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ORIGINAL ARTICLE

Comparative Clinical Trial of Paracetamol alone and Vitamin C and E as an Add on Therapy in Patients Suffering From Primary Knee Osteoarthritis

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Abstract

A randomized observational blind comparative clinical study was conducted to compare the antioxidant effect of vitamin C and E with paracetamol in patients of primary knee osteoarthritis. Subjects presenting with sign, symptoms of primary knee osteoarthritis were given paracetamol 1 gm (n=50) twice daily for 8 weeks and combinations of paracetamol 1gm bid with vitamin C (500 mg) and E (200 IU) (n=50) twice daily for 8 weeks. Subjects completed an over all evaluation of symptoms relief on 2nd, 4th and 8th weeks of completed treatment were evaluated by clinical, routine laboratory and radiographic investigations for improvement of disease conditions, also for adverse drug reaction. On completion of 8 weeks of treatment it was observed that both the treatment group patients showed significant efficacy with better results with patients receiving antioxidant therapy in primary knee osteoarthritis patients (p<0.001) and adverse drug reaction were minor and none of patients complain of any severe adverse drug reaction. Present study indicate that antioxidant therapy can be used as an effective add on therapy in primary knee osteoarthritis.

Key Words

Paracetamol, Antioxidant, Knee Osteoarthritis.

Introduction

Among all the specific joint diseases, osteoarthritis is the most frequent cause of rheumatic complaints (1). More than 80% of patients over 55 years of age usually present with x-ray evidence of osteoarthritis. Osteoarthritis commonly involves the knee, hip and hands. Knee osteoarthritis is the leading cause of chronic disability among the elderly in the United States (2). Some of Indian study showed that 92% of orthopaedicians reported the common age of presentation of hip and knee osteoarthritis are above 50 years and that the incidence increases with advancing age (3).

Knee osteoarthritis is above 55 years more common in women than men but incidence is same in both sexes under 55 years of age. Various factors implicated are age, sex, obesity, etc. but there is no uniform opinion.

Studies have shown that antioxidant have a role in osteoarthritis. Experimental studies showed beneficial effect of extra ascorbic acid added to the drinking water had a slight chondroprotective effect on the development of spontaneous lesion in the experimental osteoarthritis. Transforming growth factor (TGF- 1), when present in large amount in bone and cartilage can increase the collagen production of cultured rabbit articular chondrocytes (RAC) and might play role in the early event of cartilage repair in osteoarthritis. Ascorbic acid, when added to the culture of RAC shows TGF- induced stimulation of collagen synthesis. Ascorbic acid known as co-factor of proline hydroxylase, is of critical importance in the synthesis of functional extra collagen matrix by RAC culture (4) Studies indicate high intake of antioxidant micronutrients especially vitamin C, may reduce the risk of cartilage loss and disease progression in people with osteoarthritis, studies also found protective association with -carotene and vitamin E (5).

Treatment of osteoarthritis is aimed at reducing pain, maintaining normal mobility and minimizing disability. Drug therapy in osteoarthritis is symptomatic. NSAIDs drugs are unequivocally effective in reducing pain and improving function in patients with osteoarthritis. So far no study have been conducted to evaluate effect of vitamin C and

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E as an add on therapy with paracetamol in Indian population, so the purpose of the present study was to compare the efficacy and safety of paracetamol along with antioxidant (vitamin C and E) as an add on therapy in patients suffering from knee osteoarthritis.

Materials & Methods

The present study was conducted Present study was conducted in the Department of Pharmacology and Orthopedics, PGIMER, Chandigarh, India. The study was prospective randomized controlled clinical study (observational blind) to compare the efficacy of paracetamol with antioxidant (vitamin C and E) as add on therapy. Prior approval was taken from Institute ethics committee before initiating the trial. Total number of 125 patients with a diagnosis of primary knee osteoarthritis were included in the study. Patients were divided into two groups (Group A, B)

Total number of 125 patients were assessed under the following inclusion and exclusion criteria of the study.

(a) Patients aged 40 years and above, (b) Patients with diagnosis of primary knee osteoarthritis.

