeutic interventions in this condition.

Methods

Patients. In our service, patients with syncope of unknown origin are studied after a protocol that includes clinical history, physical examination, baseline 12-lead electrocardiogram

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Manuscript received May 16, 1994; revised manuscript received July 15, 1994, accepted August 5, 1994.

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0735-1097/95/$9.50
0735-1097(94)00336-O

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January 1995:65–9

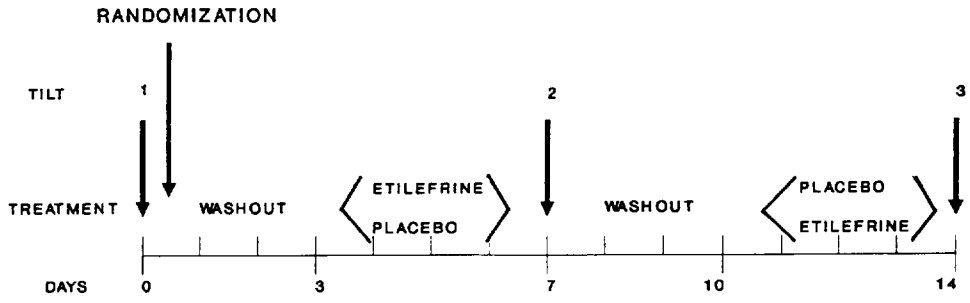

Figure 1. Study protocol. Patients with a baseline positive head-up tilt test response were randomized and had no treatment for 3 days. On the fourth day they received the first assigned treatment (placebo or etilefrine) for 4 days. On the seventh day a new head-up tilt test (TILT 2) was performed. Irrespective of the result of this test, there was a 3-day washout period. On the 10th day, the patients received the alternative treatment for 4 days, and a last test (TILT 3) was performed on the 14th day.

(ECG), 24-h ambulatory ECG monitoring and chest X-ray film. In patients with no structural heart disease and normal ECG results in whom these examinations do not disclose the etiology of syncopal episodes, a baseline head-up tilt test is performed. For the purpose of the present study, patients with a positive response to head-up tilt testing were diagnosed with vasovagal syncope and considered eligible. Patients with a history of hypertension, defined as systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg, were not considered eligible for etilefrine administration. In patients with positive baseline head-up tilt test results that showed a severe cardioinhibitory response, defined as asystole >5 s, the safety of performing three consecutive head-up tilt tests in a study protocol was considered questionable, and they were thus excluded.

From April 1992 to December 1993, head-up tilt testing was performed in 290 patients with syncope of unknown origin. Positive results were obtained in 96 patients (33%). Twenty-one patients (22%) were excluded because of previous hypertension and 11 (11%) because of a cardioinhibitory response to head-up tilt testing. Of 64 patients who were asked to participate in the study, 25 refused.

Nine of 39 patients who were randomized did not complete the protocol. Drug administration was well tolerated in all but two patients: One patient developed severe hypertension during etilefrine administration as the first assigned treatment, and he was withdrawn from the study; the other patient had epigastric discomfort during placebo therapy and declined to receive the alternative treatment. One patient developed severe gout during the study and could not repeat the head-up tilt test. Six patients did not comply with the treatment protocol and were excluded.

Thirty patients with baseline positive head-up tilt test results completed the protocol. All of these patients remained in clinically stable condition, without intercurrent illnesses, during the study period.

Study protocol. This was a double-blind randomized crossover study with oral etilefrine at a dose of 10 mg three times a day versus placebo.

The head-up tilt test protocol used in this study has been previously described and validated elsewhere (21,27,28). Patients were placed in a supine position, and an intravenous line was inserted; blood pressure was assessed by repeated measurements with an automatic sphygmomanometer (BP 103 N, Nippon Colin) every 2.5 min or more frequently if symptoms developed; the ECG was continuously monitored. Ten minutes after the insertion of intravenous line, blood pressure and heart rate were measured, and after 5 min of stable heart rate and blood pressure in the supine position, patients were tilted to 75° for 30 min. If no positive response was elicited, an isoproterenol infusion was administered at a dose of 3 μg/min over 10 min and increased to 5 μg/min for an additional 10 min. The rate of infusion was adjusted so that heart rate did not exceed 140 beats/min. Results were considered positive if syncope or presyncope developed in association with severe hypotension; in such instances the test was stopped, and the patient was placed in the Trendelenburg position until total recovery.

