Original Article

In Vivo Effects of Nonselective, Partially Selective, and Selective Non Steroidal Anti-Inflammatory Drugs on Lipid Peroxidation and Antioxidant Enzymes in Patients with Rheumatoid Arthritis: A Clinical Study

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Abstract

Background: The relationship between oxidative stress, decreased antioxidant status, and rheumatoid arthritis (RA) has been widely investigated. To date, few clinical studies have assessed the role of conventional nonsteroidal anti-inflammatory drugs (NSAIDs) in the modulation of oxidative stress in patients with RA. **Aim:** The aim of this study was to compare the effects of nonselective, partially selective, and selective cyclooxygenase (COX) inhibitors on markers of oxidative stress in patients with RA. **Materials and Methods:** Thirty RA patients were enrolled in this open label, prospective study for 12 weeks and randomly assigned to either group receiving diclofenac 100 mg, meloxicam 15 mg, or celecoxib 200 mg daily (n = 10 in each group). Patients were evaluated for superoxide dismutase (SOD) and serum malondialdehyde (MDA) as oxidative markers at the baseline and at the end of 12 weeks. Various parameters for efficacy were also assessed. **Results:** The baseline values of the SOD enzyme were significantly lower and MDA values were significantly elevated in patients randomized to the three treatment groups as compared to the control group ($P < 0.05$). MDA level was significantly decreased in patients across all the treatment groups ($P < 0.05$) after 12 weeks. There was an improvement in mean SOD enzyme levels at the end of 12 weeks; the difference for SOD was significant as compared to the baseline in the meloxicam group only ($P < 0.05$) but not in diclofenac- and celecoxib-treated patients. Significant improvement was observed in all the treatment groups as regards patient assessment of pain visual analog scale, tender and swollen joint count, and patient global assessment. **Conclusions:** Diclofenac, meloxicam, and celecoxib carry antioxidant effects to a variable extent. NSAID possesses additional mechanism independent of COX inhibition which modulates oxidative stress.

Keywords: *Antioxidant, malonaldialdehyde, nonsteroidal anti-inflammatory drug, oxidative stress, rheumatoid arthritis, superoxide dismutase*

Introduction

Oxidative stress is an imbalance between the production of free radical/reactive oxygen species (ROS) and antioxidant defenses, favoring prooxidants. ROS are unstable, short-lived, and highly reactive chemical species. Overproduction of ROS is deleterious as it can damage cell structures including lipid membranes, proteins, and DNA. Among ROS, the superoxide anion (O_2^-) plays a pivotal role in inflammation, particularly in patients with inflammatory joint disease.[1] The enzyme superoxide dismutase (SOD) neutralizes O_2^- by transforming it into hydrogen peroxide, thereby preventing the formation of highly aggressive compounds such as peroxynitrite ($ONOO^-$) and hydroxyl radical (HO). The prime target of ROS is polyunsaturated fatty acids in membrane lipids, leading to lipid peroxidation (LPO) with resultant damage to cell structure and function. The level of LPO can easily be measured by malondialdehyde (MDA), as an end product. Under normal homeostatic conditions, the production of endogenous ROS is balanced by the actions of cellular antioxidant defense systems which include enzymes (SOD, catalase, and glutathione peroxidase) and nonenzymatic species (glutathione, ascorbate, tocopherol, retinol, etc.).

Rheumatoid arthritis (RA) a chronic inflammatory, autoimmune disorder with systemic involvement is characterized by

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symmetric and erosive synovitis, mainly of peripheral joints. The fact that ROS plays an important role in chronic inflammation applies equally to pathogenesis of chronic arthropathies including RA. A number of factors such as repetitive ischemia-reperfusion injury enhanced cellular oxidative phosphorylation along with the respiratory burst of phagocytic cells (macrophages and neutrophils) which contribute to the generation of ROS in the synovial microenvironment and other tissues in RA.[2] Indirectly, the ROS are involved in the pathogenesis of RA by the activation of osteoclasts, fragmentation of cartilage, and depolymerization of hyaluronic acid leading to loss of viscosity in joints and induction of bone resorption.[3] This role of ROS in RA is further supported by the existence of a correlation between disease activity and the presence of oxidative stress in patients with RA, i.e., increased LPO products in blood, excessive production of ROS by monocytes, and neutrophils in synovial fluid, although contrary evidence does exist.

