Vitamin E for intermittent claudication

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A substantive amendment to this systematic review was last made on 19 November 1997. Cochrane reviews are regularly checked and updated if necessary.

Abstract

Background
It is thought that vitamin E may improve tolerance to intermittent claudication (i.e. pain caused by ischaemia in the muscles of the leg during exercise), thereby relieving the pain, through a variety of mechanisms.

Objective
The objective of this review was to determine the effects of vitamin E on people with intermittent claudication.

Search strategy
The reviewers searched the Cochrane Peripheral Vascular Diseases Group trials register, reference lists of relevant articles and a library specialising in literature on vitamins (most recent search performed in November 2000).

Selection criteria
Controlled trials comparing vitamin E with placebo, or other interventions, in patients with intermittent claudication.

Data collection and analysis
Both reviewers extracted data and assessed study quality independently.

Main results
Five eligible studies were found with a total of 265, predominantly male, participants. The average age was 57 years. The follow-up varied from 12 weeks to 18 months. The trials were small and generally of poor quality. The people studied were reasonably homogeneous but five different doses of vitamin E were used and four different physical outcomes were measured. No trials were identified that compared vitamin E with treatments other than placebo.

Reviewers’ conclusions
While vitamin E - which is inexpensive and has had no serious side effects reported with its use - may have beneficial effects, there is insufficient evidence to determine whether it is an effective treatment for intermittent claudication.

Synopsis

More research is needed to show if Vitamin E helps intermittent claudication

Intermittent claudication is a cramping pain, brought on by exercise and relieved by rest, that is caused by an inadequate blood flow to the calf and leg muscles. It is a symptom of atherosclerosis, a disease where fatty deposits build up in the arteries, blocking blood flow. It has been suggested that taking Vitamin E may improve blood flow and boost the body’s ability to repair. The review of trials found that more research is needed to show if Vitamin E reduces the effect of intermittent claudication. No adverse effects were found.

Background

INTERRITTENT CLAUDICATION

Intermittent claudication is a symptom of leg atherosclerosis usually exhibited in older persons, which occurs in 0.5-14% of different populations in different geographical locations (Balkau 1994). People with intermittent claudication experience pain in the calf of one or both legs when they are walking. Symptoms are caused by atherosclerosis in the major arteries of the legs, resulting in decreased blood flow. When oxygen demand increases during exercise, blood supply is inadequate, and ischaemia (oxygen shortage) develops. The cause of the pain is not clearly understood, but the ischaemia may be an explanation. When the patient takes a rest, for instance looking in a shop window, oxygen demand decreases and the pain disappears.

Major risk factors for intermittent claudication are cigarette smoking, hypertension, high cholesterol and haemostatic factors. Many patients with intermittent claudication have relatively mild complaints, but up to 20% of the patients go on to require reconstructive surgery, and 1-2% will eventually undergo amputation (Leng 1993).

Patients with intermittent claudication are advised to stop smoking and to start specific exercise programs. There are at least 15 different drugs available for the treatment of intermittent claudication, but it is uncertain how well many of them work, and certainly none of them will cure the disease. One of these drugs is vitamin E.

VITAMIN E

The treatment of intermittent claudication with vitamin E has had its proponents since the 1940’s. Case histories firstly by Shute and Vogelsang (Shute 1948), led to more valid research by means of controlled clinical trials. The evidence regarding the effects of vitamin E in intermittent claudication on symptoms rather than on the processes causing atherosclerosis will be summarised in this article.

