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**ORIGINAL RESEARCH ARTICLE**

# Effect of Vitamin E Supplementation in Rheumatoid Arthritis – A Case Control Study

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## ABSTRACT

**Aim:** We aimed to demonstrate that Vitamin E had an analgesic effect in rheumatoid arthritis (RA) by measuring reduction in painful and tender joint score and an anti-inflammatory effect by measuring reduction in swollen joint score, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP).

**Methodology:** This was a prospective, open labeled, parallel group, randomized control trial. A total of 85 patients were selected (out of 92 screened) from those attending the Rheumatology out-patient department, Stanley Medical College, Chennai. They were randomized by lots into "Control Group" (43 patients) and "Vitamin E Group" (42 patients). The Control Group received Indomethacin 25 mg BD & Chloroquine 250 mg OD, whilst the Vitamin E Group received Vitamin E 400 mg BD in addition to the above drugs for a period of 12 weeks. Joint examination (painful, tender and swollen joint scores), ESR and CRP were done at baseline and at 12 weeks.

**Results:** There was no statistically significant difference in average painful, tender & swollen joint scores, ESR or CRP between both groups at the start of the study, before drug administration. At the end of the study, there was a statistically significant decrease of all parameters in the Vitamin E group, which was not seen in the Control group, shown by paired t test (p=0.001).

**Conclusion:** The possible analgesic and anti-inflammatory effects of Vitamin E, which are demonstrated by a better improvement of both joint scores and lab markers of inflammation, highlights the possible role for Vitamin E and other anti-oxidants as safer disease-modifying anti-rheumatoid agents.

**Key words:** Vitamin E, rheumatoid arthritis, analgesic, anti-inflammatory.

## INTRODUCTION

Rheumatoid arthritis (RA) is a common disease with a prevalence of 0.5 –1% in diverse populations worldwide [1]. Once initiated, the persistent synovitis, characteristic of RA, causes progressive joint destruction and permanent deformity with resultant deterioration in quality of life and high cost to society [1,2]. Functional capacity decreases most rapidly at the beginning of the disease and it is essential to control active disease as soon as possible [3,4]. Hence prompt introduction of Disease Modifying Anti Rheumatic Drugs (DMARDs), either singly or in combination, in a step-down approach is required to prevent joint damage. Currently used drugs like Non Steroidal Anti Inflammatory Drugs (NSAIDs), DMARDs and glucocorticoids are highly toxic on long term use [2]. Therefore there exists a need for a newer disease modifying agent that is effective, yet non toxic on chronic administration.

A recent study indicated that increased oxidative stress and/or defective antioxidant status contribute to the pathology of RA. When human immunoglobulin is exposed to free radical generating systems, Ig G complexes are formed that stimulate the release of superoxide from

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normal human neutrophils, and this reaction may be self perpetuating within the rheumatoid joint. Free radicals can also play a role in autoantibody formation and lead to the production of rheumatoid factor [4-10]. Lipid peroxidation, mediated by free radicals, is a series of chemical reactions involving the oxidative deterioration of polyunsaturated fatty acids (PUFA), and may cause disruption of cell structure and function and play an important role in the etiology of many diseases. Many studies showed low levels of endogenous antioxidants in patients with RA [5-7].

Vitamin E has a major biological role in protecting polyunsaturated fats and other components of cell membrane from lipid peroxidation. Removal of the hydrogen from PUFA:H by a free radical can initiate a chain reaction. However, in biological systems, the peroxidative cascade is more likely to be terminated by Vitamin E, which is present in the cell membrane [8-10].

Our objectives were to demonstrate that Vitamin E had an analgesic effect of in RA by measuring painful and tender joint score and an anti-inflammatory effect by measuring swollen joint score, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP).

## MATERIALS AND METHODS

This was a prospective, open labeled, parallel group, randomized control trial.

A total of 85 patients were selected (out of 92 screened) from those attending the Rheumatology out-patient department, Stanley Medical College, Chennai. They were randomized by lots into "Control Group" (43 patients) and "Vitamin E Group" (42 patients). Sample size calculated based on previous studies [11] was estimated to be 40, for the design to have 90% power to detect a clinically significant difference between both groups. Approval was obtained from the Institutional Ethical Committee of Stanley Medical College prior to the start of the study. Information was given and written informed consent was obtained in the patient's native language.