Nonsteroidal anti-inflammatory drugs (NSAIDs), by virtue of their safer symptomatic relief, are rather inherently linked to the management of RA at all stages. NSAIDs inhibit the production of prostaglandins (PGs) by inhibiting one or both of the cyclooxygenase (COX) isoforms and COX (in particular COX2) being directly linked to ROS production and vice versa, suggesting a possible link between oxidative stress and inflammation-mediated induction of COX. Besides, some NSAIDs are proposed to have antioxidant properties, independent of COX activity,[4] as NSAIDs *in vitro* can scavenge ROS and inhibit oxidative respiratory burst of neutrophil triggered by various agents independent of their COX inhibition.[5] This is further supported by *in vivo* studies on patients with musculoskeletal disorders and arthritis, implying modulation of oxidative stress by NSAIDs.[6,7] Maybe, the COX-inhibition-independent mechanisms through ROS inhibition too contribute to their anti-inflammatory effects to a variable extent. Therefore, it is likely that in addition to the inhibition of PG synthesis, the anti-inflammatory actions of NSAIDs may also be due to their modulation of ROS. Thus, the present study was envisaged to address and compare the *in vivo* effects of various COX inhibitors on ROS in patients with RA.

Materials and Methods

Patients and control

Patients for the study were selected from individuals attending the routine outpatient orthopedic clinic at our institute. Thirty RA patients of either sex of ≥18 years of age, diagnosed according to the American Rheumatism Association criteria, and in functional Class I, II, and III by the criteria of American College of Rheumatology were included in the study.[8] Ten age- and sex-matched healthy volunteers were also selected for the study simultaneously. Approval of the institutional ethics committee and informed written consent of patients and healthy volunteers were obtained prior to their inclusion in the study. Individuals with concomitant rheumatic condition, active or suspected peptic ulceration, gastrointestinal bleeding, coagulation defect, renal disorder, hepatic disorder, inflammatory bowel disease, congestive heart failure, hypertension, recent proctitis, any malignant disease, and on any disease-modifying antirheumatic drug or oral corticosteroid given within 4 weeks of the first dose of the study drugs, those having allergy or medical contraindication to the study drugs, and pregnant/lactating women were excluded from the study. It was ensured that none of the participants had a history of alcohol intake, chronic smoking, and not using any vitamin supplementation or antioxidant drugs. After fulfilling the inclusion and exclusion criteria, 30 patients were recruited for a time period of 12 weeks of the study protocol and randomized to receive tablet diclofenac SR 100 mg once daily (n = 10), tablet meloxicam 15 mg once daily (n = 10), and tablet celecoxib 200 mg twice daily (n = 10), as representatives of nonselective, partially selective, and selective COX2 NSAIDs, respectively. A complete physical examination with baseline clinical assessment was done for all the patients. No dropouts were observed. Compliance was determined on the basis of patient's clinic attendance, count of pills, and patient recount, with compliance of >80% being considered as adequate. Blood samples were obtained at the baseline and at the end of the clinical study period for the analysis of oxidative stress-related analytes.

Outcome measures

Complete count of tender joints (68 joints), swollen joints (66 joints), patients assessment of pain, patient's global assessment of pain, physician global assessment of disease activity, and patients assessment of physical function using a modified Stanford Health Assessment Questionnaire was performed at the baseline and at the end of the treatment. The assessment of pain and global assessment of disease activity was recorded on a visual analog scale (VAS; 0–100 mm).

Estimation of superoxide dismutase activity and malondialdehyde

SOD activity was determined in the hemolysate based on the inhibition of autooxidation of epinephrine to adrenochrome at pH 10.2.[9] For the quantitative evaluation of lipid peroxides, their transformation into a colored compound under the effect of thiobarbituric acid was used.[10]

Statistical analysis

The results were statistically analyzed by Microsoft Excel statistic for Windows program. To test the difference between the groups, paired and unpaired Student's t-test was used for continuous variable and Chi-square for proportions. The results were expressed as mean ± standard error, and a two-tailed $P < 0.05$ was considered as

statistically significant. The correlation between the variables was examined using Pearson's correlation coefficient.

