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Effects of Flurbiprofen and Tiaprofenic Acid on Oxidative Stress Markers in Osteoarthritis: A Prospective, Randomized, Open-Label, Active- and Placebo-Controlled Trial

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ABSTRACT

Background: The relationship between oxidative stress and osteoarthritis (OA) has been widely investigated. Serum malondialdehyde (MDA), nitric oxide (NO), and Cu/Zn superoxide dismutase (SOD) levels are useful markers of oxidative stress. Because of the importance of oxidative stress markers in the pathogenesis of OA, treatment might involve modification of these markers to control oxidative stress.

Objective: The aim of this study was to compare the effects of 2 conventional NSAIDs on markers of oxidative stress in patients with OA of the knee.

Methods: This 3-week, prospective, randomized, open-label, active- and placebo-controlled study was conducted at the Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey. Adult patients with clinically and radiographically diagnosed moderate OA of the knee who were previously untreated were enrolled. Patients were randomly assigned to 1 of 3 treatment groups: flurbiprofen 100 mg PO (tablets) BID, tiaprofenic acid 300 mg PO (tablets) BID, or placebo tablets BID. Patients were evaluated using clinical assessment and laboratory testing before treatment (week 0; baseline) and at the end of week 3. The primary end points were the differences in serum MDA, NO, and SOD levels versus placebo. Clinical parameters—pain at rest and on motion—were evaluated using a 10-cm visual analog scale (0 = no pain to 10 = worst pain imaginable). The duration (in minutes) of morning stiffness was recorded by patients, using patient diaries. The differences between treatment groups were assessed using multivariate analysis.

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Results: Thirty-nine patients (20 women, 19 men; mean [SD] age, 59.0 [11.3] years) were included in the study. Mean serum MDA and NO levels were significantly decreased at 3 weeks compared with baseline in the 2 active-treatment groups (all, $P < 0.001$); these values remained statistically similar to baseline in the placebo group. Serum SOD levels were increased significantly from baseline in the 2 active-treatment groups (both, $P < 0.001$), but not in the placebo group. No significant differences in serum MDA and NO levels were found between the group receiving flurbiprofen and that receiving tiaprofenic acid. Serum SOD levels were significantly higher in the flurbiprofen group compared with the tiaprofenic acid and placebo groups (both, $P < 0.01$). The mean (SD) score for pain at rest was significantly lower at 3 weeks compared with baseline with flurbiprofen and tiaprofenic acid (both, $P < 0.001$), but not with placebo. The mean score for pain on motion was significantly reduced from baseline values only with tiaprofenic acid ($P < 0.001$). The duration of morning stiffness was significantly shorter at 3 weeks compared with baseline in all 3 study groups (all, $P < 0.001$). The mean scores for pain on motion and duration of morning stiffness were significantly reduced with tiaprofenic acid compared with placebo (both, $P < 0.05$). The study had some limitations (ie, small sample size, no blinding, the short duration of the study, and the weak correlation between serum and synovial fluid levels of NO).

Conclusions: In this comparison of the effects of 3 weeks of treatment with flurbiprofen 100 mg BID and tiaprofenic acid 300 mg BID in patients with knee OA, both treatments effectively reduced serum MDA and NO levels compared with placebo. Only tiaprofenic acid significantly improved pain at rest and on motion and duration of morning stiffness compared with placebo. (*Curr Ther Res Clin Exp.* 2005;66:335–344)

Key words: osteoarthritis, malondialdehyde, nitric oxide, superoxide dismutase, NSAIDs.