### Inclusion Criteria:

- Patients of either sex between 18-40 years of age, diagnosed to have RA as per revised American College of Rheumatology criteria, who had stable disease whilst on treatment with Indomethacin & Chloroquine for at least 3 months prior to commencement of the disease
- Duration of disease more than 6 months but less than 3 years [12]

### Exclusion Criteria:

- History of treatment with complementary or alternative medicine
- Patients who had been treated with corticosteroids, immunosuppressants or any DMARD except chloroquine in the 3 months prior to enrollment in the study
- Patients with diabetes, hypertension, liver or renal dysfunction or any other chronic illness
- Pregnant or lactating women
- Patients with extra-articular features or severe disease

Painful, swollen & tender joint scores were recorded in the enrolled patients. The joint score indicates the total number of painful / tender / swollen joints. Joint examination was done at baseline and at 12 weeks. Baseline investigations done at the start of the study included complete blood counts, bleeding and clotting times, random blood sugar, serum creatinine & aminotransferases. ESR and CRP were measured at baseline and at 12 weeks.

The Control Group received Indomethacin 25 mg BD & Chloroquine 250 mg OD, whilst the Vitamin E Group received Vitamin E 400 mg BD in addition to the above drugs for a period of 3 months (**Figure 1**). The patient was considered to be compliant with study medication if he/she took at least 80% of the medication during the study period. Compliance was recorded by a daily drug reminder chart and confirmed by examining the number of unutilized capsules in each medication pack.

### Statistical Analysis:

The data obtained at the end of this study were analyzed using SPSS Data Editor Software. Student independent t test and student paired t test were used to analyze the results, as applicable. P value $\leq 0.05$ was considered significant.

## RESULTS

The majority of patients in this study were in the age group 30 – 50 years and more than 80% were females. There is no significant difference in sex distribution between both groups.

There was no statistically significant difference in average painful, tender & swollen joint scores, ESR or CRP between both groups at the start of the study, before drug administration, as shown by student independent t test. At the end of the study, there was a statistically significant decrease of all

parameters in the Vitamin E group, which was not seen in the Control group, shown by paired t test. Comparison of mean joint scores, ESR and CRP of both groups, by student independent t test, at the end of the study showed a statistically significant difference between groups in joint scores and CRP (**Table 1**). The difference in mean ESR at the end of the study, between groups was not statistically significant.

The difference between mean pre and post test scores for all measured parameters was higher in the Vitamin E group when compared to the Control group (**Figure 2 & Table 2**).

**Table 1: Comparison of Mean Pre and Post Test Scores**

| Parameters | Group | Mean ± 2SD | | Paired t test |
|---|---|---|---|---|
| | | 0 months | 3 months | |
| **Painful joint score** | Control | 11.77 ± 6.12 | 10.69 ± 8.6 | P = 0.2 |
| | Vitamin E | 11.6 ± 6.02 | 4.43 ± 7.24 | **P = 0.001** |
| Independent t test | | P = 0.8 | **P = 0.001** | |
| **Tender joint score** | Control | 9.1 ± 7.06 | 8.03 ± 8.74 | P = 0.23 |
| | Vitamin E | 8.98 ± 7.32 | 2.17 ± 6.64 | **P = 0.001** |
| Independent t test | | P = 0.87 | **P = 0.001** | |
| **Swollen joint score** | Control | 4.26 ± 5.52 | 3.51 ± 7.24 | P = 0.3 |
| | Vitamin E | 3.63 ± 5.42 | 1.43 ± 5 | **P = 0.001** |
| Independent t test | | P = 0.33 | **P = 0.001** | |
| **ESR** | Control | 8.77 ± 9.26 | 8.54 ± 9.64 | P = 0.77 |
| | Vitamin E | 10.6 ± 16.42 | 7.43 ± 13.16 | **P = 0.001** |
| Independent t test | | P = 0.22 | P = 0.39 | |
| **CRP** | Control | 8.31 ± 10.16 | 9.75 ± 10.42 | P = 0.68 |
| | Vitamin E | 8.62 ± 10.22 | 4.5 ± 7.06 | **P = 0.001** |
| Independent t test | | P = 0.22 | **P = 0.001** | |

**Table 2: Percentage Of Reduction / Increase In Scores**

| Parameters | % of Reduction / Increase | |
|---|---|---|
| | Control group | Vitamin E group |
| Painful joint score | -9.17 | -61.8 |
| Tender joint score | -11.7 | -75.8 |
| Swollen joint score | -17.6 | -60.6 |
| ESR | -2.6 | -29.9 |
| CRP | +3.73 | -53.8 |