Results

All the patients in the three groups completed the study. The demographic characteristics and baseline biochemical parameters of RA patients being treated with diclofenac, meloxicam, and celecoxib are summarized in Table 1.

The mean values of hemoglobin concentration and erythrocyte sedimentation rate were comparable among the treatment groups at the baseline after randomization. The mean values of serum MDA and activity of SOD enzyme in erythrocytes in patients of different treatment groups and controls at the baseline and after completion of 12 weeks are shown in Figure 1 and Table 2.

The baseline values of SOD enzyme concentration in all RA patients were significantly lower than that in the control group ($P < 0.05$). This difference was more significant ($P < 0.01$) in RA patients randomized to diclofenac and meloxicam groups. A significant elevation ($P < 0.05$) of the baseline MDA values was observed in patients randomized to all the three treatment groups as compared to the control group but significantly more ($P < 0.01$) in patients randomized to meloxicam and celecoxib groups. Prior to treatment, the baseline oxidative stress parameters (SOD and MDA) among the treatment groups did not have significant differences when compared to each other [Table 2].

At 12 weeks, a significant decrease ($P < 0.05$) in MDA levels was observed in patients across all the treatment groups as compared to the baseline values. The change in mean MDA levels was greater in the celecoxib group, followed by nearly similar changes in diclofenac- and meloxicam-treated groups. The MDA levels in the three treatment groups were comparable to control values at the end of the study period. All the three treatment groups registered an improvement in the mean SOD enzyme levels at the end of 12 weeks; the difference was significant as compared to the baseline in the meloxicam group only ($P < 0.05$) but not in diclofenac- and celecoxib-treated patients. However, the improvement in SOD levels of diclofenac- and celecoxib-treated patients was such that it was comparable to controls at 12 weeks, i.e., the mean values were closer to control values. The maximum percentage change in the mean SOD values was observed in the diclofenac group, followed by celecoxib and least in the meloxicam-treated group. The mean SOD enzyme and MDA concentration across all the three treatment groups was comparable at the end of the study period.

A statistically significant improvement was observed in all the treatment groups as regards patient assessment of pain VAS, tender and swollen joint count, and patient and physician global assessment [Table 3]. There was significant correlation between patient's ($n = 30$) assessment of pain and patient's global assessment of pain and MDA ($r = 0.41$, $P = 0.02$ and $r = 0.38$, $P = 0.04$ respectively). Further, a negative correlation existed between SOD and MDA levels in the patient group ($r = -0.37$, $P = 0.04$). No other significant correlation was observed between clinical outcome measures and oxidative stress parameters.

Table 1: Demographic characteristics and biochemical parameters in rheumatoid arthritis patients treated with diclofenac, meloxicam, and celecoxib

	Diclofenac	Meloxicam	Celecoxib
Number of patients	10	10	10
Mean age (years)*	48.9±3.12	47.8±2.24	43.3±5.41
Range	27-60	38-60	20-80
Sex (female:male)	6:4	10:0	7:3
Functional class in patients of RA			
I	1	2	0
II	4	6	6
III	5	2	4
Rheumatoid factor (+ve)	8	7	7
C-reactive protein (+ve)	8	8	8
Erythrocyte sedimentation rate (mm/h)*	66.3±9.66	72.2±9.10	66.0±9.27
Haemoglobin (g/dl)*	11.09±0.47	10.26±0.76	10.40±0.41
Total leukocyte count*	8628±509.98	8173±835.71	8104±748.88
Serum urea (mg/dl)*	15.8±1.13	16.9±1.41	15.3±1.11
Serum creatinine (mg/dl)*	0.82±0.03	0.80±0.02	0.82±0.03
SGOT (IU/dl)*	21.9±1.71	21.8±2.04	22.9±1.63
SGPT (IU/dl)*	15.6±1.42	13.8±1.05	21.0±1.27
Bleeding time (s)*	222.5±15.39	206.0±8.72	204.0±10.08

*Values expressed as mean±SE. SE: Standard error; SGPT: Serum glutamic pyruvic transaminase; SGOT: Serum glutamic oxaloacetic transaminase; RA: Rheumatoid arthritis