INTRODUCTION

The relationship between oxidative stress and osteoarthritis (OA) has been widely investigated since the 1990s. Malondialdehyde (MDA) is the end-product of lipid peroxidation; superoxide dismutase (SOD) is a superoxide radical-scavenging enzyme; and nitric oxide (NO) is a free radical synthesized from L-arginine by NO synthetase. Serum MDA, NO, and Cu/Zn SOD levels are useful markers of oxidative stress. OA is considered a degenerative disease of the cartilage but also involves some synovial inflammation.[1,2] Oxidative damage has been shown to have an aging effect on the cartilage, which leads to OA in studies in humans, animals, and in vitro.[3,4]

Reactive oxygen species (ROS), mostly NO, play a pivotal role in the pathologic process of OA, mainly by contributing to tissue degradation caused by inflammation.[1,3,5] Although oxidative stress is known to lead to an increased risk for OA, the precise mechanism remains unclear.[3]

The potential role of ROS in joint swelling, cellular infiltration, and pain remains controversial.[1] Some studies have shown that oxidative stress markers play a role in different cellular phases of OA.[4,6] Two studies have reported that the serum levels of these markers may predict disease activity.[7,8]

NSAIDs have been considered to function as active oxygen inhibitors. However, the mechanisms of such inhibitory activity remain unclear.[9]

Because of the importance of oxidative stress markers in the pathogenesis of OA, treatment might involve modification of these markers to control oxidative stress. The aim of this study was to determine the efficacy and tolerability of 2 conventional NSAIDs on markers of oxidative stress in patients with OA of the knee.

PATIENTS AND METHODS

This 3-week, prospective, randomized, open-label, active- and placebo-controlled study was conducted at the Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey. Sample collection was performed after receipt of written informed consent from each subject in accordance with the International Federation of Clinical Chemistry and the Declaration of Helsinki. The study was approved by the Ethics Committee of Cerrahpasa Medical Faculty.

Patients aged ≥18 years with moderate OA of the knee (diagnosed at a physical medicine and rehabilitation outpatient clinic using clinical and radiographic assessment with American College of Rheumatology criteria[10]) and who had not previously received treatment for OA were recruited for the study. Eligible patients were asked to participate voluntarily in the study; they were not compensated.

Patients who had clinically significant laboratory abnormalities related to hepatic or renal dysfunction or infectious disease, or who had a history of hepatic, renal, or hematopoietic disorders were excluded. Patients who were pregnant or breast-feeding also were excluded.

Within 1 week after screening and enrollment, patients were randomly assigned to 1 of 3 study groups: flurbiprofen 100 mg PO (tablets) BID, tiaprofenic acid 300 mg PO (tablets) BID, or placebo tablets BID. All study drugs were self-administered for 3 weeks. Randomization was performed according to age, sex, height, weight, body mass index, disease duration, and baseline pain scores (at rest and on motion) and duration of morning stiffness. Calculations were performed using Unistat version 5.1.03 (Unistat Ltd., London, United Kingdom).

Patients were assessed clinically using physical examination, including vital sign measurements and visual analog scale (VAS) scores and laboratory analysis (measurements of serum MDA, NO, and SOD) at baseline and at the end of the third week of treatment.

Preparation of Samples

The primary end points were the differences in serum MDA, NO, and SOD levels between the active-treatment groups and the placebo group. Blood samples were obtained by using venipuncture, centrifuged at 3000 rpm for 10 minutes at

4°C, and stored at 0°C to 4°C until analysis (≤3 months). Serum was assayed for levels of MDA, NO, and SOD.

Efficacy

Pain and Morning Stiffness

Pain at rest and on motion was evaluated using a 10-cm VAS (0 = no pain to 10 = worst pain imaginable).[11] The duration of morning stiffness (in minutes) was recorded by patients, using patient diaries.

Laboratory Parameters

Lipoperoxidation was assessed using the MDA level, which was estimated using the thiobarbituric acid method.[12] The serum MDA level was calculated using an extinction coefficient (1.56×10^5) and was expressed as nmol/mL.

Serum NO levels (μmol/L) were estimated using a calorimetric assay kit (Roche Diagnostics, Somerville, New Jersey).[13]

Serum SOD levels (U/mL) were determined using the method described by Sun et al,[14] with an assay involving the inhibition of nitroblue tetrazolium reduction by superoxide anions.