Patients who fulfilled the inclusion criteria gave informed consent to participate in the study. The sequence of treatments, etilefrine or placebo, was randomized for each patient included (Fig. 1). After a positive response to the first head-up tilt test, patients were randomized, and no treatment was given for 3 days. On the fourth day the first assigned treatment was begun: 10 mg of etilefrine (two 5-mg tablets) or placebo (two tablets) three times a day, for 4 days. A second head-up tilt test with the first assigned treatment was repeated on the fourth day of treatment (i.e., 7 days after the baseline test). After that, there was a 3-day washout period, and the patients then received the alternative treatment for 4 days. On the fourth day, a third head-up tilt test was performed under treatment, 7 days after the previous test. For each patient all repeated tests were performed at the same hour of the day as the first baseline test, and the last dose of the assigned treatment was administered 1 h before the test.

The protocol was approved by the ethical committee of our institution.

Statistical analysis. Analysis of repeated tests performed during the two different treatments used the chi-squared test for paired observations (McNemar test), taking into consider-

Table 1. Baseline Characteristics of Both Study Groups*

	ET-PL (n = 15)	PL-ET (n = 15)
Gender (M/F)	6/9	10/5
Age (yr)	44 ± 22	48 ± 16
SBP (mm Hg)	137 ± 15	140 ± 16
HR (beats/min)	76 ± 9	72 ± 13
Num sync		
<3	9	8
3–10	4	3
>10	2	4
Time sync–tilt		
<1 mo	6	5
1–4 mo	5	5
>4 mo	4	5

*p = NS for both groups. Data presented are mean value ± SD or number of patients. ET-PL = patients with etilefrine as the first assigned treatment; F = female; HR = heart rate; M = male; Num sync = number of previous syncopal episodes; PL-ET = patients with placebo as the first assigned treatment; SBP = systolic blood pressure; Time sync–tilt = time interval between last syncopal episode and tilt.

Table 2. Results of Sequential Head-Up Tilt Test With Etilefrine or Placebo

Response	Tilt 1	Tilt 2		Tilt 3
+	n = 30	Etil (n = 10)	10 →	Etil (n = 7)
		Plac (n = 10)	10 ↗	Plac (n = 5)
−	n = 0	Etil (n = 5)	2 ↘	Etil (n = 8)
		Plac (n = 5)	8 →	Plac (n = 10)

Of the 30 patients who had a positive (+) baseline (Tilt 1) head-up tilt test response, only 20 had a positive response with treatment, 10 with etilefrine (Etil) and 10 with placebo (Plac). During the third test (Tilt 3), only 12 patients had a positive response, 7 with etilefrine and 5 with placebo. Only 10 of the 20 patients with positive results on the second test (Tilt 2) had a positive response during the third test, whereas 8 of the 10 patients with a negative (−) response during the second test had a negative response during the third test ($p < 0.05$). A negative response to a head-up tilt test was observed in 13 patients (43%) with etilefrine and 15 (50%) with placebo.

ation only discordant results between treatments. To eliminate the possible training effect that repeated testing could have on the response to head-up tilt testing, we performed two separate analyses. First, we compared the results obtained with etilefrine versus placebo in the first treatment period with the chi-squared test as if the design were a parallel one. Second, we compared the results of the second and third head-up tilt tests, irrespective of the assigned treatment, using the McNemar test.