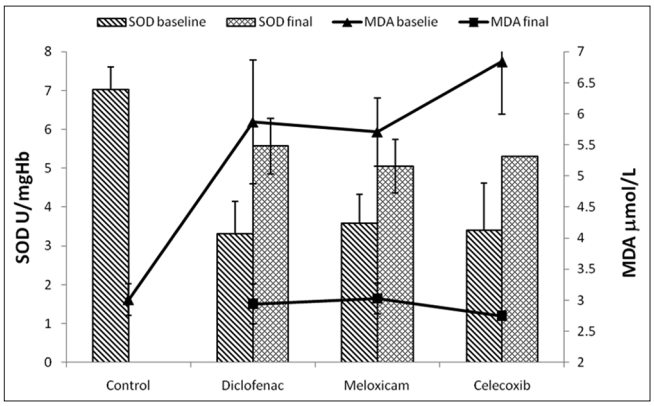

Figure 1: Changes in MDA level and SOD activity in patients treated with diclofenac, meloxicam, and celecoxib (MDA: Malondialdehyde; SOD: Superoxide dismutase)

Table 2: Comparison of superoxide dismutase and malondialdehyde concentrations of control and patients with rheumatoid arthritis

	Control	Diclofenac		Meloxicam		Celecoxib	
		Baseline	Final	Baseline	Final	Baseline	Final
SOD (U/mgHb)	7.02±0.58	3.31±0.83*	5.57±0.68	3.58±0.74*	5.05±0.72$^{\#,a}$	3.41±1.2$^{\$}$	5.3±0.69
Mean change			0.682		0.411		0.554
MDA (µmol/L)	3.01±0.25	5.87±1.0$^{\$}$	2.94±0.42$^{\#}$	5.71±0.55*	3.03±0.32$^{\#}$	6.84±0.84*	2.75±0.25$^{\#}$
Mean change			−0.499		−0.469		−0.597

All values expressed in mean±SE. *P<0.01; $^{\$}P$<0.05, in corresponding group compared to control; $^{\#}P$<0.05 as compared to baseline in treatments groups; ^{a}P<0.05 as compared to controls. SOD: Superoxide dismutase; MDA: Malondialdehyde

Table 3: Outcome measures in patients of rheumatoid arthritis treated with diclofenac, meloxicam, and celecoxib

	Diclofenac (n=10)		Meloxicam (n=10)		Celecoxib (n=10)	
	Baseline	Final	Baseline	Final	Baseline	Final
Tender joints count (n)	33.8±1.93	23.4±1.87*	33.3±2.06	22.4±1.26*	31.5±1.77	20.8±1.27*
Change (%)$^{\#}$		30		32		33.80
Swollen joints count (n)	23.2±1.19	14.7±0.59*	21.8±1.70	15.4±1.10*	20.8±1.67	13.2±0.79*
Change (%)$^{\#}$		36		28.20		34.10
Patient assessment of pain (VAS)^{a}	61.5±3.73	38.9±2.08*,$^{\$}$	64.5±3.08	42.1±2.51*	66.4±3.41	47.2±2.68*
Change (%)$^{\#}$		35		34.50		27.70
Physician global assessment (VAS)^{a}	51.4±3.26	32.4±1.68*,$^{\$}$	51.3±1.28	34.7±2.20*	57.8±2.41	41.2±2.44*
Change (%)$^{\#}$		34.60		32.20		27.80
Patient global assessment (VAS)^{a}	53.8±3.46	36.8±2.05*,$^{\$}$	58.0±3.27	38.5±2.62*	60.4±3.12	43.8±2.11*
Change (%)$^{\#}$		30.70		32.40		26.20
Patient assessment of physical function on modified MHAQ§	17.4±1.93	12.7±0.63*	17.3±1.14	12.1±0.48*	16.3±0.83	11.9±0.46*
Change (%)$^{\#}$		25.30		28.20		25.80

^{a}Score of 0 is best, 10 is worst; §Score of 8 is best, 32 is worst; $^{\#}$Based on mean values; *P<0.001 baseline versus final values in corresponding treatment groups; $^{\$}P$<0.05 versus celecoxib group at end of week 12. All values expressed as mean±SE. VAS: Visual analog scale (mm); MHAQ: Modified health assessment questionnaire; SE: Standard error

