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Effect of Colchicine on Total Antioxidant Capacity, Antioxidant Enzymes and Oxidative Stress Markers in Patients with Knee Osteoarthritis

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ABSTRACT

Background/Aim: We aimed to investigate the effects of colchicine on clinical recovery, as well as oxidative stress markers and total antioxidant capacity (TAC) in whole blood of patients with knee osteoarthritis (OA). **Materials and Methods:** Sixty patients with grade 2 - 3 knee OA according to ACR knee OA criteria whom examination of the knee joint synovial fluid by polarized light microscopy demonstrated CPDD crystals existence were included in the study. Fifty healthy subjects were included as a control group. Patients were divided randomly into two groups. The first group (paracetamol group) was given only paracetamol 3 gr daily p.o and the second group (colchicine and paracetamol group) was given colchicine 1.5 gr and paracetamol 3 gr daily p.o for six months. For outcome measures WOMAC and VAS were used. Superoxide dismutase (SOD), Catalase (CAT) ezyme activities and Glutathione (GSH) and Malondialdehyde (MDA) levels and TAC all were measured. **Results:** WOMAC scores were improved in both patient groups compared with pre-treatment evaluation ($p < 0.025$). WOMAC morning stiffness scores were significantly more improved in colchicine group compared with paracetamol group ($p > 0.05$). TAC was signifcantly increased only in colchicine/paracetamol group. Oxidant parameter MDA levels were significantly decreased in both paracetamol group and colchicine/paracetamol group. CAT, SOD enzyme activities and GSH levels did not change before and after treatment protocols in both patient groups. **Conclusion:** Both paracetamol 3000 mg/day and 3000 mg paracetamol plus 1.5 gr/day colchicine is effective in the treatment of patients with knee osteoarthritis. But the addition of colchicine to paracetamol produced significantly greater symptomatic benefit than paracetamol alone. Our study also showed that colchicine lowers whole blood MDA which is a lipid peroxidation compound and elevates TAC levels in patients with knee OA. This may show probable disease modifying effect of colchicine in knee OA which require further long period laboratory and radiologic investigations.

Keywords: Knee Osteoarthritis; Colchicine; Paracetamol; Total Antioxidant Capacity; Malondialdehyde; Oxidative Stres

1. Introduction

Osteoarthritis (OA) is a chronic degenerative disorder of multifactorial etiology characterized by loss of articular cartilage and changes in the underlying bone at the joint margins. OA is a leading cause of chronic joint pain and disability at older ages, largely due to knee and hip involvement. The etiology of OA is unclear. Mechanical, biochemical, metabolic, endocrine, genetic and environmental factors seem to play a role [1].

The incidence of osteoarthritis increases steeply after 50 years of age and the proportion of elderly people in the population continues to increase. More than 13% of Americans aged 55 to 64 years, and more than 17% of Americans aged 65 to 74 years, have pain and functional limitations related to knee OA [2].

Basic calcium phosphate (BCP) and calcium pyrophosphate dihydrate (CPPD) crystals are commonly found in osteoarthritic joints. These crystals have been found in the synovial fluid of 60% of patients with knee OA and over 90% of a small group of patients with grade-4 OA [3,4].

Clinical and experimental data suggest a pathogenic

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role for calcium-containing crystals in cartilage destruction and OA development and progression [5].

Oxidative demage to collagen (oxidative DNA demage etc.) has also important role in etiopathogenesis of OA. Decreased joint fluid antioxidants and increased reactive oxygen species (ROS) have been shown in osteoarthritic joints compared to joints with macroscropically intact cartilage and subacute injury. ROS induced by IL-1β and TNF-α can directly cleave proteoglycans and collagen, modulate signaling pathways and activate MMPs, as well as alter chondrocyte apoptosis and cellular synthetic activity [4,6-24].

Recently there has been increase in trials on disease/ structure-modifying agents in OA (e.g. MMP inhibitors, glucosamine or chondritin sulphate, colchicine, strontium ranelate, biphosphonates and diacetylrhein/diacerein). This is an area of active research at present. Preclinical studies of potential disease modifying agents are promising. In clinical studies, generally, radiological joint space narrowing or width have been used as the structural outcome measure in these trials. More advanced compositional MRI techniques, and laboratory cartilage markers might enable to detect early cartilage changes before radiographic joint space narrowing becomes evident [25-27].