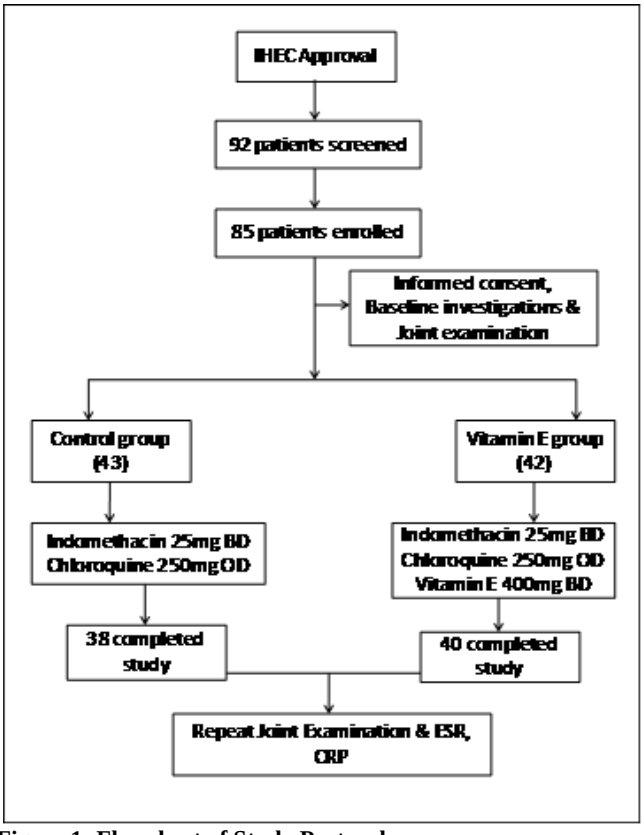


**Figure 1: Flowchart of Study Protocol**

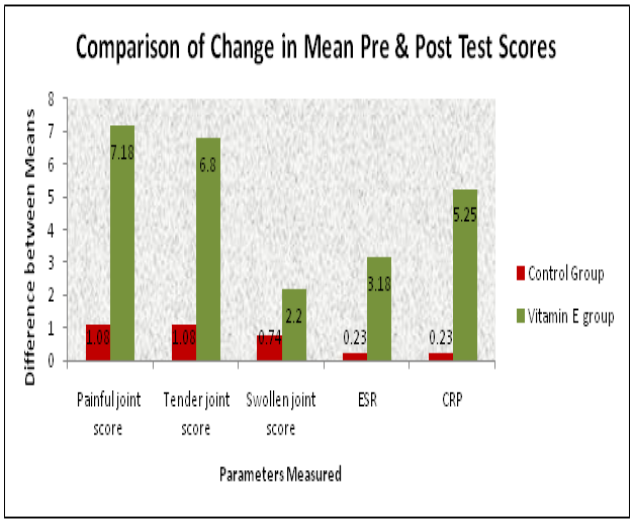


**Figure 2: Comparison of Differences between Groups in Mean Pre & Post Test Scores**

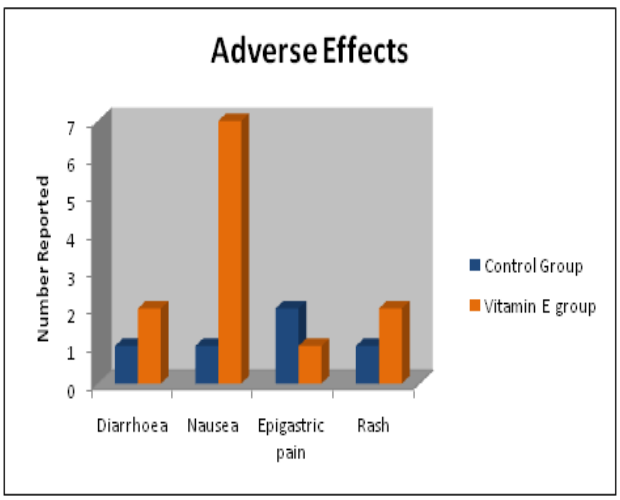


**Figure 3: Adverse Effects Reported during the Study**

## DISCUSSION

The treatment of rheumatoid arthritis aims to ameliorate symptoms and prevent progressive joint damage. Increasing evidence for the role played by free radicals suggests that antioxidant therapy may play an alternative approach [12]. This study was done to evaluate the analgesic & anti-inflammatory action of Vitamin E. Previous studies indicated that antioxidants might protect people with established disease from disease progression [13].