Patients were excluded if they reported with (a) H/o trauma of knee or other joint under study, (b) Presence of deformity in the joint due to other underlying disease, (c) H/o previous surgery on joints, (d) Neurological or vascular conditions affecting joints, (e) Peptic ulcer disease, (f) Hepatic or renal insufficiency, (g) Prior intolerance or hypersensitivity to NSAIDS, (h) Anemia, bleeding diasthesis, unstable medical condition like diabetes mellitus, heart failure etc., (i) Patients with other concomitant medication

All the patients were subjected to radiographic examination A.P. and lateral view of knee joint. X-ray was studied for evidence of knee osteoarthritis. The degree of osteoarthritis was graded according to the Lawrence and Kellergen criteria's given below: Grade I: small osteophytes of doubtful significance, Grade II: definite osteophytes but joint space not impaired, Grade III: moderate diminution of joint space, Grade IV: extensive loss of joint space with sclerosis of subchondral bone. Following routine investigations were carried out: Routine haemogram for Hb, TLC, DLC, Liver function test (SGOT, SGPT, Alkaline phosphate, bile acids, bilirubin, total protein, albumin, globulin), Kidney function test (blood urea, S.creatinine, S.uric acid, S.sodium, S.potassium, S.bicarbonate), Routine examination urine, Routine examination stool for occult blood, Blood sugar (fasting and postprandial) Above mentioned investigations were carried out during the 1st visit and after completion of treatment. After randomization of 115 patients included in the study of either sex and similar demographic profile,

patients were divided into two groups. Group A: total 50 patients were included in the study. Patients were given tab. Paracetamol 1 gm twice daily for 8 wks period. Group B: total 50 patients were included in the study. Patients were receive paracetamol 1gm twice daily with Vitamin C 500 mg BD and Vitamin E 200 IU twice daily for 8 weeks period.

Patients were examined on 1st visit, then on 2nd visit (after two weeks), 3rd visit after (fourth weeks) at the time of completion of treatment period (8th weeks). Pain intensity before the drug therapy was recorded on the visual analogue scale, then on every visit. The pain intensity was score rest and in squatting position. The range of scoring of visual analogue scale is 0-10 (0-no pain, 10-maximum severe pain). In case of patient with swelling of knee joint, joint was palpated, range of motion, temperature and tenderness were measures on 1st visit then on every visit till the completion of drug therapy in every group. Patients taking any other medications were given wash out period before starting the drug therapy.

Fig 1. Enrollment and Randomization of the Study Patients of Primary Knee Osteoarthritis





Table 1. Base Line Characteristics in 100 OA Patients

Table 2. Age Relationship of Patients (N=25) Each Group

No. of natients	Group A	Group B	Age group	Group A	Group B	
ite of patients	Group /1	Group D	40-50	20(40%)	16(32%)	
	50	50	51-60	18(36%)	20(40%)	
Age			61-70	12(24%)	12(24%)	
Range	37.00-70.00	35.00-80.00	71-80	-	2(4%)	
Mean \pm S.D.	52.80 ± 9.20	54.84 ± 10.64	81-90	-	_	
Sex				 		
Male	36%	16%	Table 3: Body Weight Relationship of Patient (N=25)			
Female	64%	84%	Body weight (kg) Group A Group B			
Symptom present	100%	100%		-8/ 0100 F	<u>F</u> -	
Investigations :			40-50	_	_	
Haemogram	10.01 1.01		51-60	10(20%)	8(16%)	
Hb (me an \pm SD)	12.94 ± 1.34	12.0400 ± 0.7059	61-70	10(20%) 12(24%)	12(24%)	
TLC (me an \pm SD)	8030.40 ± 1517.40	6468.00 ± 451.59	71.80	12(24%) 20(40%)	12(2470) 16(2207)	
Disclasses	1517.49		/1-00	20(40%)	10(32%)	
Blood sugar	07 (0) 0 01	70.00 + 10.51	81-90	4(8%)	-	
Fasting	$8/.60 \pm 9.31$	78.08 ± 10.51	91-100	4(8%)	6(12%)	
Post prancial (PP)	115.88 ± 20.75	111.52 ± 0.04	two-way ANOVA test and student's 't' test. The p va			
	5.10 ± 6.90	5.06 ± 1.56	< 0.05 was considered as statistically significant.			
$\Lambda P \& I a teral view$	Grade L 8	Grada I: 10	Results		2	
A.I. & Lateral view	Grade-II · 34	Grade-II · 28	Table 1 show	s the base line	characteristics of 100	
	Grade-III: 8	Grade-III ·12		s une base nine (characteristics of 100	
Loint Involvement	Grade-III. 6		osteoartnritis pa	itients with kne	e osteoartnritis. The	
Control group	Unilateral 6	Unilateral 00 Bilateral 50	patients belonging of group-A and group-B were			
Control group	Bilateral 44		comparable with reference to age, sex, presence of			
		Dimenul 50	symptoms. Baseline investigations and presence of			

