Vitamin E is ineffective for symptomatic relief of knee osteoarthritis: a six month double blind, randomised, placebo controlled study

C Brand, J Snaddon, M Bailey, F Cicuttini

Abstract

Objective—There is a putative role for antioxidant treatment in osteoarthritis (OA) based on animal, epidemiological, and human clinical studies. Vitamin E, a fat soluble vitamin, is one of the major dietary antioxidants. Short term clinical studies using vitamin E in the form of \( \alpha \)-tocopherol suggested a benefit over placebo of similar dimension to that of diclofenac for relief of OA pain.

Methods—A six month, double blind, randomised, placebo controlled study of vitamin E 500 IU/day was carried out. Primary outcome measures were pain, stiffness, and function. Statistical analysis was performed on an intention to treat basis.

Results—77 patients were included in the study. Vitamin E showed no benefit over placebo at one month, three months, or six months for any of the outcome measures. The placebo group had higher pain levels (p=0.15) and body mass index (p=0.03) at baseline, and lower pain levels (p=0.02) at completion of the study. Radiological score, exercise score, age, or antioxidant intake at baseline or six months did not differ between the groups. The reasons for the better performance of the placebo group are uncertain but may relate to the initially higher pain score and subsequent regression to the mean.

Conclusions—Vitamin E shows no benefit for the management of symptomatic knee OA. The role of vitamin E in preventing OA progression is currently under investigation.

(Oman Rheum Dis 2001;60:946–949)
Vitamin E treatment of knee OA

Body mass index (BMI; weight/height$^2$ in

Height was measured to the nearest 0.1 cm

removed) with a single pair of electronic scales.

The primary outcome measures were pain,

and function dimensions as derived
from WOMAC. Patients were asked to rate the

change in these dimensions since their last visit

on a 5 cm visual analogue scale (VAS). The incidence of pain in each

knee in the month before review was assessed

(less than 10 days, 10–15 days, more than half

the month, every day). A categorical measure of pain severity for the 24 hours before review

was documented (none, slight, mild, moderate,

severe, extreme). Observer global assessment

of current severity was also documented.

Secondary outcome measures included analge-
sic and NSAID usage (0 = never used; 1 =
rarely used; 2 = used a few days/week; 3 = used
most days/week; 4 = used daily).

Subjects completed a questionnaire that
included demographic data and current physi-
cal activity. Weight was measured to the near-
est 0.1 kg (shoes, socks, and bulky clothing
removed) with a single pair of electronic scales.
Height was measured to the nearest 0.1 cm
(shoes and socks removed) with a stadiometer.

Body mass index (BMI; weight/height$^2$ in

kg/m$^2$) was calculated. Dietary intake of
vitamin E, using a food questionnaire, was
completed by patients at the start and end of
the study.

Radiography before inclusion into the study
included a weightbearing anteroposterior
tibiofemoral view in full extension and skyline
patella view. The blinded radiographs were
read on two separate occasions by one investi-
gator at completion of the study. Radiographic
scoring of tibiofemoral OA and patellofemoral
OA was made using a standardised radiographic
atlas. The intraobserver reliability
ranged between 0.87 and 0.92 for joint space
narrowing and osteophytes at the tibiofemoral
and patellofemoral joints.

STATISTICAL ANALYSIS

Primary analysis was performed on an inten-
tion to treat basis. Baseline characteristics were
compared using the two sample $t$ test. Cate-
gorical variables were compared at baseline
using the $\chi^2$ test for equal proportions. The
mean differences at six months were assessed
with paired $t$ tests, and adjustments for baseline
differences made using covariate analysis.

Results from the multivariate model are
presented as adjusted means, with the adjust-
ment made according to the method of least
squares. Repeated measurement analysis was
used to compare differences between vitamin E
and placebo at each visit. With 38 patients in
each arm, the study had an 80% power to
detect a 30% improvement in each of the three
dimensions, where mean/SD in the whole
population at baseline were pain (87.9/39.2),
stiffness (43.4/21.7), and function (329.6/
173.5).

