Failure of Alpha Tocopherol to Influence Chest Pain in Patients with Heart Disease

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Claims for vitamin E in angina pectoris have not been based on controlled observations. Even some negative reports have not been adequately controlled as to nonspecific factors. Hence, this study of the effects of alpha tocopherol on cardiac pain used a method of investigation carefully controlled as to psychologic factors which might affect the patient's response or the examiner's interpretation of results. The dose of synthetic alpha tocopherol acetate (300 mg. by mouth daily for two or more months) was the same as that recommended by advocates of this form of therapy as optimum in most cases. The results failed to indicate that the vitamin possessed any advantage over the placebo for treatment of either effort angina or mixed types of cardiac and somatic chest pain.

DURING the course of our studies on the visceral and somatic components of chest pain in patients with heart disease,[1–4] Vogelsang, Shute and Shute[5–9] and Molotchick[10] reported beneficial effects of vitamin E on "anginal pain" and heart disease. It occurred to us that the relief of pain in such cases might be due, at least in part, to effects of vitamin E on the voluntary muscles rather than on the heart. This concept was supported by the fact that animals deprived of vitamin E show reversible changes in both cardiac[11, 12] and skeletal[13, 14] musculature, and by reports on the usefulness of vitamin E in the muscular dystrophies and somatic pain syndromes such as fibromyositis.[15–18]

We decided, therefore, to classify chest pain in our cardiac patients according to visceral and somatic components, and to evaluate by the blind-test method the effect of alpha tocopherol on these components in parallel series of control and treated subjects. The need for such a blind-test study is emphasized by Vogelsang, Shute and Shute themselves,[9] as well as by recent editorial comment.[19] The latter concludes: "Subjective benefits claimed [for vitamin E] may justify a series of well controlled experimental studies in human heart disease to determine whether purely psychologic or real physiologic changes are involved." Unfortunately, neither the initial favorable reports on vitamin E therapy,[5–10] nor later negative results of other investigators[20–21] were based on observations adequately controlled with respect to nonspecific factors.

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The synthetic alpha tocopherol (Ephynal Acetate) and matching placebo tablets were supplied by Hoffmann-La Roche, Inc.

METHODS

Forty-one ambulatory patients with chronic chest pain and with arteriosclerotic and/or hypertensive heart disease were selected at random from the Cardiac Clinic. Three patients refused to continue their medication after varying periods of time and are discussed later. Thirty-eight patients completed the course of therapy, 19 having received synthetic alpha tocopherol and 19 a matching placebo tablet.

The study was conducted according to stringent blind-test methods. After preliminary study the patients were paired and matched with respect to sex, age, cardiovascular status, duration and type of chest pain, and other pertinent factors (table 1). One of each pair was allotted by chance to either the control (placebo) or treated (vitamin) group. It may be seen from table 1 that the two groups are closely comparable. None of the examiners knew whether vitamin or placebo was being administered to any particular patient. The physician (S.H.R.) who administered the medication never examined the patients. Even in the analysis of the data the final evaluation of the effect of medication was made in each case without knowledge as to whether the patient was in the treated or control group.

These 38 patients exhibited three types of chest pain: (1) effort angina—pain in any part of the chest regularly induced by walking and promptly relieved by rest and/or nitrites (14 treated, 13 control); (2) constant chest pain—pain present most of the time to a greater or lesser degree (2 treated, 1 control); and (3) intermittent chest pain unlike effort angina

(2 treated, 2 control). We regard the chest pain in the first group as being primarily of cardiac origin and in the latter two groups as being chiefly somatic. Two patients had both effort angina and constant pain (both control). During the preliminary period of observation, two patients with effort angina became free of their chest pain a few days before medication was begun (1 treated, 1 control). We kept these patients in the study in order to note whether pain recurred while on medication; in neither instance, however, was there recurrence of chest pain.

None of the patients had pain on breathing, such as characterizes pleurisy or intercostal neuralgia, nor was the pain traceable to any pulmonary lesion.

To evaluate effects on the somatic factor of cardiac pain, at each visit the presence and location of tender areas in the chest muscles were noted on special charts, together with a description of pain reference induced by pressure on specific trigger areas.[2] Areas of spontaneous pain, whether constant or related to effort, were also mapped. The muscles examined included the sternalis, pectoralis major and minor, serratus anterior, erector spinae (especially the multifidus and iliocostalis), and other scapular and interscapular muscles. These examinations were repeated at each visit, usually every two or three weeks. A total of 365 visits were made by the 41 patients, exclusive of those for laboratory tests.