Fig 2. Outcomes of Pain Parameters on VAS During Different Visit and After Completion of Treatment Period



Table 4. Outcomes of Pain Parameters on VAS During Different Visit and After Completion of Treatment Period

Be fore therapy					After therapy					p-value
Group	Number of	1 st visit	2 nd visit		3 rd visit		4 th visit			
-	patients	R	S	R	S	R	S	R	S	
А	50	7.48 ± 1.71	8.16 ± 1.74	6.76 ± 1.854	6.92 ± 1.52	5.56 ± 1.95	6.08 ± 1.65	4.28 ± 1.83	4.88 ± 1.66	<0.001
В	50	7.52 ± 2.6	8.56 ± 2.48	6.72 ± 2.22	7.52 ± 2.18	5.84 ± 2.23	6.24 ± 2.18	3.72 ± 1.99	4.12± 1.62	< 0.001

During the treatment period, patients from all the groups were evaluated for any adverse reaction due to drug therapy. All the patients were given physiotherapy along with drug therapy (*Fig-1*).

Statistical analysis

All the patients data were be entered into the database program. Comparative evaluation was carried out using

osteoarthritis changes on x-ray knee (A.P. and Lateral view), and body weight of patients (*Table-1-3*).

Baseline investigations: Heamogram, total leukocytic count (TLC), blood sugar (fasting, post-prandial), hepatic enzyme (SGOT, SGPT) and uric acid were within normal range in all patients. On knee X-ray (A.P. & L. view) in group A patients were Grade-I : 8, Grade-II : 34, Grade-

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III: 8 criteria. In Group-B were Grade-I: 10, Grade-II: 28, Grade-III: 12, majority of patients in both the groups were mild to moderate osteoarthritis and most of patients had bilateral knee osteoarthritis.

Adverse drug reaction in two month follow up in group-A: six patients reported with symptoms of mild gastritis, two patients complain of nausea at the end of the eight weeks of treatment. In group-B, four patient complained of dyspepsia and two patients complain of skin rash but all the ADR in group A&B were mild and none of the patients withdrew because of adverse drugs reaction.

Efficacy of drug therapy in group A, patients on paracetamol alone: 44 (88%) patients showed significant improvement of pain and only 6 (12%) patients did not respond after four weeks of therapy. In group B on paracetamol alone with vitamin C & E: 48 patients (96%) showed significant improvement and only two patients (8%) reported no improvement after four weeks of therapy.

In group A, at the end different visit and after of the completion treatment VAS was significantly reduced (p<0.001). Comparative statistical analysis between group A and group B at second weeks and forth weeks shows both the groups are comparable and on comparison it was found to be statistically non-significant. At the end of completion of treatment (eight weeks) Group B showed better efficacy and it was statistically significant (p<0.001) (*Fig 2 & Table 4*)