MECHANISMS OF ACTION

An important function of vitamin E in the body is the protection of polyunsaturated fatty acids (PUFA’s) from oxidation. PUFA’s are highly susceptible to oxidation by endogenous free radicals which are formed and needed in normal (cell) metabolism. Exogenous free radicals, absorbed for instance from cigarette smoke, also cause oxidation. The cell damage that occurs in ischaemic periods in all tissues is probably caused by free radicals. In vitro and in vivo animal studies have shown that vitamin E protects mitochondria from the consequences of experimentally-induced ischaemia (Ferrari 1983). Animal studies have shown that the most frequently occurring symptom in vitamin E deficiency is myopathy, including myopathy of the heart muscle (Maechlin 1984). In patients with vitamin E deficiency abnormal erythrocytes and sometimes anaemia are found. In these patients vitamin E increases the life-span of red blood cells (Leonard 1971; Farrell 1977). Deformability of red blood cells may be enhanced by vitamin E, since PUFA’s incorporated in the...
membranes are protected from oxidation. Finally, vitamin E inhibits platelet aggregation (Steiner 1982). Other, more controversial, hypotheses about the actions of vitamin E include its ability to lower blood cholesterol levels (Hermann 1979; Howard 1982; Stamper 1983; Cloarec 1987), and to stimulate the formation of collateral vessels (Haeger 1982). An improvement of physical working capacity by vitamin E supplementation is also subject to controversies (Shephard 1983; Simon-Schnass 1988).

How could this information translate into mechanisms of action? Vitamin E might improve tolerance to the schema that occurs during exercise, if indeed it eliminates free radicals. Also it might influence the process of atherosclerosis by stopping further deterioration; but this would be difficult to prove. It has been shown that patients with ischaemic heart disease and patients with peripheral arterial disease have higher plasma lipid peroxide concentrations than controls (Stringer 1989). Inhibition of peroxidation by vitamin E might influence beneficially the balance between oxidative damage and the body’s repair mechanisms. Finally, it may influence platelet aggregation and affect red blood cells, improving blood flow, which might account for some beneficial effect on the symptoms of intermittent claudication.

**DOSAGES OF VITAMIN E**

To interpret the dosages, we need to note that eight compounds have vitamin E activity, the most active being alpha-tocopherol. The vitamin E activity of 1 mg synthetic dl-alpha-tocopherol acetate is equivalent to 1 IU of vitamin E. Dl-alpha-tocopherol has a potency of 1.1 IU/mg. The activity of naturally occurring d-alpha-tocopherol is 1.49 IU/mg, and of its acetate 1.36 IU/mg (RDA 1980).

Dietary intake ranges up to about 10 mg per day from various sources including the less active tocopherols and tocotrienols (Rimm 1993; Stamper 1993).

**Objectives**

The objective of the review was to assess the evidence about the efficacy of vitamin E on subjective and objective outcomes in patients with intermittent claudication: perception of pain, disability, walking distance, ankle-arm blood pressure index, walking distance until onset of pain on a standard treadmill, and the occurrence of vascular surgery, amputation or death. The follow-up period should have been at least three months.

**Results**

We found five controlled trials of vitamin E for intermittent claudication published between 1953 and 1975 (Boyd 1963; Hamilton 1953; Livingstone 1958; Westheim 1975; Williams 1962). All studies included subjects with grade II or III disease using Boyd’s grade classification of severity of disease. His grade II would correspond to Fontaine’s stage II (Fontaine 1954). Three studies were excluded since they were cohort studies (Batgriff 1949; Haeger 1982; Semple 1974). All showed favourable outcomes for the groups treated with vitamin E. The letter of Housley and McFadyen 1974 (Housley 1974) discusses the results of a placebo control group without specifying whether vitamin E or another drug was used as the active treatment.

The five controlled trials lasted for between 12 weeks and 18 months, measured four different physical outcomes, and used five different doses of vitamin E. All trials showed positive effects on one of their main outcomes. Pooling of the data appeared to be sensible because of differences in the interventions and, more importantly, in the reported outcomes. However, the two trials which lasted approximately 8 months, and used similar doses, both reported patients’ subjective evaluation of the treatment. These results have been pooled and indicated a favourable effect. Given the relatively high frequency of outcomes, we used the relative risk, not the odds ratio, as the measure of effect. Using a fixed effects model the relative risk (95% CI) was 0.6 (0.4-0.9) and the random effects model yielded 0.6 (0.3-1.2). By contrast, the pooled odds ratio was 0.35, which clearly does not reflect the relative risk in these studies.

No study reported any serious side effects.