Tolerability

Tolerability was assessed using subject interviews.

Statistical Analysis

The calculated power of the trial was 82%. The differences in pain scores and laboratory values between the 3 study groups were assessed using multivariate analysis with the Bonferroni and Dunnett tests. $P < 0.05$ was considered statistically significant.

RESULTS

Thirty-nine Turkish patients (20 women, 19 men; mean [SD] age, 59.0 [11.3] years) were included in the study (**Table I**). The flurbiprofen, tiaprofenic acid, and placebo groups comprised 12, 14, and 13 patients, respectively. No statistically significant differences in baseline characteristics were found between the 3 groups.

Efficacy

Laboratory Results

The mean serum levels of MDA, NO, and SOD before and after treatment are shown in **Table II**.

Mean (95% CI) MDA levels at 3 weeks of treatment were significantly decreased compared with baseline in the active-treatment groups (flurbiprofen: 3.13 [2.67–4.06] vs 4.57 [3.87–5.34] nmol/mL; tiaprofenic acid: 2.86 [2.58–3.17] vs 4.05 [3.72–4.46] nmol/mL; both, $P < 0.001$), but not in the placebo group. No sig-

Table I. Demographic characteristics of the study patients (N = 39).* Values are presented as mean (SD) unless otherwise noted.

Characteristic	Flurbiprofen (n = 12)	Tiaprofenic Acid (n = 14)	Placebo (n = 13)
Age, y	57.0 (15.0)	62.0 (9.4)	58.0 (9.7)
Sex, no.			
Male	6	7	6
Female	6	7	7
Country of origin			
Turkey	12	14	13
Height, m	1.55 (0.07)	1.61 (0.01)	1.68 (0.13)
Weight, kg	72.0 (10.0)	73.0 (9.9)	74.0 (13.0)
BMI, kg/m^2	30.0 (4.1)	28.0 (3.0)	26.0 (4.3)
Disease duration, y	5.0 (4.3)	5.6 (3.3)	4.7 (3.5)
Disease severity			
Score for pain at rest†	4.5 (3.6)	3.5 (3.2)	3.0 (2.2)
Score for pain on motion†	8.3 (1.8)	8.3 (1.8)	6.4 (1.5)
Duration of morning stiffness, min	13.1 (3.6)	17.0 (12.5)	21.0 (11.1)

BMI = body mass index.
*No significant differences were found between the 3 groups.
†As measured on a 10-cm visual analog scale (0 = no pain to 10 = worst pain imaginable).

Table II. Oxidative stress markers as measured in the serum before (baseline) and after 3 weeks of treatment with flurbiprofen (n = 12), tiaprofenic acid (n = 14), or placebo (n = 13) in patients with osteoarthritis of the knee. Values are presented as mean (95% CI).

Marker/Treatment	Baseline	3 Weeks	*P*
MDA, nmol/mL			
Flurbiprofen	4.57 (3.87–5.34)	3.13 (2.67–4.06)	<0.001
Tiaprofenic acid	4.05 (3.72–4.46)	2.86 (2.58–3.17)	<0.001
Placebo	4.02 (3.75–4.39)	3.99 (3.56–4.25)	NS
NO, µmol/L			
Flurbiprofen	23.18 (21.16–26.22)	18.28 (14.95–28.15)	<0.001
Tiaprofenic acid	23.71 (20.40–25.63)	18.18 (15.63–21.19)	<0.001
Placebo	23.26 (19.28–27.78)	22.65 (20.19–24.75)	NS
SOD, U/mL			
Flurbiprofen	22.39 (20.17–24.05)	25.22 (23.26–26.51)*	<0.001
Tiaprofenic acid	23.51 (20.18–25.76)	24.89 (23.50–25.87)	<0.001
Placebo	22.94 (20.28–25.94)	23.71 (21.59–25.28)	NS

MDA = malondialdehyde; NO = nitric oxide; SOD = superoxide dismutase.
*$P < 0.01$ versus the tiaprofenic acid and placebo groups.

nificant differences in mean MDA levels were found between the active-treatment groups and the placebo group at 3 weeks.