Initial laboratory work included electrocardiorgams, x-ray examinations of the heart and spine, complete blood counts, urinalysis, blood chemistry, and determination of blood sedimentation rates. The electrocardiograms were repeated at intervals during the study, and other tests as indicated.

Special tests included the following:

1. Measurement of the patient's capacity for effort without pain, or exercise tolerance. At intervals of several weeks this test was carried out according to the two-step technic under standard conditions previously described.[25, 26] In 9 patients the results of the test were inconclusive because of indecisive end points. On 13 patients the test could not be performed because pain on effort was not present, or because pain in the joints of the lower extremities prevented walking over steps, or because of intermittent claudication.

2. Measurement of skeletal muscle power. A spring-device grip recorder, standardized in arbitrary units, was used to measure the strength of the grip in each hand.

3. Measurement of skeletal muscle endurance. Deep pain was produced by contraction of the forearm muscles during ischemia by a technic similar to that of Lewis,[27] Harrison and Bigelow,[28] and others. The pressure in the cuff was raised to a minimum of 200 mm. Hg, or if the systolic blood pressure was more than 150 mm., to 50 mm. above this. A metronome, set for one beat per second, was used to maintain a constant rate of thirty flexor contractions per minute. On alternate beats, the patients closed and opened the fingers; the two movements were recorded as a unit by a mechanical counter. The patient stopped when there was so much pain that he could no longer keep up with the metronome. The end point was usually quite sharp: sudden inability to move the fingers on account of pain.

The plan of medication was as follows: Alpha tocopherol was given in doses of 200 mg. daily by mouth for two weeks, and then 300 mg. daily. This was administered in divided doses of 100 mg. each.

TABLE 1.—*Initial Status of Treated and Control Groups with Respect to Various Factors*

Factors	Alpha tocopherol (19 cases)	Placebo (19 cases)
	(no. cases)	(no. cases)
Sex: Males	9 (47%)	13 (68%)
Females	10 (53%)	6 (32%)
Age: Average	61 yrs.	59 yrs.
Range	(49–72)	(47–77)
Chest pain		
Duration: Average	6.1 yrs.	7.4 yrs.
Range	($\frac{1}{2}$–15)	($\frac{1}{6}$–15)
Type: Effort angina	15 (79%)	14 (74%)
Somatic pain	4 (22%)	5 (27%)
Cardiovascular		
Hypertension	6 (32%)	8 (42%)
Previous myocardial infarction	9 (47%)	7 (36%)
Abnormal electrocardiogram	8 (42%)	11 (58%)
Congestive heart failure	0 (0%)	0 (0%)
Miscellaneous		
Somatic pain syndromes (exclusive of chest)	12 (63%)	13 (68%)
Osteoarthritis of spine	19 (100%)	19 (100%)
Diabetes mellitus	1 (5%)	2 (11%)
High blood sedimentation rate	2 (11%)	2 (11%)
Anemia	0 (0%)	0 (0%)

A similar number of the matching placebo tablets was prescribed. For the 38 patients in the final series, administration of alpha tocopherol averaged sixteen weeks (ten to twenty weeks), and of the placebo 16.6 weeks (ten to twenty weeks). The 3 patients of the original series who discontinued medication (alpha tocopherol), stopped the drug because of increased chest pain in one, two, and five weeks, respectively. Use of iron salts and mineral oil was prohibited because it has been suggested that these substances might interfere with the absorption of alpha tocopherol.[5, 9, 29] Nitroglycerine and digitalis, if in use, were continued as before.

Results*

Chest Pain. It may be seen from table 2 that the response to medication was essentially the same for alpha tocopherol and for the placebo. Thus, no improvement was noted in 63 per cent of the 19 treated subjects and in 73 per cent of the 19 controls. Subjective improvement was reported by 37 per cent of the treated patients and by 27 per cent of the controls. Two of the control subjects who were classed as unimproved had intercurrent clinical complications—one patient developed congestive heart failure and the other, an acute myocardial infarction. These complications occur naturally in the course of arteriosclerotic heart disease, and in so small a series it cannot be considered statistically significant that both of these patients were in the control group. It may be noted that the only changes observed in the serial electrocardiograms occurred in the patient with the infarction, and these changes were related to this acute episode.

When the effect of medication was analyzed with respect to visceral and somatic components of chest pain, it was found that the results were again similar in the treated and control groups (table 3).

