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RESEARCH ARTICLE

Effects of Vitamin C and Vitamin E in rheumatoid arthritis - A randomized, open label, and comparative study in a tertiary care hospital

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of autoimmune origin. It affects many organs and joints symmetrically. The involvement of reactive oxygen species (ROS) in the pathogenesis of RA is significant. Oxidative stress occurs when there is excess production of pro oxidants (ROS) and decrease in the level of antioxidants causing oxidative damage to tissues. Anti-oxidants such as Vitamins C and E are very effective in controlling free-radical induced inflammation. Apart from providing symptomatic relief they also modify the disease. **Aims and Objectives:** The aim of the study was to study the efficacy of Antioxidants Vitamins C and E as an add-on therapy to standard treatment in the management of RA compared to standard treatment alone. **Materials and Methods:** This was an open label randomized comparative study. In this study, 96 patients were screened and 60 patients were included. They were randomly divided into 30 each in study and control group. Control group received T. Hydroxy chloroquine 400 mg OD and T. Indomethacin 25 mg BD (standard treatment), study group received standard treatment plus T. Vitamin C 500 mg, and Vitamin E 400 mg for 8 s. They were followed for 4 weeks. Improvement of patients was monitored by, pain by visual analog scale, tender joint score, swollen joint score, disease activity score 28, inflammatory markers (ESR, CRP), and every 4 weeks till 12 weeks. **Results:** All the 60 patients included in this study completed the study. After 8 weeks of treatment in the study group there is statistically significant improvement in pain score, tender joint score, swollen joint score and DAS score. Similarly, statistically significant reduction in inflammatory markers includes ESR and CRP. In the follow-up period, the improvement in study group was sustained. **Conclusion:** Adding Vitamins C and E over and above the standard treatment can be a new approach in the treatment of RA.

KEY WORDS: Rheumatoid Arthritis; Oxidative Stress; Anti-Oxidants; Vitamin C; Vitamin E

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of autoimmune origin. It affects many organs and joints symmetrically.[1] Rheumatic arthritis is a common disease which affects the joints causing severe disability which is more common in women than men.[2] The pathological changes include cytokine mediated inflammation and CD4+T cell producing antibodies against cyclic citrulinated peptides which contribute to the joint lesions.[3] Antibodies are produced against citrulinated fibrinogen, alpha–enolase, type II collagen and vimentin and the immune complexes get deposited in the joints and contribute to tissue injury.[3]

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The involvement of reactive oxygen species (ROS) in the pathogenesis of RA is significant.[4] Lipid peroxidation of cell membrane induced by free radicals increase the

production of nonenzymatic synthesis of inflammatory mediators like isoprostones (8iso PGF2 alpha) causing chronic inflammations.[5] When the ROS binds to the cellular proteins causes modification in the structure which are targeted by immune system producing antibodies against these proteins. The Ag-Ab complex with in the joint space destroys the chondrocytes, and cartilages.[6] Oxidative stress occur when there is excess production of pro oxidants (ROS) and decrease in the level of antioxidants causing oxidative damage to tissues.[7]

Vitamin E scavenges peroxyl radical and prevents propagation of free radical by forming tocopherol radicals.[8] It affects oxidation of arachidonic acid and causes inhibition of iso-prostanes.[9] Vitamin E also inhibits central pain processing which causes analgesic action.[10] Vitamin C acts as ROS stabilizer and inhibits oxidative stress and reduces oxidative DNA damage, thereby acting as a good antioxidant.[11] It also has synergizing action with vitamin E to decrease production of iso-prostanes. It maintains antioxidant pool by regenerating other antioxidants like Vitamin E.[12]

Current management of RA includes nonsteroidal anti-inflammatory drugs, corticosteroids and disease-modifying antirheumatic drugs (DMARD), physiotherapy, and rest. Early treatment with DMARDs can reduce mortality and they need poly pharmacy for better control of disease. This study is conducted to identify the utility of anti-oxidants such as Vitamins C and E in RA patients when given along with standard treatment.

MATERIALS AND METHODS

This study was conducted in a tertiary hospital in rheumatology department after getting approval from institutional committee and patient consent after explaining procedure in their local language during period of august to may. Patients aged 40–60 years of both gender groups fulfilling the American College association criteria for RA were included in the study. Pregnant, lactating women and patient with severe cardiac renal, liver disease, malignancy, and patient on steroids were excluded from this study.

Out 98 patients screened, sixty were included and split into control and study groups of thirty through method of simple randomization. Oral Indomethacin BD dose 25 mg and Oral Hydroxychloroquine OD dose were administered to control group and for study group in addition to these drugs, oral Vitamin E OD 400 mg and oral Vitamin C OD 500 mg given for the period of 8 weeks.