**Discussion**

There are a number of important criticisms of all studies. (1) Small numbers in all trials meant that baseline values were not necessarily equal between the trials. Several trials noted important differences between the groups in the baseline values of their outcome variables, but only one (Hamilton 1953) did analyses to adjust for this. (2) Most trials were done before much was known about the causes of circulatory disease and hence smoking habits, blood pressure, weight, diet and other important characteristics of the groups were not compared. For this condition, it would also be important to compare the prevalence of osteoarthritis, usage of pain medication such as aspirin, prior treatments and co-interventions. (3) Randomisation procedures are not well described, and some studies may have analysed a post-hoc sub-group of the original trial. (4) The relevance and comparability of the physical endpoints (e.g. standing on tiptoes) was not clear.

Concise descriptions of prognostic factors are essential to detect subgroups which might react positively to vitamin E supplementation. In the trials discussed above, only mean age and duration of symptoms were described. Exclusion of patients with other causes of pain such as osteoarthritis was mentioned only once. In no trial was more than one dose used and so the optimal level could not be assessed. For reasons of efficiency, it can be argued that this should be done only after a positive effect has been demonstrated. In two experiments only were post-treatment effects assessed. The most important weakness, as stated before, was the small number of patients enrolled.

One study (Hamilton 1953) was criticised for using vegetable oil as the source of vitamin E. Boyd (Boyd 1963) states that, in the early 1950’s, the content of tocopherol in wheat-germ oil was often considerably less than the declared value, due to inaccurate measurements. He estimated that the 450 mg dose used by Hamilton might represent a true alpha-tocopherol content of about 40 mg. It should be noted that the exact nature of the ‘vitamin E’ used was not always stated in the other studies.

The active period for conducting vitamin E trials in intermittent claudication was around 1955 - 1975, and it was not possible to contact the trialists for clarification on unpublished data. Publication bias may be a greater concern in this review than in reviews where the evidence is more recent. All trials used patients who were not eligible for surgery and most specified that patients with diabetes were excluded. We do not think that there is enough data to recommend using vitamin E in patients with intermittent claudication. Furthermore, no trials comparing the effects of vitamin E to other possible treatments were found. Finally, the validity and clinical relevance of the different performance tests that have been used can be questioned. Hence it was not possible to put the positive trends displayed in most trials into perspective.

**Reviewers’ conclusions**

**Implications for practice**

The evidence regarding the effects of vitamin E on intermittent claudication, with the above-stated limitations in mind, is slightly in favour of vitamin E. As no trials comparing the effects of vitamin E to other possible treatments were found, it was not possible to put the positive trends displayed in most trials into perspective. Given that, to date, no serious side effects have been reported and that synthetic vitamin E is very cheap, some people might consider it worth trying.

**Implications for research**
Larger, well-designed, double-blind trials using a range of subjective and objective outcome measures are necessary to confirm or reject the results of the existing studies and to assess optimal dosage levels. The exact method of randomisation and relevant baseline characteristics of the groups need to be described. Intention-to-treat analyses should be performed and reported. In addition, a three-arm or factorial trial comparing vitamin E to another treatment as well as to placebo would be useful. Trials allowing evaluation of vitamin E treatment on amputation rate, need of vascular surgery or death would be preferable.

Notes

Tables

Characteristics of included studies

**Study**  
Boyd 1963

**Methods**  
States 'blind'. No reported withdrawals or losses to follow up.

**Participants**  
Country: United Kingdom. 33 men, all grade 2; mean age 59, duration of symptoms 2 years. Vitamin E group had lower performance at baseline.

**Interventions**  
Treatment: 400 mg/day alpha-tocopherol, 17 patients (analysed); Placebo: lactose, 16 patients (analysed). Duration 13 weeks.

**Outcomes**  
Walking: distance to pain and distance to halting. Distance to halting increased 130 yards in the vitamin E group and decreased 150 yards in the control group, p<0.01.

**Notes**  
This paper mainly describes the longitudinal experience with 1476 patients seen in this clinic over 6 years who were treated with vitamin E. It was not stated when the study was done in this 6 year period or why only these 33 subjects were chosen for the trial.

**Allocation concealment**  
B - Unclear

**Study**  
Hamilton 1953

**Methods**  
Double-blind. Two controls were lost to follow up.

**Participants**  
Country: United Kingdom. 41 non-diabetic men, mean age 55, mean duration of symptoms 3.6 years. Approximately half had grade 2 disease and half had grade 3 disease. Vitamin E group had better baseline performance.