In 2 patients, trigger areas present in the chest muscles on the initial examination disappeared during medication (1 treated, 1 control). Five patients who were without such areas of deep tenderness at the start, remained so. In all other patients, the same tender areas in the

Table 2.—*Response to Medication for All Types of Chest Pain*

Response of chest pain	Alpha tocopherol	Placebo
	(no. cases)	(no. cases)
Total	19	19
No improvement	12 (63%)	14 (73%)
Improvement	7 (37%)	5 (27%)

Table 3.—*Response to Medication According to Type of Chest Pain**

Type of chest pain	Response of chest pain	Alpha tocopherol	Placebo
		(no. cases)	(no. cases)
Effort angina	Total	15	14
	Same	10 (67%)	9 (64%)
	Better	5 (33%)	3 (22%)
	Worse	0 (0%)	2 (14%)
Somatic chest pain (constant and intermittent)	Total	4	5
	Same	2 (50%)	3 (60%)
	Better	2 (50%)	2 (40%)
	Worse	0 (0%)	0 (0%)

* Two patients appear twice in this analysis since they have both effort angina and constant chest pain. The two patients who became free of chest pain just before start of medication are excluded.

Table 4.—*Influence of Medication on Capacity for Work of Cardiac Muscle (Exercise Tolerance Test)*

	Alpha tocopherol (8 cases)	Placebo (8 cases)
Average no. trips before medication	17 (4–25)	23 (4–39)
Net change at end of medication	+6% (−70% to +125%)	+110% (−29% to +633%)

Table 5.—*Analysis of Data in the Seven Patients Who Considered Their Chest Pain Improved by Medication (Alpha Tocopherol)*

Basis of patient's evaluation	Exercise tolerance net change at end of study (%)
Effort angina	
Can now walk 6 or 8 blocks without pain, formerly only 2 blocks	−70
Now walks same distance as before medication, but pain is less severe	−12
Can walk much further without pain: now 46 blocks, formerly only 2½ blocks	+6
Attacks occur less often now than before medication	−5
Can continue walking a little distance after onset of pain whereas before he had to stop at once	+20
Intermittent chest pain	
Attacks now occur at longer intervals; pain just as severe during attacks	Not done, old leg injury
Attacks occur less often and are also less severe	−17

* A preliminary report has been made.[30]

chest muscles persisted throughout the period of observation (15 treated, 16 control).

Satisfactory exercise tolerance tests were obtained on 16 patients (8 treated, 8 controls). Analysis of the results (table 4) reveals an average net increase of 6 per cent in exercise tolerance for the treated group, and 110 per cent for the control group. This average value of 110 per cent includes one patient in the control group who had a very large percentage increase in exercise tolerance (633 per cent). This patient had had an acute myocardial infarction six months prior to the initial exercise tolerance test, and it is likely that the final test five months later reflects spontaneous improvement in myocardial function during recovery from this acute episode.

Seven patients said that they were much better as the result of alpha tocopherol medication (table 5). It should be noted that the improvement is a matter of degree, rather than total relief of pain. The majority of these did not show a corresponding improvement in exercise tolerance. Furthermore, the patients on placebo medication who said they were much better (table 6) made exactly the same kind of statements regarding relief of pain as did those on alpha tocopherol. This indicates the need for parallel series. In fact, one patient expended his supply of the placebo tablets two days before his final visit and stated that his chest pain became much worse in those two days.

Skeletal Muscle. Objective evidence of improvement in this function was also lacking. The measurements of grip, that is, muscle strength, showed a net change after medication of −5 per cent for the treated, and +2 per cent for the control group (table 7). Similarly, with respect to skeletal muscle endurance or capacity for work during ischemia, the net change after medication is similar for the vitamin-treated and the placebo-treated subjects. The increase of 14 per cent and 25 per cent for treated and control groups, respectively, may be due to training.

Hypertension. It has been recommended that doses of only 150 mg. of alpha tocopherol be given initially to patients with hypertension because larger doses raise the blood pressure.[9] Our data show that the blood pressure was not elevated by 200 mg. and 300 mg. doses of alpha tocopherol, even in the 2 patients with systolic blood pressure levels of 210 and 220 mm. Hg respectively. Furthermore, in none of the 6 pa-

TABLE 6.—*Analysis of Data in the Five Patients Who Considered Their Chest Pain Improved by Medication (Placebo)*

Basis of patient's evaluation	Exercise tolerance net change at end of study (%)
Effort angina	
Can now walk 12 blocks without pain, formerly only 2 blocks	+633
Attacks of pain much less severe	0
Can now walk 3 blocks without pain, formerly only 1 block	Test refused
Intermittent chest pain	
Less severe chest pain	Not done, intermittent claudication
Constant and effort angina	
No more constant pain. Pain still occurs on walking as before	+200

TABLE 7.—*Influence of Medication on Capacity for Work of Skeletal Muscle*

	Alpha tocopherol (19 cases)		Placebo (19 cases)
Muscle strength (grip)	Average no. units before medication	38 (19–59)	47 (22–62)
	Net change at end of medication	−5% (−40% to +32%)	+2% (−42% to +32%)
Endurance during ischemia (deep pain tolerance)	Average no. contractions before medication	44 (27–92)	44 (20–86)
	Net change at end of medication	+14% (−48% to +96%)	+25% (−36% to +100%)

tients with hypertensive heart disease who received alpha tocopherol, was there any significant lowering of the blood pressure.