Furthermore there are studies in the literature, on slow acting disease/structure-modifying effects of colchicine in knee OA. The rationale using colchicine as disease/ structure-modifying drug to manage OA resides in the fact that calcium-containing crystals are frequently seen in OA (3, 4), and colchicine has been shown to be beneficial in preventing calcium crystal-induced inflammation (pseudogout). When used to treat gouty arthritis, colchicine is believed to work by inhibiting microtubule dependent cell infiltration and IL-1β production. However, *in vitro* and *in vivo*, colchicine also reduces monosodium urate (MSU)-induced ROS production by neutrophils [28-31].

Taking into account that increased incidence of calcium-containing crystals (from 60% upto 90%), decreased joint fluid antioxidants and increased reactive oxygen species (ROS) in osteoarthritic joints, we aimed to investigate the effects of colchicine on clinical recovery, oxidative stress markers and total antioxidant capacity (TAC) in whole blood of patients with knee osteoarthritis.

2. Materials and Methods

Sixty patients with grade 2 - 3 knee osteoarthritis according to ACR knee OA criteria whom examination of the knee joint synovial fluid by polarized light microscopy demonstrated CPDD crystals existence were included in the study. Fifty healthy subjects who have similar demographic characteristics with patient group were included as a control group. The study protocol, consent form and all recruitment materials were approved by the ethical Board of the University of Yuzuncu Yil University, Van, Turkey, and the study was conducted in accordance with the Declaration of Helsinki. Patients were divided randomly into two groups. The first group (paracetamol group) was given only paracetamol 3 gr daily p.o and the second group (colchicine and paracetamol group) was given colchicine 1.5 gr and paracetamol 3 gr daily p.o.

The patients with diabetes, gouty arthritis, secondary knee osteoarthritis due to inflammatory joint diseases, a history of intraarticular corticosteroid and/or hyaluronic acid injections, and a history of oral glucosamine, colchicine use during the last 6 months, chronic alchohol consumption, chronic liver and kidney diseases, smokers, a history of antioxidant vitamin and/or mineral use during the last six months were excluded.

One of the primary clinical outcome measures was change in the WOMAC-Western Ontario and McMaster Universities Arthritis Index. The WOMAC has been used extensively in the quantitative assessment of knee OA, and has been proven to be effective in assessing functionality, pain in patients suffering from knee OA. Turkish WOMAC has been found valid and reliable [32].

Another clinical outcome measure was 100 mm VAS (visual analog scale) for pain measuremet.

Before drug treatment start and after the last treatment dose (6 months later), 7 mL sample of venous blood was taken in the morning before breakfast from each patient and control subjects. Serum samples were stored at −20˚C until analysis.

2.1. Oxidant/Antioxidant Status Analysis

2.1.1. Superoxide Dismutase (SOD) Enzyme Analysis

SOD enzyme activity was measured using Genesys 10 UV-VIS Scanning spectrophotometer by Randox-Ransod enzyme kit at 505 nm and 37˚C.

2.1.2. Catalase (CAT) Enzyme Activity Determination

Catalase enzyme activity was measured by reading the absorbance with a spectrophotometer (Genesys 10 UV Scanning UV/VIS Spectrophotometer) set at 240 nm based on Aebi method.

2.1.3. Glutathion (GSH) Determination

GSH samples were measured by using a spectrofluorimetry (Jasco 6000 USA) with excitation at 345 nm and emission at 425 nm.

2.1.4. Total Antioxidant Capacity (TAC)

Ready-kit was used according to the measurement method.

2.1.5. Malondialdehyde (MDA) Determination

Levels of MDA which is a peroxidation product of lipid

metabolism were analyzed spectrofluorimetrically, using the modified method by Hegde *et al.* [33]. The MDA was measured by a spectrofluorimetry (Jasco 6000, USA), with excitation at 520 nm and emission at 555 nm.

All outcome measures were performed before colchicine tretment and just after of colchicine treatmet finish (6 months later).

2.2. Statistical Analysis

Results were expressed as mean and standard deviation (SD). Statistical analysis was carried out using the SPSS program (version 11.5 software, SPSS Inc. Chicago, Illinois, USA). For the comparison of groups, independent student t test, ANOVA, Kruskal Wallis and Mann-Whitney U test were used. Categorical variables were evaluated with Pearson's chi-square test. Within the same group comparisons in terms of the difference between pretreatment and posttreatment measurements were investigated by the dependent t-test or Wilcoxon signed rank test. P values of less than 0.05 were regarded as significant.

3. Results

Demographic data of the groups were presented in **Table 1**. There was no significant difference between groups in terms of demographic variables.

VAS scores according to patient and doctor evaluations of the tretment groups were presented in **Table 2**. Only Colchicine group showed statistically significant change after the treatment in terms of VAS scores compared with pre-treatment evaluation.