**Interventions**  
Treatment: 450 mg natural vitamin E (see notes)/day, n=20 (analysed); Control: identical in appearance, arachis oil, n=19 (analysed). Duration: 12 weeks.

**Outcomes**  
Change in number of circuits walking over steps and duration of pain after cessation. In the last month the vitamin E group had a slightly higher increase in the number of circuits (0.62 +/- 1.38 [SEM]) and shorter pain (14.9 +/- 7.1 [SEM] secs). Correcting for baseline variation between the groups reduces these differences. Subjective assessment by patient: improvement, no change, deterioration. Vitamin E group: 8, 12, 0. Placebo group: 6, 14, 1.

**Notes**  
Later work indicates that the vitamin E content of these capsules may have been much lower e.g. only about 50 mg/day (Boyd 1963).

**Allocation concealment**  
A - Adequate

**Study**  
Livingstone 1958

**Methods**  
Double-blind. Three in each group withdrawn.

**Participants**  
Country: United Kingdom. 40 non-diabetic men, mean age 56, duration of symptoms > 5 years. Half had grade 2 disease and half had grade 3 disease. Vitamin E group had lower performance at baseline.

**Interventions**  
Treatment: 600 mg vitamin E/day, n=17 (analysed); Control: placebo 'indistinguishable', n=17 (analysed). Duration: 40 weeks.

**Outcomes**  
Change in number of circuits of stepping up and down two steps 18" high; pace for each subject controlled. Vitamin E group increased by 15 circuits, control group by 2.5 circuits; no statistics were calculated or SDs given. Subjective assessment by patient: improved, no change, withdrawn owing to complications of the disease. Vitamin E group: 13, 4, 3. Placebo group: 2, 15, 3.
Notes At least some of the patients withdrawn should have been counted as failures.

Allocation concealment B - Unclear

Study Westheim 1975

Methods States 'randomised'. Double-blind. Six vitamin E and 2 controls lost to follow up.

Participants Country: Norway. 31 women, 49 men; non-diabetic; mean age 63. Duration of symptoms 4.3 years (vitamin E group) and 3.0 years (control group). About 90% had grade 2 disease, the remainder grade 3. Vitamin E group had better performance at baseline.

Interventions Treatment: 900 mg/day of D-alpha-tocopheryl acetate for 2 months, 300 mg/day for the next 6 months, n=34 (analysed). Control: placebo, n=38 (analysed). Duration: 8 months.

Outcomes Number of times standing on tiptoes at a rate of 35 times per minute. Vitamin E group improved from 42 to 57; Control group improved from 36 to 44 (p for comparison between groups <0.2). Subjective improvement graded better, unchanged or worse. Vitamin E group 21, 13, 1 Placebo group 19, 17, 2.

Notes As D-alpha-tocopheryl acetate was used, the equivalent vitamin E dose is about 36% higher (see background).

Allocation concealment B - Unclear

Study Williams 1962

Methods Allocated 'at random' by pharmacist. Double-blind. Report of 33 patients out of a 71 patient trial in which exclusion criteria were applied after randomisation.

Participants Country: Canada. 71 patients randomised: 33 patients (1 women) analysed. Mean age 60, mean duration of symptoms 3.5 years in the vitamin E group, 4.7 years in the control group.

Interventions Treatment: 1600 mg/day alpha-tocopherol, n=17 (analysed); Control: similar capsule containing sodium bicarbonate n=16 (analysed). Mean duration: 18 months in the vitamin E group and 10 months in the control group.

Outcomes Distance walked on electric treadmill at a pace to suit each subject. Vitamin E group improved 258 yards versus a decrease of 1 yard in the control group.

Notes Given the difference in follow up time the results are uninterpretable.

Allocation concealment B - Unclear

References

References to studies included in this review
Boyd 1963 (published data only)

Hamilton 1953 (published data only)

Livingstone 1958 (published data only)

Westheim 1975 (published data only)

Williams 1962 (published data only)

* indicates the major publication for the study

Additional references
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