Mean (95% CI) NO levels were significantly decreased at 3 weeks of treatment compared with baseline in the active-treatment groups (flurbiprofen: 18.28 [14.95–28.15] vs 23.18 [21.16–26.22] μmol/L; tiaprofenic acid: 18.18 [15.63–21.19] vs 23.71 [20.4–25.63] μmol/L; both, $P < 0.001$), but not in the placebo group. No significant difference was found in these levels between the 2 active-treatment groups and the placebo group at 3 weeks.

The mean SOD levels at 3 weeks were significantly higher compared with baseline in both active-treatment groups (flurbiprofen: 25.22 [23.26–26.51] vs 22.39 [20.17–24.05] U/mL; tiaprofenic acid: 24.89 [23.50–25.87] vs 23.51 [20.18–25.76] U/mL; both, $P < 0.001$), but not in the placebo group. At 3 weeks of treatment, this level was significantly higher in the flurbiprofen group compared with the tiaprofenic acid and placebo groups (both, $P < 0.01$).

Pain and Morning Stiffness

After 3 weeks of treatment, the mean (SD) score for pain at rest was significantly decreased from baseline in the flurbiprofen group and the tiaprofenic acid group (flurbiprofen: 1.5 [1.9] vs 4.5 [3.6]; tiaprofenic acid: 1.6 [1.7] vs 3.5 [3.2]; both, $P < 0.001$) but not in the placebo group (**Table III**). Mean (SD) scores for pain at rest were significantly lower in the flurbiprofen and tiaprofenic acid groups compared with that of the placebo group at 3 weeks (both, $P < 0.05$). No significant difference was found between the 2 active-treatment groups.

Table III. Efficacy parameters before (baseline) and after 3 weeks of treatment with flurbiprofen (n = 12), tiaprofenic acid (n = 14), or placebo (n = 13) in patients with osteoarthritis of the knee. Values are presented as mean (SD).

Parameter/Treatment	Baseline	3 Weeks	*P*
Score for pain at rest*			
Flurbiprofen	4.5 (3.6)	1.5 (1.9)†	<0.001
Tiaprofenic acid	3.5 (3.2)	1.6 (1.7)†	<0.001
Placebo	3.0 (2.2)	2.5 (2.1)	NS
Score for pain on motion*			
Flurbiprofen	8.3 (1.8)	7.3 (2.2)	NS
Tiaprofenic acid	8.3 (1.8)	3.4 (1.7)†	<0.001
Placebo	6.4 (1.5)	5.1 (2.7)	NS
Duration of morning stiffness, min			
Flurbiprofen	13.1 (9.6)	3.8 (6.9)	<0.001
Tiaprofenic acid	17.0 (12.5)	3.8 (6.9)†	<0.001
Placebo	21.0 (11.1)	15.0 (11.3)	<0.001

*As measured on a 10-cm visual analog scale (0 = no pain to 10 = worst pain imaginable).
†$P < 0.05$ versus the placebo group.

The mean (SD) scores for pain on motion were significantly lower at 3 weeks compared with baseline in the group treated with tiaprofenic acid (3.4 [1.7] vs 8.3 [1.8]; $P < 0.001$). In the flurbiprofen group (7.3 [2.2] vs 8.3 [1.8]) and the placebo group (5.1 [2.7] vs 6.4 [1.5]), the mean (SD) scores for pain on motion did not change significantly. After 3 weeks of treatment, the mean score for pain on motion was significantly lower with tiaprofenic acid compared with placebo ($P < 0.05$). No significant difference was found between the 2 active-treatment groups.