Toxicity. No toxic effects were attributable to these doses of alpha tocopherol. The 3 patients who insisted on discontinuing the vitamin therapy because of increased pain were subject to spontaneous exacerbations of chest pain prior to this medication. Other complaints during vitamin administration were palpitation, spots before the left eye, and sleepiness. On the other hand, 3 patients who received the placebo blamed it for causing nausea, constipation, and weakness, respectively.

Discussion

Evaluation of drug therapy in cardiac pain is fraught with pitfalls due to the many nonspecific factors that may contribute to relief of pain in this condition.[4] It is because of this that we took care to establish a control group as similar as possible to the treated group (table 1), and to conduct the study under doubly blind conditions. Not only were the patients unaware of the nature of the agent being administered, but also those who examined the patients and evaluated the results were ignorant of the material given in any particular case.

As we have indicated, the response to alpha tocopherol was essentially the same as that to the placebo, namely, subjective relief of pain in 37 per cent and 27 per cent, respectively (table 2). These figures are in accord with the observations of Evans and Hoyle[31] that the administration of a placebo to patients with angina pectoris was accompanied by a diminution of pain in 40 per cent of the cases.

Our results fail to confirm those of Shute, Shute, and Vogelsang[6] who reported some degree of improvement in 96 per cent of 84 patients with "anginal pain" on daily doses of about 200 mg. to 300 mg. of alpha tocopherol; 5 of their patients received 400 mg. and one, 600 mg. daily. They regard a dose of 200 mg. as optimum in 80 per cent of cardiac cases.[9] As for the speed of effects, they state[9] "A favorable response to tocopherol therapy may begin at once, but oftener does not appear for 5 to 10 days." They noted that occasionally a therapeutic result may not appear for as long as six weeks. According to these criteria, the periods of about two and one-half to five months, during which our patients received "optimum" doses of alpha tocopherol, represent adequate time for clinical trial.

Failure of alpha tocopherol to relieve angina pectoris has likewise been reported by others. Ravin and Katz[20] gave the equivalent of 250 mg. of alpha tocopherol daily to 11 patients with effort angina for an average of fourteen weeks (four to twenty-four weeks). Levy and Boas[21] administered 200 mg. to 800 mg. of alpha tocopherol daily to a similar group of 8 patients for from three to twelve weeks. Baer, Heine, and Gelfond[22] employed a daily dose of 300 mg. to 400 mg. of vitamin E in 5 such patients. Makinson, Olesky, and Stone[23] gave 150 mg. daily of vitamin E to patients with angina pectoris for three weeks. None of these investigators found unequivocal improvement in cardiac pain. Ball[24] gave 300 mg. of alpha tocopherol daily to 10 such patients for at least six weeks, and observed some diminution of pain in 4, but noted that this effect was comparable to the 40 per cent improvement which follows administration of a placebo to patients with angina pectoris.

Summary and Conclusions

1. Effects of synthetic alpha tocopherol and a placebo were compared by the blind-test method in 41 ambulatory patients with chronic chest pain and heart disease (chiefly arteriosclerotic and hypertensive). Thirty-eight patients completed the course of medication; 19 received the vitamin, and 19 the placebo.

2. Most of the patients (76 per cent) had effort angina alone; the remainder exhibited mixed types of cardiac and somatic chest pain.

3. Synthetic alpha tocopherol was given by mouth in daily doses of 200 mg. for about two weeks, and 300 mg. thereafter. A similar number of matching placebo tablets was given.

4. The average duration of administration of the vitamin was sixteen weeks (ten to twenty weeks) and of the placebo, 16.6 weeks (ten to twenty weeks).

5. No toxic effects of these doses of alpha tocopherol were noted.

6. The effects of medication on chest pain

and on objective measurements of cardiac and skeletal muscle function were similar for the group given alpha tocopherol and for the controls who received the placebo.

7. Our results fail to confirm the reported benefits of alpha tocopherol in cardiac pain.

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