Pre and post-treatment WOMAC scores of the patient groups were presented in **Table 3**. Post-treatment WOMAC scores were improved in both patient groups compared with pre-treatment evaluation ($p < 0.025$). WOMAC morning stiffness scores were significantly more

Table 1. Demographic properties of the groups.

Variables	Control	Paracetamol	Colchicine/ Paracetamol	p-Value
Age	56.7 ± 6.7	55.4 ± 6.2	57.6 ± 7.1	0.452
Gender				0.895
Male (n)	19 (38.0%)	13 (43.3%)	12 (40.0%)	
Female (n)	31 (62.0%)	17 (56.7%)	18 (60.0%)	
Kellgren Grade				0.598
Grade II	-	11 (36.7%)	13 (43.3%)	
Grade III	-	19 (63.3%)	17 (56.7%)	

Table 2. Pre-treatment and post-treatment VAS scores of the patient groups.

Variables	Pre-treatment (mean(SD))	Post-treatment (mean(SD))	p-Value[a]	Change (mean(SD))	p-Value[b]
$VAS_{patient}$					0.645
Paracetamol	77.5 (17.25)	74.0 (17.25)	0.060	–4.0 (8.00)	
Colchicine/Par	79.0 (11.50)	76.0 (14.00)	0.010	–4.0 (8.50)	
VAS_{doctor}					0.662
Paracetamol	75.5 (7.25)	74.0 (15.25)	0.043	–3.0 (9.25)	
Colchicine/Par	73.0 (17.25)	68.0 (15.50)	0.033	–3.5 (12.00)	

[a]Comparisons between pre-treatment and post-treatment within the same groups, according to the Bonferroni correction p value < 0.025 was considered statistically significant for the results; [b]Comparisons between the groups in terms of treatment-related change, p-value < 0.05 was considered statistically significant for the results.

Table 3. Pre-teratment and post-treatment WOMAC scores of the patient groups.

Variables	Pre-treatment (mean(SD))	Post-treatment (mean(SD))	p-Value[a]	Change (mean(SD))	p-Value[b]
Pain					0.988
Paracetamol	11.5 (4.00)	11.0 (3.25)	0.008	–1.0 (2.25)	
Colchicine/Par	11.0 (5.00)	9.5 (4.25)	0.011	–1.0 (3.00)	
Morning stiffness					0.039
Paracetamol	1.0 (2.25)	1.0 (2.00)	0.206	0.0 (0.00)	
Colchicine/Par	3.0 (4.25)	2.0 (3.25)	0.005	–1.0 (1.25)	
Physical activity					0.755
Paracetamol	38.0 (11.00)	36.5 (14.25)	0.027	–2.5 (6.50)	
Colchicine/Par	34.5 (17.00)	31.0 (13.25)	0.021	–2.0 (8.25)	
Total					0.280
Paracetamol	12.2 (6.50)	11.5 (6.08)	0.002	–1.0 (1.91)	
Colchicine/Par	13.3 (8.75)	11.9 (5.56)	0.002	–1.0 (2.85)	

[a]Comparisons between pre-treatment and post-treatment within the same groups, according to the Bonferroni correction p-value < 0.025 was considered statistically significant for the results; [b]Comparisons between the groups in terms of treatment-related change, p-value < 0.05 was considered statistically significant for the results.

improved in colchicine group compared with paracetamol group ($p > 0.05$).

Baseline oxidant and anti-oxidant levels of the control group and the treatment groups were presented in **Table 4**. There were statistically significant differences between control group and treatment groups in terms of baseline MDA levels ($p < 0.001$). Baseline MDA levels were higher in treatment groups than control group.

Comparisons of pre-treatment and post-treatment oxidant and antioxidant levels of the patient groups were presented in **Table 5**. Total antioxidant capacity (TAC) was signifcantly increased only in colchicine/paracetamol group. Oxidant parameter MDA levels were significantly decreased in both paracetamol group and colchicine/paracetamol group. Catalase (CAT), superoxide dismutase (SOD) enzyme activities and glutathione (GSH) levels did not change before and after treatment protocols in both patient groups.

4. Discussion

In this study, the effects of colchicine on whole blood oxidant load, antioxidant capacity and clinical recovery in patients with OA were investigated. In the current study we found that baseline MDA levels were higher in patients with OA than healthy control group. Baseline SOD, CAT enzyme activities, GSH, and TAC levels were not differed between groups. When compared to baseline MDA levels, post-treatment MDA levels significantly decreased in only the group receiving colchicine/paracetamol. Post-treatment TAC levels were also increased significantly in only the group receiving colchicine/paracetamol. No significant changes were observed in post-treatment SOD, CAT enzyme activities and GSH levels in both groups.