Patient were assessed for pain by visual analog score and disease activity score 28 (DAS28). Laboratory parameter CRP and ESR (inflammatory markers) were also measured periodically every 4 weeks for the duration of 3 months. In the DAS score for tenderness and swelling score 1 was given and 0 score to absence of swelling and tenderness in multiple joints. DAS28 score value <3.2 indicates "low disease activity" and the value >5.1 means "high disease activity." After 8 weeks of study period patient were followed for another 4 weeks, and no dropout was found. Results of study were analyzed using Epi-info software, distribution of age and sex by analysis of variance and Pearson's Chi-square test, and clinical parameter and laboratory parameters by student's paired *t*-test.

RESULTS

In this study, all the patients were in the age group between 20 and 60 years and maximum number of patient were between 30 and 40 years. At the end of 8 eight weeks, there is significant reduction in VAS pain score in the study group with $P < 0.01$ compared to control group it was 0.13. Similarly tender joint score value of Mean 3.08 and SD 0.96 and $P < 0.001$ was seen in study group compared to control group Mean 12.05, SD 3.31, $P = 0.07$. Results of Swollen joint score in the control group at the end of 8 weeks was of Mean value 6.02, SD 1.732, $P = 0.122$, but in study group after 8 weeks with significant reduction of score seen with Mean 2.55,SD 1.58, $P = –0.01$. Disease activity score of study group was more significant with $P = 0.001$ in study group in contrast to control group $P = 0.41$. 56% of patients in study group showed reduction in ESR value after 8 weeks of treatment with added Vitamins C and E compared to standard control group of patients where only 6% reduction is seen. Regarding CRP value, 89% patient in study group showed significant reduction of <6 but in control group only 16% patients showed CRP value of <6 [Tables 1-3].

DISCUSSION

RA is a chronic autoimmune disease which involves multiple organs and joints. Disease progression leads to tissue destruction and deformities.[12] The major contributing factor in pathogenesis is oxidative stress. Antioxidants can play a significant role in the treatment.[13] Vitamins C and E are used in addition to standard treatment in this study. 60 patients are enrolled out of 96 screened and are randomized to study group and control group of 30 in each group. Assessments of clinical parameters included swollen, painful, tender joint scores, and DAS score. CRP and ESR included as laboratory inflammatory markers. The study group showed significant improvement in all clinical scores and lab parameters.

In a similar Riordan Clinic study,[14] intravenous Vitamin C on RA patients resulted in 44% decrease in CRP levels. However, in this study, 90% reduction in CRP level observed after Vitamins C and E supplements. As per Kou *et al*.[15] systematic review and meta-analysis study, Vitamin E on patients with RA had reduced pain in multiple joints. Here

Table 1: Clinical assessment scores

Clinical assessment scores	Control group				*P*-value	Study group				*P*-value
	Day 0		End of 8 weeks			Day 0		End of 8 weeks		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
VAS pain score	7.06	1.26	6.30	0.915	0.13	6.90	0.923	3.06	0.97	0.01
Tender joint score	14.2	3.82	12.05	3.31	0.07	6.90	0.923	3.08	0.96	0.001
Swollen joint score	7.73	2.46	6.02	1.732	0.122	7.66	2.76	2.55	1.58	0.01
DAS score	5.39	0.18	4.8	0.15	0.41	5.26	0.2	3.1	0.30	0.001

Table 2: Lab parameters-ESR

Group	Day 0 (mm/h)		AT 8 Weeks (mm/h)		%Reduction from baseline
	Mean	SD	Mean	SD	
Control	27.27	2.75	25.2	0.916	6
Study	28.20	4.51	12.05	0.96	56

Table 3: Lab parameter-CRP

Mean CRP	Base line		AT 8 weeks	
	No. of patients	%	No. of patients	%
Control				
>6	30	100	25	84
<6	0	0	5	16
Study				
>6	30	100	3	11
<6	0	0	27	89

also there is an improvement in status of pain and swollen joints.

During the course of 4 weeks follow-up, the improvement seen in the patients on anti-oxidants is maintained and no exacerbation is seen. This shows that antioxidants have a role in the treatment of RA. This study has the limitation of small number of patients and short duration and may need large group of patients in various population for more validity.

CONCLUSION

It can be concluded that anti-inflammatory action of anti-oxidants such as Vitamins E and C play a role in reducing pain and disease modification in RA patients. Hence, adding them over and above the standard treatment can be a new approach in the treatment of RA.

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