Discussion

The aim of this study was to evaluate the modulation of oxidative stress by various NSAIDs in patients of rheumatoid disease. SOD catalyzes the dismutation of superoxide radical into H_2O_2 and acts as the first line of defense against ROS. RA patients in our study demonstrated significantly low erythrocyte SOD activity than in the controls, which is in agreement with the previous studies.[11] Decreased SOD levels in patients of RA indicate the degradation of this anti-oxidant enzyme by free radicals primarily superoxide or hydrogen peroxide during the detoxification process.[11,12] In the present study, serum MDA levels were significantly elevated in patients which is in agreement with other studies where higher levels of MDA have been reported in patients with RA.[12] Rise in MDA levels could be due to excessive oxidative damage generated in patients of RA. It is proposed that blood samples from patients with RA are more prone to LPO owing to an impaired antioxidant defense system.

In the present study, we evaluated the effect of NSAIDs on oxidative stress in terms of SOD enzyme in erythrocytes and MDA. Our finding is consistent with an earlier study showing that the daily doses of NSAIDs increase the circulating levels of SOD, which combat ROS, in RA patients.[4] In an earlier study, the *in vivo* effects of meloxicam, celecoxib, and ibuprofen were investigated for free radical metabolism of erythrocytes in patients with osteoarthritis (OA).[13] The results showed an impairment of enzymatic and nonenzymatic antioxidants in erythrocytes, with a significant decrease in SOD, in all treatment groups, despite some differences in action mechanisms of all NSAIDs. On the contrary, in our study, all the three NSAIDs increased the mean SOD level, which was significant in meloxicam treated patients as compared to the baseline and insignificant in the diclofenac and celecoxib groups, though comparable to control group. A comparison of celecoxib and tenoxicam in patients of OA treated for 4 weeks showed the modulatory effect of NSAIDs on free radical metabolism. The study showed an increase in levels of SOD and a decrease in MDA levels after administration of both drugs though insignificant as compared to baseline values and a significant decrease in nitrite levels too.[6] It has been observed that NO is mainly responsible for altering chondrocyte functions in OA due to abundant production, whereas oxygen radicals are primarily involved in articular destruction in RA compared to OA. There is a paucity of data examining the role of NSAIDs in the modulation of oxidative stress in patients of RA. Thus, our findings – modulation of oxidative stress presenting as

a reduction in MDA levels and change in SOD levels to varying extent by NSAIDs with different mechanisms of action – are in agreement with these studies. In a similar study, an evaluation of flurbiprofen and tiaprofenic acid on markers of oxidative stress in patients of OA treated for 3 weeks found a significant increase in serum SOD enzyme activity and a significant reduction in MDA and NO levels as compared to baseline in both groups of patients, supporting our findings.[7]

LPO, a hallmark of oxidative tissue injury, is found to be elevated in patients of RA. Meloxicam, a preferential COX2 inhibitor, is reported to reduce MDA concentrations both *in vivo* and *in vitro* in aluminum-treated animals showing a neuroprotective effect.[14] Diclofenac, a nonselective COX inhibitor, at therapeutic and higher concentrations, exerts a significant inhibition of H_2O_2 forced erythrocytic membrane LPO, suggesting the involvement of NSAID in oxidative/antioxidative processes of human erythrocytes.[15] Furthermore, celecoxib, a selective COX2 inhibitor, has shown the ability to inhibit LPO and scavenge hydroxyl radicals, leading to conclude that the mechanism for inhibition of radical generation may be due to direct scavenging or by donating reducing equivalents to peroxyl radicals by celecoxib.[16] These studies support the result of our study that NSAIDs modulate oxidant status to a varying extent as a result of different actions on oxidant/antioxidant mechanisms.