Results

Four hundred patients underwent telephone
screening, of whom 158 were interviewed. Sev-
enty seven patients (45 female, 32 male)
fulfilled study inclusion criteria and were
randomly allocated to one arm of the study.
Seventy two patients completed the study. Five
withdrew before study completion (three
owing to treatment failure, one relocated unex-
pectedly overseas, one developed osteonecrosis).

Completion was not significantly different
between the groups (vitamin E 96.8 (SE 1.4) v
placebo 93.6 (SE 3.0), p=0.3).

Table 1 presents baseline characteristics of
all patients entered into the study. There were
no significant baseline differences between the
vitamin E and placebo groups except for BMI,
which was higher in the placebo group (30.5 v
27.6, p=0.03). Pain levels were also higher in
this group, but the difference was not signifi-
cant (p=0.15). One patient in each group was
taking vitamin E supplementation before study
entry. Fourteen patients in each group were
receiving NSAID treatment when they entered
the study. Two patients receiving vitamin E and
two receiving placebo stopped their NSAID
during the six month study, and one further
patient received vitamin E during this time. Mean
differences in dietary vitamin E at six months did not differ
significantly (mean difference vitamin E −1.6
The significance of changes over time was assessed by a visit by group interaction. All values adjusted for sex, ethnicity, age, antioxidant intake, arthritis score, exercise level, and BMI = body mass index; NSAID = non-steroidal anti-inflammatory drug.

Table 2 Repeated measurement analysis of vitamin E versus placebo over six months. (adjusted means)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>Change between group over time (p value)</th>
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</thead>
<tbody>
<tr>
<td>Pain‡</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E (SE)</td>
<td>49.23</td>
<td>82.84</td>
<td>67.23</td>
<td>71.54</td>
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<tr>
<td>Placebo (SE)</td>
<td>61.67</td>
<td>83.61</td>
<td>79.39</td>
<td>66.70</td>
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<tr>
<td>p Value*</td>
<td>0.09†</td>
<td>0.93</td>
<td>0.17</td>
<td>0.59</td>
<td>0.24</td>
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<tr>
<td>Stiffness†</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Vitamin E (SE)</td>
<td>25.70</td>
<td>41.77</td>
<td>34.47</td>
<td>34.14</td>
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<tr>
<td>Placebo (SE)</td>
<td>28.75</td>
<td>39.58</td>
<td>35.23</td>
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<tr>
<td>p Value*</td>
<td>0.45</td>
<td>0.66</td>
<td>0.88</td>
<td>0.92</td>
<td>0.43</td>
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<tr>
<td>Function†</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E (SE)</td>
<td>209.44</td>
<td>304.70</td>
<td>258.08</td>
<td>279.69</td>
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<tr>
<td>Placebo (SE)</td>
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<td>320.54</td>
<td>305.07</td>
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<tr>
<td>p Value*</td>
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<td>0.63</td>
<td>0.16</td>
<td>0.99</td>
<td>0.44</td>
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<td>Pain frequency</td>
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<td></td>
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<tr>
<td>Vitamin E (SE)</td>
<td>2.92</td>
<td>2.72</td>
<td>2.47</td>
<td>2.08</td>
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<tr>
<td>Placebo (SE)</td>
<td>2.92</td>
<td>2.82</td>
<td>2.67</td>
<td>2.34</td>
<td></td>
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<tr>
<td>p Value</td>
<td>0.99</td>
<td>0.74</td>
<td>0.48</td>
<td>0.39</td>
<td>0.72</td>
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<tr>
<td>Categorical pain</td>
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<td></td>
</tr>
<tr>
<td>Vitamin E (SE)</td>
<td>1.83</td>
<td>1.86</td>
<td>1.66</td>
<td>1.82</td>
<td></td>
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<tr>
<td>Placebo (SE)</td>
<td>2.12</td>
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<td>1.86</td>
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<tr>
<td>p Value</td>
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<td>0.87</td>
<td>0.35</td>
<td>0.12</td>
<td>0.12</td>
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<td>Observer global assessment</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E (SE)</td>
<td>1.84</td>
<td>1.63</td>
<td>1.51</td>
<td>1.66</td>
<td></td>
</tr>
<tr>
<td>Placebo (SE)</td>
<td>1.99</td>
<td>1.72</td>
<td>1.74</td>
<td>1.45</td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td>0.46</td>
<td>0.63</td>
<td>0.22</td>
<td>0.30</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*Significance in differences between least squares means. †All values adjusted for sex, ethnicity, age, antioxidant intake, arthritis score, exercise level, and body mass index. ‡The significance of changes over time was assessed by a visit by group interaction.