In this study, one group of patients received Vitamin E along with their routine NSAID and DMARD (Indomethacin & Chloroquine). They were compared with another group of patients who received only Indomethacin & Chloroquine. The study duration was for 3 months.

In this study, average painful joint, tender joint and swollen joint scores were used to clinically evaluate disease activity. Joint scores indicate the total number of painful, tender or swollen joints in a patient. Erythrocyte Sedimentation Rate (ESR) & C-Reactive Protein (CRP), acute phase reactants, were used as laboratory markers of inflammation.

Out of 92 patients screened, 85 patients were included in the study. They were randomized into Control & Vitamin E groups, 42 and 43 in number respectively. There were 6 dropouts, 4 from Control group and 2 from Vitamin E group and were excluded in statistical analysis (Figure 1). None of the dropouts were due to adverse effects.

Common side effects of oral Vitamin E at therapeutic doses were nausea, flatulence, diarrhea, fatigue, hypertension, myopathy & thrombophlebitis. At doses >1200 mg/day, there was an increase in bleeding tendency due to decreased Vitamin K absorption [14,15]. Patients were therefore screened for hypertension and abnormal coagulation profile before inclusion in the study. None of the study participants developed any elevation in blood pressure. Adverse effects noted during the course of the study are shown in (**Figure 3**).

The majority of patients in this study were in the age group 30 – 50 years, and more than 80% of patients were female. This was in correlation with established demographic reports [16]. The effectiveness of Vitamin E in reducing active joint disease was evident clinically by a decrease in painful joint, tender joint and swollen joint scores, and by a decrease in ESR and CRP. All parameters were found to be reduced significantly in the Vitamin E group, but the decrease was not statistically significant in the control group (Tables 1 & 2, Figure 2).

The reduction in painful joint and tender joint scores in the Vitamin E group indicates that Vitamin E has analgesic activity. This is in correlation with the results of Edmonds SE *et al* who showed that repeated oral doses of Vitamin E was superior to standard analgesics when added to existing anti-rheumatoid medication [17]. The mechanism of analgesic activity hypothesized by them was a central analgesic effect due to suppression of nitric oxide (NO) by Vitamin E [18,19]. NO lowers the threshold of nociceptors and facilitates nociceptive transmission within central pathways. Vitamin E also inhibits protein kinase C, which plays an important part in signal transduction triggered by neurotransmitters and cellular stimuli [17].

Also, the significant decrease in swollen joint score, ESR and CRP, in the Vitamin E group, indicates an anti-inflammatory effect for Vitamin E. This is also in correlation with the results of McAlindon TE *et al* who showed that the antioxidant property of Vitamin E contributed to anti-inflammatory effect due to inhibition of formation of reactive oxygen species [18-20]. Their study also showed that high doses of Vitamin E protected people with established RA from disease progression [13, 20, 21]. In another study done by Singh U *et al* there was a decrease in CRP levels after therapy with Vitamin E [23].

Vitamin E blocks arachidonic acid formation from phospholipids and inhibits cyclo-oxygenase and lipoxygenase activity [20, 22]. Vitamin E also inhibits the release of pro inflammatory cytokines, the chemokine IL-8 and plasminogen activator inhibitor (PAI-1) and monocyte adhesion. Vitamin E is also involved in the regulation of intercellular signaling and cell proliferation through modulation of protein kinase C [8].Vitamin E is the most potent dietary antioxidant and it seems to uncouple joint inflammation and destruction in transgenic mouse models of arthritis, with a beneficial effect on joint destruction [4].

This study also shows that the addition of Vitamin E to the existing therapeutic regimen improves the clinical response and decreases disease activity to a greater extent than with routine DMARDs alone. The possible analgesic and anti-inflammatory effects of Vitamin E, which are demonstrated by a better improvement of both joint scores and lab

markers of inflammation, highlights the possible role for Vitamin E and other anti-oxidants as safer disease-modifying anti-rheumatoid agents. In view of its low cost, safety and efficacy, it can be further investigated as a primary DMARD.