Nevertheless, it is known that some NSAIDs exert antioxidant properties independent of their effects on COX activity.[4] Although the exact mechanism of action is not known, studies have shown that NSAID eliminates oxygen species, superoxide radical in particular, reacting competitively with superoxide in a concentration-dependent manner, independent of their COX activity.[17] The free radical scavenging activity of diclofenac has been demonstrated in experimental models of different cell-free systems.[5] It is reported that diclofenac improves SOD activity by increasing the substrate linkage activity to the enzyme catalytic site and thus improves antioxidant defenses.[18] The inhibition of superoxide will lead to the diminished formation of H_2O_2 and downstream secondary radicals such as HOCl and OH. These observations support our findings where a group of patients receiving diclofenac showed a greater increase in SOD levels and a decreased MDA level at the end of the study. Similarly, ROS-scavenging activity of oxicams (tenoxicam, piroxicam, and meloxicam) was evaluated *in vitro* using different noncellular systems which suggested that oxicams were more reactive against ROS than nimesulide and ibuprofen.[19,20] Considering these data and our results, where all NSAIDs have demonstrated anti-oxidative properties despite different mechanisms, it can be assumed that the modulation of oxidative stress is independent of their COX activity and that the COX selectivity has not much role to play as far as oxidative outcome is concerned.

A possible link between oxidative stress and inflammation-mediated induction of COX is also suggested by studies. COX pathway causes the generation of ROS (peroxides and superoxide anion) and these peroxides themselves can trigger COX activity. However, an estimation of plasma and urinary levels of isoprostane and MDA (markers of LPO) in CCl_4-treated rats showed partial inhibition of these by NSAIDs and to a varying extent. The suppression of nonenzymatic LPO rather than the diminution of the catalytic generation of isoprostane and MDA by cyclogenesis may have caused the decrease in their levels by NSAIDs, suggesting an additional mechanism for NSAIDs separate from anti-inflammatory action.[21] The primary anti-inflammatory mechanism of NSAIDs is the inhibition of COX enzyme; however, many studies have demonstrated that they carry certain additional mechanisms of which one is the modulation of oxidative status. In a recent study, the *in vivo* effects of meloxicam, tenoxicam, and piroxicam on blood SOD activity in patients of OA revealed a significant increase in SOD activity in patients treated with piroxicam, whereas, contrary to our results, an insignificant change was observed in meloxicam- and tenoxicam-treated patients. The varying extent of influence by different oxicams enabled us to conclude that SOD activity was not based on COX inhibition.[22]

Although the inhibition of COX isoforms and anti-inflammation by diclofenac, meloxicam, and celecoxib are nearly similar in our study reflected by the patient's clinical outcomes, the treatment did not exert similar effects on SOD activity. Thus, the difference in anti-oxidative property between different NSAIDs could not be explained by their inhibitory potency on COX enzymes or their anti-inflammatory effects. Nevertheless, previous data also suggest that the ability of NSAIDs to scavenge ROS/reactive nitrogen species and that inhibition of respiratory burst of neutrophils contribute to their anti-inflammatory property.[5,16] Thus, COX selectivity seems to play no role in the efficacy of various NSAIDs in RA patients, as the adverse effect profile and COX selectivity were not in favor of outcomes in patients as seen in the present study. As far as the antioxidant activity of various NSAIDs is concerned in our study, the COX selectivity did present a variable impact on the parameters of oxidative stress. Hence, the probable antioxidant mechanism of NSAIDs as separate criteria looks more attractive than COX selectivity. A categorization of NSAIDs in terms of additional properties based on antioxidants and other properties rather than COX selectivity seems more appropriate in future. The correlation between SOD and MDA in our study reinforces that oxidative stress brings about compensatory changes in levels of antioxidants.

The present study had certain shortcomings such as limited number of patients leading to low statistical power, short duration of the study, and limited evaluative methods for estimation of oxidative stress. Our data warrant further

studies to assess the interaction of NSAIDs with antioxidant enzymes in patients both for long- and short-terms with a broader scope for therapeutic benefits and adverse effects. Keeping in view the small sample size of the study, caution is to be exercised while applying the findings of this study.

To conclude, our study has shown that diclofenac, meloxicam, and celecoxib carry antioxidant effects though to a variable extent. Although free radicals are generated during PG synthesis by COX activity, COX inhibition alone does not explain the antioxidant effects demonstrated by NSAIDs in our study. This also emphasizes that NSAID possesses additional mechanisms independent of COX inhibition which modulates oxidative stress and may help in selecting NSAIDs with additional antioxidant criteria besides COX inhibition. Further knowledge of the underlying mechanisms may give a new direction to the therapeutic approach for RA patients.

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Conflicts of interest

There are no conflicts of interest.

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