As well as colchicine treated group showed more improvement in clinical recovery parameters such as WOMAC and VAS scores than control and paracetamol treated groups. Our clinical recovery results are in accordance with previous studies by Ediz L. *et al.* and Das K. *et al.* [28,34].

Basic calcium phosphate (BCP) and calcium pyrophosphate dihydrate (CPPD) crystals are commonly found in osteoarthritic joints. These crystals have been found in the synovial fluid of 60% of patients with knee OA and over 90% of a small group of patients with grade-4 OA

Table 4. Pre-treatment (baseline) laboratory findings of control and treatment Groups.

Variables	Control	Paracetamol	Colchicine/ Paracetamol	p-Value
CAT	56.4 (18.30)	54.8 (13.02)	59.2 (18.97)	0.328
GSH	0.98 (0.09)	1.0 (0.17)	0.99 (0.06)	0.743
TAC	25.0 ± 5.78	24.0 ± 7.25	21.6 ± 5.31	0.081
MDA	5.7 (1.11)[a,b]	6.6 (1.32)[a]	6.1 (1.94)[b]	<0.001
SOD	228.7 (72.52)	214.3 (90.97)	221.5 (124.23)	0.749

[a]Statistically significant difference between control group and paracetamol group ($p < 0.001$); [b]Statistically significant difference between control group and clchicine group ($p < 0.001$).

Table 5. Comparison of pre-treatment and post-treatment oxidant and antioxidant levels of the patient groups.

Variables	Pre-treatment (mean(SD))	Post-treatment (mean(SD))	p-Value[a]	Change (mean(SD))	p-Value[b]
Catalase					0.738
Paracetamol	54.8 (13.02)	60.2 (16.52)	0.645	–0.09 (20.42)	
Colchicine/Par	59.2 (18.97)	62.1 (16.62)	0.866	0.47 (20.32)	
GSH					0.560
Paracetamol	1.0 (0.17)	1.0 (0.12)	0.949	0.01 (0.14)	
Colchicine/Par	0.99 (0.06)	1.0 (0.07)	0.271	0.01 (0.11)	
TAC					0.206
Paracetamol	24.0 ± 7.25	24.6 ± 7.10	0.754	0.6 ± 10.32	
Colchicine/Par	21.6 ± 5.31	25.3 ± 5.55	0.018	3.7 ± 7.67	
MDA					0.817
Paracetamol	6.6 (1.32)	5.6 (1.24)	0.002	–0.64 (1.87)	
Colchicine/Par	6.1 (1.94)	5.6 (0.84)	0.014	–0.83 (2.22)	
SOD					0.727
Paracetamol	214.3 (90.97)	228.7 (72.52)	0.610	20.4 (98.87)	
Colchicine/Par	221.5 (124.23)	221.5 (95.15)	0.696	34.3 (109.37)	

[a]Comparisons between pre-treatment and post-treatment within the same groups, according to the Bonferroni correction p value < 0.025 was considered statistically significant for the results; [b]Comparisons between the groups in terms of treatment-related change, p value < 0.05 was considered statistically significant for the results.

[3,4].

These crystals induce and maintain inflammation and ROS production in osteoarthritic joint and hence degredate more and more cartilage and produce pain and finally joint impairment occurs. To the best of our knowledge this is the first study in the literature evaluates colchicine effects on whole blood oxidant load and antioxidant levels in patients with knee OA. Our study showed that colchicine lowers whole blood MDA which is a lipid peroxidation compound and elevates TAC levels in patients with knee OA. Namely colchicine has antioxidant activity and also enhances total antioxiant capacity. However in this study, colchicine has no effect on whole blood SOD, CAT enzyme activities and GSH levels in patients with knee OA.

The current treatment of OA is primarily focused on relief of the symptoms by use of rapid action drugs (analgesics, cycloxygenase (COX-2) specific inhibitors and NSAIDS). These drugs do not effect the underlying pathogenesis of OA, thus have minimal role in modifying disease course and improving quality of life [35,36].

In conclusion both paracetamol 3000 mg/day and 3000 mg paracetamol plus 1.5 gr/day colchicine is effective in the treatment of patients with knee osteoarthritis. But the addition of colchicine to paracetamol produced significantly greater symptomatic benefit than paracetamol alone. Our study also showed that colchicine lowers whole blood MDA which is a lipid peroxidation compound and elevates TAC levels in patients with knee OA. This may show probable disease modifying effect of colchicine in knee osteoarthritis which require further long period laboratory and radiologic investigations.

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