The mean (SD) duration of morning stiffness was significantly less at 3 weeks compared with baseline in all 3 study groups (all, $P < 0.001$). After 3 weeks of treatment, the duration of morning stiffness was significantly shorter with tiaprofenic acid compared with placebo ($P < 0.05$) (**Table III**). No significant difference was found between the 2 active-treatment groups.

Tolerability

Adverse effects (AEs) were experienced by 3 of the patients receiving flurbiprofen (2 patients, mild dyspepsia; 1 patient, moderate headache) and 4 of those receiving tiaprofenic acid (3 patients, mild dyspepsia; 1 patient, mild meteorism). None of the patients discontinued the study medication due to an AE.

DISCUSSION

Evidence supporting the relationship between oxidative stress markers and the pathogenesis of OA is increasing. However, the effects of NSAIDs on this oxidative cycle are not yet clear.[3,9] In patients with OA, ROSs are produced in greater amounts than in healthy individuals, resulting in joint-tissue damage.[2] Mazzetti et al[6] found that cells from patients with OA produced higher levels of NO than did those from patients with rheumatoid arthritis (RA). However, the harmful effects of free oxygen radicals and NO on chondrocytes were found to be more prominent in patients with RA, suggesting that NO may play a major role in altering chondrocyte function in OA. Also, some studies have suggested that cell death in OA-affected chondrocytes is principally NO-mediated apoptosis.[15,16]

Studies of the effects, other than clinical efficacy, of NSAIDs on ROS are limited. Bartosiewicz et al[17] reported that serum MDA level and serum oxidation capacity were decreased in patients with OA receiving piroxicam, whereas they did not change in patients with RA receiving piroxicam therapy. Gonzalez et al[18] demonstrated that the generation of oxygen by polymorphonuclear cells was decreased after 15 days of treatment with diclofenac and aceclofenac in 30 patients with severe OA of the knee. In this study, the generation of oxygen reached normal values after 180 days. MDA levels in the serum and synovial fluid showed significant correlation in patients with RA or OA. However, no statistically significant difference in mean (SD) synovial fluid MDA level was found between RA (0.17 [0.07] nmol/mL) and OA (0.16 [0.09] nmol/mL).[19] A weak correlation was found between serum and synovial fluid nitrate/nitrite levels ($r = 0.35$; $P = 0.037$) in patients with primary knee OA.[20] Total SOD activity was found

to be ~3-fold higher in control synovial fluid compared with normal human serum, but 300-fold lower than in human tissue.[21]

In the present study, we found that tiaprofenic acid and flurbiprofen (to a lesser extent) have significant effects on serum levels of MDA, NO, and SOD with regard to their clinical efficacy. Because OA is a catabolic process of cartilage tissue, it is crucial to evaluate the proinflammatory cytokines and ROS in OA. These data extend our previous observations[22] and suggest an inflammatory component in OA. In addition, this study may present a new research outcome measurement in the evaluation of the therapeutic efficacy of drugs in OA. An objective parameter to evaluate patients with OA is still lacking; therefore, biochemical parameters reflecting oxidative stress might be helpful in the future assessment of OA. However, there are some conflicting results with NSAIDs and their effects on the cyclooxygenase pathway. Pilbeam et al[23] found that currently available NSAIDs, including flurbiprofen, were unlikely to distinguish completely between the effects mediated by prostaglandin G/H synthase (PGHS)-2 or PGHS-1 in their experimental studies.

Although there were some limitations (ie, small sample size, no blinding, short treatment duration, and a weak correlation between serum and synovial fluid levels of NO), the results of the present study suggest that tiaprofenic acid is more effective in the treatment of the clinical findings of OA compared with placebo; the only significant differences in pain on motion and morning stiffness were between the tiaprofenic acid and placebo groups. Both flurbiprofen and tiaprofenic acid significantly reduced pain at rest compared with placebo. Similarly, both tiaprofenic acid and flurbiprofen were associated with decreased serum levels of oxygen radicals and NO. To date, few clinical studies have assessed the role of conventional NSAIDs in decreasing serum oxygen radicals and NO in patients with OA. The in vitro effects of NSAIDs and paracetamol on oxidative stress–related parameters of human erythrocytes were shown in the study by Orhan and Sahin.[24] However, in that study, tiaprofenic acid at a therapeutic dose was associated with a decrease in glutathione S-transferase activity and significant inhibition of selenium-dependent glutathione peroxidase at a higher dose.