Our results do not support a role for vitamin E in the treatment of symptoms in knee OA. We showed no benefit of vitamin E in any measure of pain score, nor in stiffness or function. Observer assessment demonstrated no significant differences. Analgesia or NSAID usage, surrogate markers of clinical efficacy, did not change significantly between those taking vitamin E compared with those receiving placebo. At six months, the deterioration in pain score was less in the placebo group than in the vitamin E group after adjusting for age, sex, BMI, radiological score, analgesic and anti-inflammatory drug use. When the earlier time points, one month and three months, were examined, again no significant benefit of vitamin E compared with placebo was seen.

Our results differ from the study of Machtey and Ouaknine. Those authors found a 52% improvement in the group treated with vitamin E compared with 4% in the placebo group. However, they studied only 32 patients. OA was present at any site and subjects were randomly allocated into a short term (10 day crossover) study comparing vitamin E 600 mg/day with placebo. The administrators of the treatment were not blinded. The outcome measures included a simple daily patient recorded global improvement scale and frequency of analgesic intake. The small number, heterogeneous site of OA, short duration of treatment, and lack of double blinding limit interpretation of these results. A pilot study of vitamin E efficacy in 50 patients with OA (site not specified in the abstract) in a double blind, placebo controlled trial of over six weeks' duration found that vitamin E (400 IU) was better than placebo for pain relief and reducing the frequency of analgesic treatment. A further three week randomised, double blind, comparative study of vitamin E (400 mg/day) versus diclofenac (50 mg three times daily) in 34 patients with hip OA or 19 with knee OA showed that the two agents had equal efficacy. Given the small numbers of patients with OA at each site, this study may have been underpowered to detect a difference in treatment efficacy between the two groups. Our study showed no significant difference even when we examined earlier time points of one and two months.

The reason why placebo performed better than vitamin E is unclear. The only significant baseline difference between the two groups was BMI, which one could postulate might be associated with earlier and more severe OA. However, a final analysis allowed adjustment for this variable. In addition, there was no difference in radiological OA score between the two groups at baseline, and no differences at baseline or at six months in the frequency of use of analgesic and anti-inflammatory drugs. Possibly, although we adjusted for baseline pain score, this still, in part, represents regression to the mean because the placebo group had more significant pain at the start of the study than the vitamin E group.

Overall drug compliance in the study participants was very high and dietary intake assessment of antioxidants showed no significant difference between the two groups. As serum levels of vitamin E were not determined we cannot exclude the possibility that differences in antioxidant levels might have existed and influenced the final results. However, given the high dose of vitamin E supplementation, this is unlikely to be the case. In addition, because we only examined symptoms in this
study, we cannot exclude the possibility that vitamin E affects progression of knee OA. No randomised controlled trial data exist to support this. This is currently mainly supported by observational data such as the Framingham Study, which has suggested a reduction in the prevalence, but not the incidence, of knee OA in those with a high dietary intake of vitamin E.

No adverse effects were associated with vitamin E in our study. This is consistent with published reports, which suggest that short term vitamin E use is safe.20 However, there has been some doubt about its long term use after a report of an increase in cerebral haemorrhage among men taking vitamin E for 5–8 years.21 Despite the widespread, community interest in the use of “natural” treatments in OA, our data do not support the use of vitamin E for treatment of symptoms in knee OA, and emphasise the importance of testing such treatments in double blind randomised studies. Such caution is reinforced by the failure of randomised controlled trials to support observational studies suggesting a better cardiovascular prognosis in subjects with high antioxidant intake.22

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