Results

The study included 30 patients (16 [53%] men, 14 [47%] women; mean [±SD] age 46 ± 19 years, range 16–84). The first assigned treatment was etilefrine in 15 patients and placebo in the other 15. Baseline characteristics, such as gender distribution, age, baseline systolic blood pressure and heart rate, number of previous syncopal episodes and time elapsed from last syncope to head-up tilt test, are shown in Table 1 (p = NS for both groups). The positive response to the first head-up tilt test occurred during the first 30 min (i.e., without isoproterenol) in 13 patients (43%) and during the last 20 min (i.e., with isoproterenol infusion) in 17 (57%). Mean heart rate in the supine position in the whole group before the test was 74 ± 11 beats/min at baseline, 75 ± 13 beats/min with etilefrine and 75 ± 14 beats/min with placebo (p = NS). Mean systolic blood pressure was 138 ± 15 mm Hg at baseline, 131 ± 19 mm Hg with etilefrine and 134 ± 16 mm Hg with placebo (p = NS).

Head-up tilt test results (Table 2) were negative in 13 patients (43%) with etilefrine and 15 (50%) with placebo (p = NS). With both etilefrine and placebo, head-up tilt test results remained positive in 10 patients (33%) but became negative in 8 (27%). Results were negative with etilefrine and positive with placebo in five patients (17%) and negative with placebo but positive with etilefrine in seven (23%). Statistical analysis for paired observations in the 12 patients who had discordant responses with etilefrine and placebo showed no significant differences. Negative responses achieved with etilefrine or placebo were observed irrespective of the finding that a positive response to the baseline test occurred either with or without isoproterenol infusion. Among the 13 patients with a positive response during the first head-up tilt test without isoproterenol, 5 (38%) had a negative response with etilefrine and 4 (31%) with placebo. Of the 17 patients with a positive response during the first test with isoproterenol, 8 (47%) had a negative response with etilefrine and 11 (65%) with placebo. Of the 32 positive responses observed with either etilefrine or placebo, 25 (78%) occurred during the same time period as the baseline test (with or without isoproterenol), and only 6 (22%) showed discordance in the period of positive response. As a consequence of the high rate of negative conversion of positive responses with placebo, the statistical power of the study was only 10%.

To eliminate the possible training effect that repeated testing could have on the response to head-up tilt, we compared the results obtained with etilefrine with those obtained with placebo during administration as the first assigned treatment as if the study design were a parallel one (Table 2). Of the 15 patients with etilefrine as the first test treatment, 5 (33%) had negative results; of the remaining 15 patients with placebo as the first assigned treatment, 5 (33%) also had negative results (p = NS).

Because of the apparent lack of efficacy of etilefrine in preventing syncopal response to head-up tilt testing compared with placebo, we analyzed the possible effect of repeated head-up tilt testing irrespective of the assigned treatment (Table 2). In the second test (the first one with treatment), 20 patients (67%) had a positive response, whereas this was reduced to 12 (40%) in the last head-up tilt test. Of these 20 patients with a second positive test response, 10 (50%) had a negative response in the last test, whereas 8 (80%) of the 10 patients with a second negative test response had a negative response in the last head-up tilt test (chi-square analysis for

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paired observations with continuity correction factor 3.8, $p < 0.05$).

Discussion

Efficacy of etilefrine. Our results show that oral etilefrine at a dose of 10 mg three times a day is not superior to placebo in preventing syncopal response to head-up tilt testing in patients with vasovagal syncope with a positive response at baseline testing. Etilefrine is an alpha-agonist drug with a strong vasoconstrictor effect that was first proposed by Raviele et al. (8) as an effective treatment in patients with vasovagal syncope, either in preventing a positive response to head-up tilt testing or in reducing recurrence during follow-up. In our study, head-up tilt testing results were negative in 43% of patients with etilefrine, but this rate was not superior to the rate of negative responses observed with placebo. When our trial was designed, the suggested doses of etilefrine to treat patients with vasovagal syncope were 15 to 30 mg daily (8). In fact, the lack of modification of baseline arterial blood pressure observed between the baseline head-up tilt test and that performed with etilefrine suggests that in our study, etilefrine may not have had a measurable pharmacologic effect, perhaps because the doses were not high enough to achieve a consistent vasoconstrictor action. However, with higher doses an increasing rate of side effects, such as hypertension and gastric discomfort, are to be expected. Consequently, our results do not rule out the possibility that higher doses could be effective.