The fact that spontaneous overproduction of NO has been found in patients with OA, but not in patients with RA, might indicate the presence of inflammatory factors (eg, autocrine cytokines or growth factors in osteoarthritic cartilage[25]) or might be due to constitutively increased NO synthase in patients with OA.[26] The main reason for the reduced generation of NO in the active-treatment groups in the present study might have been the inactivation of the inflammatory factors and/or NO synthase.

On the other hand, the increased serum level of SOD in patients with OA found in the present study might indicate that oxygen radicals can be degraded effectively with flurbiprofen or tiaprofenic acid. In this process, detoxification of oxygen radicals might be more effective with flurbiprofen compared with tiaprofenic acid based on the findings in the present study. In addition, one

pharmacokinetic study[9] showed that the hydrogen peroxide level in the serum was decreased with flurbiprofen.

CONCLUSIONS

In this study of patients with knee OA, flurbiprofen 100 mg BID and tiaprofenic acid 300 mg BID were effective in reducing markers of oxidative stress. Flurbiprofen seemed more potent in detoxification of oxygen radicals. However, only tiaprofenic acid significantly reduced pain (at rest and on motion) and duration of morning stiffness compared with placebo in this study. The medications were well tolerated.

REFERENCES

1. Henrotin Y, Deby-Dupont G, Deby C, et al. Active oxygen species, articular inflammation and cartilage damage. *EXS.* 1992;62:308–322.
2. Chen BX, Francis MJ, Duthie RB, et al. Oxygen free radical in human osteoarthritis. *Chin Med J (Engl).* 1989;102:931–933.
3. Yudoh K, Nguyen T, Nakamura H, et al. Potential involvement of oxidative stress in cartilage senescence and development of osteoarthritis: Oxidative stress induces chondrocyte telomere instability and downregulation of chondrocyte function. *Arthritis Res Ther.* 2005;7:R380–R391.
4. Tiku ML, Shah R, Allison GT. Evidence linking chondrocyte lipid peroxidation to cartilage matrix protein degradation. Possible role in cartilage aging and the pathogenesis of osteoarthritis. *J Biol Chem.* 2000;275:20069–20076.
5. Henrotin YE, Bruckner P, Pujol JP. The role of reactive oxygen species in homeostasis and degradation of cartilage. *Osteoarthritis Cartilage.* 2003;11:747–755.
6. Mazzetti I, Grigolo B, Pulsatelli L, et al. Differential roles of nitric oxide and oxygen radicals in chondrocytes affected by osteoarthritis and rheumatoid arthritis. *Clin Sci (Lond).* 2001;101:593–599.
7. Yang P, He X, Yang Z, et al. Effects of bushen huoxue decoction on nitric oxide (NO) in serum, articular cartilage and synovium in rabbits of knee osteoarthritis. *J Tradit Chin Med.* 2004;24:149–152.
8. Pham TN, Rahman P, Tobin YM, et al. Elevated serum nitric oxide levels in patients with inflammatory arthritis associated with co-expression of inducible nitric oxide synthase and protein kinase C-eta in peripheral blood monocyte-derived macrophages. *J Rheumatol.* 2003;30:2529–2534.
9. Kimura K. Mechanisms of active oxygen species reduction by non-steroidal anti-inflammatory drugs. *Int J Biochem Cell Biol.* 1997;29:437–446.
10. Altman R, Asch E, Bloch D, et al, for the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. *Arthritis Rheum.* 1986;29:1039–1049.
11. Bolognese JA, Schnitzer TJ, Ehrich EW. Response relationship of VAS and Likert scales in osteoarthritis efficacy measurement. *Osteoarthritis Cartilage.* 2003;11:499–507.