Discussion

The treatment of osteoarthritis is aimed at management of pain, maintaining normal mobility and minimizing disability. Drug therapy in osteoarthritis is symptomatic. Presently paracetamol is the most widely prescribed recommended drugs in osteoarthritis because of its safety profile and after withdrew of some of COX II inhibitor from market (1). Several studies have been conducted in the recent past for evaluation of antioxidant effect on osteoarthritis, study revealed that tenoxicam may have antioxidant effects, and that celecoxib and tenoxicam may reduce nitrite levels, indicating an alteration of NO pathways in osteoarthritis patients (6) But the study conducted to evaluate the effect of diclofenac alone or in combination with alpha-tocopherol did not produce a consistent effect on the CL response of whole blood or isolated PMNs of healthy or osteoarthritic patients (7) Another study showed addition of vitamin C is essential for the formation of collagen and proteoglycan and has been shown to minimized surgically induced arthritis in guinea pigs, no controlled trial has examined its effect on human osteoarthritis, The study demonstrated effect is less than half as pronounced as commonly reported for NSAID etc. the finding of the study showed acceptable intake of vitamin C this would be of importance considering the large prevalence of osteoarthrosis (8). Present study also showed additional benefit with add on therapy of vitamin C and E compare to Group A(< 0.001). But some of study reported with no benefit with Vitamin E. In a double blind, placebo controlled trial, 136 patients with knee OA were randomized to receive vitamin E (500 IU) or placebo for 2 years, to determine whether vitamin E affects change in cartilage volume in patients with knee osteoarthritis, study showed Vitamin E does not appear to have a beneficial effect in the management of knee OA: it does not affect cartilage volume loss or symptoms (9). Similarly other study results suggest that iodine, but not selenium, deficiency should be corrected in Tibetan children with Kashin-Beck disease (10). Ekmekcioglu C et al, reported the role of antioxidant therapy particularly in osteoarthritis, due to possible antiinflammatory effects, like sulfur baths are widely used for the treatment of rheumatic diseases. The results suggested that a sulfur bath therapy could cause a reduction in oxidative stress, alterations of SOD activities, and a tendency towards improvement of lipid levels (11). Similarly Piscoya J et al, showed the ability of cat's claw, an Amazonian medicinal plant, to treat osteoarthritis of the knee, collect safety and tolerance information and compare the antioxidant, and anti-inflammatory actions of Uncaria guianensis and Uncaria tomentosa in vitro. The results suggested that a sulfur bath therapy could cause a reduction in oxidative stress, alterations of SOD activities, and a tendency towards improvement of lipid levels (12) Several clinical trial also reported beneficial effect, a study of 16-week randomized, double-blind, placebo-controlled crossover trial of a combination of glucosamine HCl (1,500 mg/day), chondroitin sulfate (1,200 mg/day), and manganese ascorbate (228 mg/day) in degenerative joint disease (DJD) of the knee or low back was conducted. The combination therapy relieves symptoms of knee osteoarthritis. A larger data set is needed to determine the value of this therapy for spinal DJD. Short-term combination therapy appears to be safe in this setting (13). Our study also showed clinical benefit from four weeks onward, so antioxidant should be continue for the longer duration to get the maximum benefit in patients of knee osteoarthritis, however efficacy is only predicted in patients with mild to moderate osteoarthritis. On statistical analysis between the two groups, Group B showed better efficacy than Group A at the end of 8th weeks of treatment (p < 0.001). Over the last few years, different antioxidants, and particularly vitamin C and E,



have received considerable attention in the treatment of human diseases. However, the concept of using antioxidant nutrients as potential remedies is not new. As early as the sixties, first case reports have described beneficial effects of vitamin E in the therapy of osteoarthritis. Nonetheless, most of the following studies were not conducted properly, thus, not allowing valid inferences about the efficacy of vitamin E. Newer studies with sound methodology have shown a beneficial effect in rheumatic diseases, mainly in the reduction of pain (14,15). So large prospective with longer duration study is required in near future.

Conclusion

Paracetamol alone is efficacious and add on with antioxidant and paracetamol in the treatment of primary knee osteoarthritis patients showed better efficacy which is found to be statistically significant at the end of eight weeks (p<0.001). So in future lager prospective and longer duration trial should be conducted to established long term safety and tolerability of antioxidant therapy in primary knee osteoarthritis patients.

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