## REFERENCES


1. MacGregor AJ, Silman J; Classification and Epidemiology; *Rheumatology*, vol 1, 3rd edn: 757-762; Hochberg, Silman, Smolen, Weinblatt, Weismann (eds); Mosby Elsevier.
2. Quinn MA, Green MJ, Emery P; Evaluation and Management of early inflammatory polyarthritis; *Rheumatology*, vol 1, 3rd edn: 885-91; Hochberg, Silman, Smolen, Weinblatt, Weismann (eds); Mosby Elsevier.
3. Doherty M, Lanyon P, Ralston SH; Musculoskeletal disorders; *Davidson's Principles and Practice of Medicine*, 20th edn: 1105; Hunter, Boon, Colledge, Walker (eds); Churchill Livingstone Elsevier.
4. Abeles AM, Pillinger MH; Neuropeptides, Free Radicals and Nitric Oxide; *Rheumatology*, vol 1, 3rd edn: 140-144; Hochberg, Silman, Smolen, Weinblatt, Weismann (eds); Mosby Elsevier.
5. Mahajan A, Tandon VR; Antioxidants and Rheumatoid Arthritis; *Journal of Indian Rheumatological Association*; 2004 : 12 : 139-142.
6. Situnayake RD, Thurnham DI, Kootathep S, Chirico S, Lunec J, Davis M, McConkey B; Chain breaking antioxidant status in rheumatoid arthritis: clinical and laboratory correlates; *Ann Rheum Dis* 1991; 50: 81-6.
7. Krishnamohan S, Venkatramana G; Status of lipid peroxidation, glutathione, ascorbic acid, vitamin E and antioxidant enzymes in patients with osteoarthritis; *Ind J Med Sci* 2007 Jan; 61(1):9-14.
8. Ozkan Y, Yardym-Akaydyn S, Sepici A, Keskin E, Simsek B; Oxidative status in rheumatoid arthritis; *Clin Rheum* 2007; 26(1) 64-8.
9. Duthie GG; Fat Soluble Vitamins; *Human Nutrition and Dietetics*, 10th edn, 226-36; Garrow, James, Ralph (eds); Churchill Livingstone.
10. K. Bagchi, S. Puri; Free radicals and antioxidants in health and disease; *Eastern Mediterranean Health Journal*; 1998; 4:2:350-60.
11. Edmonds SE, Winyard PG, Guo R, Kidd B; Putative Analgesic Activity of Repeated Oral Doses of Vitamin E in the Treatment of Rheumatoid Arthritis; *Annals of Rheumatic Disease* 1997 (56) 649-55.
12. Lipsky PE; Rheumatoid Arthritis; *Harrison's Principles of Internal Medicine*, vol 2, 16th edn: 1968-76; Kasper, Fauci, Braunwald, Hauser, Longo, Jameson (eds); Mc-Graw Hill.
13. Steudel W, Hurford E, Zapol WM; Inhaled Nitric Oxide, Basic Biology and Clinical Applications; *Anaesthesiology*; vol 91, no.4, Oct 1999: 1090-1112.
14. McAlindon TE, Jacques P, Zhang Y, Hannan MT, Alibadi P, Weissman B, Rush D,Levy D; Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? *Arthritis and Rheumatism* 1996; 39:648-656.
15. Colin Dollery; *Therapeutic Drugs*, vol 2, 2nd edn, V46-47.
16. Bendich A, Machlin LJ; Safety of oral intake of Vitamin E; *American Journal of Clinical Nutrition*; 1988; 48(6)12-9.
17. Praveen Kumar, Michael Clark; Rheumatology and Bone disease; 555-64; *Kumar and Clark Clinical Medicine*; 6th edn; Elsevier Saunders.
18. Coderre TJ; The role of excitatory amino acid receptors and intra cellular messengers in persistent nociception after tissue injury in rats; *Mol Neurobiol* 1993; 7: 229-46.
19. Morris R, Southern E, Gittins S R, Devente J, Garwhaite G A; The NO-cGMP pathway in neonatal dorsal horn; *Eur J Neurosci* 1994; 6: 876-9.
20. Douglas C, Chan A C, Choy P C; Vitamin E inhibits platelet phospholipase A2;*Biochim Biophys Acta* 1986; 876: 639-45.
21. Doumerg C; Study of clinicalexperiments of d-alpha tocopheryl quinone in rheumatology; *Therapeutique* 1969: 43: 676-8.
22. Redanna P, Rao M K, Reddy C; Inhibition of 5-lipoxygenase by Vitamin E; *FEBS Lett* 1985; 193: 39-43.

23. Singh U, Devaraj S, Jialal H; Vitamin E, oxidative stresses and inflammation; *Annual Review of Nutrition*; 2005;25:151-74.