12. Angel MF, Ramasastry SS, Swartz WM, et al. The critical relationship between free radicals and degrees of ischemia: Evidence for tissue intolerance of marginal perfusion. *Plast Reconstr Surg.* 1988;81:233–239.
13. Green LC, Wagner DA, Glogowski J, et al. Analysis of nitrate, nitrite, and [15N]nitrate in biological fluids. *Anal Biochem.* 1982;126:131–138.
14. Sun Y, Oberley LW, Li Y. A simple method for clinical assay of superoxide dismutase. *Clin Chem.* 1988;34:497–500.
15. Blanco FJ, Guitian R, Vazquez-Martul E, et al. Osteoarthritis chondrocytes die by apoptosis. A possible pathway for osteoarthritis pathology. *Arthritis Rheum.* 1998;41: 284–289.
16. Chaturvedi V, Handa R, Rao DN, Wali JP. Estimation & significance of serum & synovial fluid malondialdehyde levels in rheumatoid arthritis. *Indian J Med Res.* 1999; 109:170–174.
17. Bartosiewicz G, Mezes M, Nemet J. Changes in lipid, peroxide, and anti-oxidant blood levels during piroxicam (Hotemin) treatment. *Ther Hung.* 1993;41:67–71.
18. Gonzalez E, de la Cruz C, de Nicolas R, et al. Long-term effect of nonsteroidal antiinflammatory drugs on the production of cytokines and other inflammatory mediators by blood cells of patients with osteoarthritis. *Agents Actions.* 1994;41:171–178.
19. Hashimoto S, Ochs RL, Komiya S, Lotz M. Linkage of chondrocyte apoptosis and cartilage degradation in human osteoarthritis. *Arthritis Rheum.* 1998;41:1632–1638.
20. Karan A, Karan MA, Vural P, et al. Synovial fluid nitric oxide levels in patients with knee osteoarthritis. *Clin Rheumatol.* 2003;22:397–399.
21. Marklund SL, Bjelle A, Elmqvist LG. Superoxide dismutase isoenzymes of the synovial fluid in rheumatoid arthritis and in reactive arthritides. *Ann Rheum Dis.* 1986; 45:847–851.
22. Uzun H, Tuzun S, Ozaras N, et al. The effect of flurbiprofen and tiaprofenic acid on serum cytokine levels of patients with osteoarthrosis. *Acta Orthop Scand.* 2001;72: 499–502.
23. Pilbeam CC, Fall PM, Alander CB, Raisz LG. Differential effects of nonsteroidal antiinflammatory drugs on constitutive and inducible prostaglandin G/H synthase in cultured bone cells. *J Bone Miner Res.* 1997;12:1198–1203.
24. Orhan H, Sahin G. In vitro effects of NSAIDs and paracetamol on oxidative stress-related parameters of human erythrocytes. *Exp Toxicol Pathol.* 2001;53:133–140.
25. Clancy RM, Amin AR, Abramson SB. The role of nitric oxide in inflammation and immunity. *Arthritis Rheum.* 1998;41:1141–1151.
26. Amin AR, Di Cesare PE, Vyas P, et al. The expression and regulation of nitric oxide synthase in human osteoarthritis-affected chondrocytes: Evidence for up-regulated neuronal nitric oxide synthase. *J Exp Med.* 1995;182:2097–2102.

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Update

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Correction

After publication of "Effects of Flurbiprofen and Tiaprofenic Acid on Oxidative Stress Markers in Osteoarthritis: A Prospective, Randomized, Open-Label, Active- and Placebo-Controlled Trial." (*Curr Ther Res Clin Exp.* 2005;66:335–344.) we were notified by the authors that formal approval for the study was not received from the ethics committee of Cerrahpasa Medical Faculty. The authors apologize for the oversight.

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