Limitations of head-up tilt test. Unexpectedly, the most relevant findings of our study were the low rate of positive responses observed either with placebo or etilefrine, suggesting a low reproducibility of the test, and the trend toward a progressive loss of positive responses with repeated testing.

Repeated head-up tilt testing has been used by many investigators to assess the efficacy of different interventions, such as beta-adrenergic blocking agents (10,11,15,29–31), disopyramide (7,11,12), etilefrine (8), fludrocortisone (11), scopolamine (11,15,32), fluoxetine (9), verapamil (13) or pacemakers (1,16–21). In many of these reports, the conversion of a previously positive head-up tilt test result to a negative response has been taken as evidence of therapeutic benefit. However, almost all of these studies have not been controlled trials. To our knowledge, only Morillo et al. (12) and Fitzpatrick et al. (15) have evaluated the effectiveness of drugs in head-up tilt testing in a controlled trial, and they did not find any beneficial effect when compared with placebo. In fact, the high rate of negative conversion of a positive response with placebo seen in our study (50%), which resulted in its low statistical power (10%), stresses the need to carry out controlled studies to assess any therapeutic benefit in vasovagal syncope.

For head-up tilting to be of use in evaluating the beneficial effect of any therapeutic intervention, the test must be highly reproducible. The reproducibility of an initially negative response is high and has shown little variation between different series, ranging from 85% to 100% (22–26,33). However, the reproducibility of positive responses is lower and less uniform, ranging from 36% to 92% (22–26,33,34). These observations suggest that the data on reproducibility of the test are not consistent enough to allow the use of head-up tilting as the standard test for guiding therapy.

In our patients, the progressive loss of positive responses observed in sequential head-up tilt testing suggests a low reproducibility rate. Alternative explanations are the phenomenon of regression to the mean or even the inclusion of the patient in a therapeutic trial (Hawthorne effect) (35).

Aware that the lack of high reproducibility could invalidate the test for guiding therapy, some investigators have required two consecutive baseline positive head-up tilt tests before using it as a therapeutic guide (15,18,21,29). Morillo et al. (12) and Fitzpatrick et al. (15) showed that after two consecutive baseline tests with positive results, 25% and 30% of patients had negative results in a third head-up tilt test with placebo. Our results show that even after the presence of two consecutive positive responses to head-up tilt testing there is a 50% probability that a third head-up tilt test will have negative results in the absence of a proved pharmacologic effect. These results suggest that two consecutive positive responses to head-up tilt testing are not enough to ensure reproducible positive responses in subsequent testing. Some reports (8,9) have evaluated the efficacy of more than one drug with consecutive head-up tilt testing. According to our data, the greater the number of repeated tests performed, the higher the possibility of achieving a negative response irrespective of whether any pharmacologic effect has been achieved.

Therefore, our results, although representing a data-generated hypothesis, suggest that the use of head-up tilt testing in assessing clinical efficacy of therapeutic interventions in an individual patient may have serious limitations. As suggested in our study, a negative response under any treatment does not necessarily mean that a beneficial therapeutic action has been achieved. Therefore, head-up tilt testing should be used to assess the global efficacy of pharmacologic or nonpharmacologic therapeutic interventions only in the setting of controlled trials.

Conclusions. Our study suggests that oral etilefrine at a dose of 10 mg three times a day was not effective in preventing a positive response to head-up tilt testing in patients with syncope and a positive baseline test. However, the possible effectiveness of the drug cannot be definitely ruled out because of the low statistical power of the study. Additionally, the rate of negative responses with placebo was up to 50%, with a significant trend to a decreased rate of positive responses with consecutive head-up tilt testing. These data suggest that repeated head-up tilt testing may be unreliable for assessing the individual efficacy of drugs in patients with syncope and positive head-up tilt test results and controlled, randomized, parallel trials are needed to assess the real efficacy of any treatment in these patients. In addition, our data-generated hypothesis of a trend toward a diminishing rate of positive responses with repeated tilting should be tested in appropriately designed prospective trials.

We are grateful to Dolors Bofill, RN, and Montse Campanyà, RN, for their support in the performance and scheduling of sequential head-up tilt testing.

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