

Comparative Efficacy and Tolerability of Nimesulide and Piroxicam in Osteoarthritis with Specific Reference to Chondroprotection : A Double Blind Randomised Study

V Roy*, U Gupta*, S Sharma**, B K Dhaon***, N P Singh****, P Gulati*****

The aim of the study was to assess the efficacy, tolerability and Chondroprotection afforded by nimesulide, a selective cyclooxygenase-2 inhibitor and piroxicam in a randomised, double blind, controlled clinical trial in 90 patients suffering from osteoarthritis of the knee joint. A significant improvement in the osteoarthritis severity index at 2 weeks ($p < 0.01$) and an improvement in physicians assessment of global arthritic condition at 4 weeks ($p < 0.01$) was seen with both the treatments. A significant decrease in articular index of joint tenderness ($p < 0.05$) at 8 weeks and in self assessment of handicap at 4 weeks ($p < 0.05$), in comparison to baseline, was observed only in patients receiving nimesulide. Rescue therapy was required by a greater percentage of patients being administered piroxicam. Functional capacity improved in 64% of the patients on nimesulide and 74.5% of the patients receiving piroxicam. Adverse effects were observed in 6 patients on nimesulide and 9 patients receiving piroxicam. No significant difference was found in any of the efficacy and tolerability parameters between the two treatment groups. Magnetic resonance imaging evaluation of the knee joint of 10 patients showed no significant change in the articular cartilage and associated joint structures after 6 months of the therapy with both the treatments. The results show that nimesulide and piroxicam are comparable in efficacy and tolerability in patients suffering from osteoarthritis.

Osteoarthritis is a degenerative disease that inevitably leads to joint failure^{1,2}. Nonsteroidal anti-inflammatory drugs (NSAIDs) have a pivotal role in the management of this condition³. Nimesulide is a selective COX-2 inhibitor⁴, which appears to exert its anti-inflammatory, analgesic and antipyretic activity through a number of novel mechanisms; hence, has a better tolerability profile^{5,6}. Nimesulide has a pharmacodynamic profile suggestive of a reduced propensity to cause adverse gastrointestinal effects⁵. The principal advantage of piroxicam, is its long half life which permits the administration of a single daily dose⁷.

There is evidence that few NSAIDs including nimesulide, may influence various aspects of cartilage metabolism, suggesting chondroprotective activity^{8,9}. Objective clinical data on the response of human cartilage to NSAID therapy are absent and how such benefit should be measured remains unclear⁸. Magnetic resonance imaging (MRI) has been proposed to be a better technique for detecting early cartilage changes in osteoarthritis^{10,11}. The use of this technique to identify changes in cartilage structure in osteoarthritic patients before and after NSAID treatment has so far not been reported⁸. Therefore, the present study was conducted to compare the efficacy and tolerability of nimesulide and piroxicam in osteoarthritic patients and to observe if these agents have any chondroprotective action as assessed by magnetic resonance imaging.

METHODS

This study was conducted in the orthopaedic outpatient clinic of Lok Nayak Hospital, New Delhi, India. The study was approved by the ethics committee of the hospital. Informed consent was obtained from the patients.

A total of 90 patients of either sex, in the age group 42-80 years were initially included in the study. They were all newly diagnosed patients with osteoarthritis of the knee joint, for at least 6 months before the study, and a Steinbrocker functional capacity of class I, or II¹². The diagnosis was made by clinical history, physical examination, radiological examination and haematological investigations (erythrocyte sedimentation rate, total leucocyte count, differential leucocyte count, rheumatoid factor) and patients fulfilling the American College of Rheumatology criteria for osteoarthritis of the knee joint were enrolled¹³.

The exclusion criteria were as follows: the presence of non-degenerative joint diseases (infectious, microcrystalline), severe and disabling arthritis with an eligibility for surgical intervention, treatment with intra-articular injections of corticosteroids within the month preceding the study, history of hypersensitivity to NSAIDs, presence of an active peptic ulcer, pregnancy, lactation, history of hepatic, renal and haematopoietic disease, patients receiving other NSAIDs, or any other medications

and history of alcohol intake.

Patients were randomly administered orally either nimesulide (nimulid) 100mg twice a day or piroxicam 20mg once a day with an identical placebo once a day, after meals, for 8 weeks and 10 patients in whom magnetic resonance imaging was done, continued the treatment for 24 weeks. No other medication likely to interfere with the investigational drugs was permitted. Compliance was ensured by counting the number of tablets left at each visit. Patients who did not take the study medicine for more than 3 days were considered as dropouts. Paracetamol (tablet 500mg), was chosen as rescue therapy in addition to the prescribed treatment if pain relief as judged by the patient was inadequate⁶. The clinical assessment of the patients included the following:

(a) Osteoarthritis severity index as an indicator of degree of functional impairment¹⁴. (b) Joint circumference. (c) Joint swelling¹⁵. (d) Articular index of joint tenderness. (e) Patients' self assessment of their handicap. (f) Patients' self assessment of the efficacy of the treatment. (g) Physicians' assessment of the patients arthritic condition^{6,15}. (h) The amount of rescue therapy taken. (i) The functional capacity.

Magnetic resonance imaging was performed at baseline and after 24 weeks of treatment in 10 patients.

A global evaluation of tolerability as reported by the patient was done on a 4-point verbal rating at each follow-up visit.

The patients were called for follow-up after every two weeks for 8 weeks. Ten patients were further observed thereafter every 2 weeks for 24 weeks. The efficacy and tolerability of the treatments were assessed at baseline and at every visit.

Statistical analysis was done by Students' t-test, Wilcoxon sign test and Mann Whitney tests whenever applicable.

RESULTS

A total of 90 patients (41 nimesulide, 49 piroxicam) were initially enrolled in the study. Both the groups were comparable with respect to age, sex, and duration of disease (Table 1). Seventy patients completed the study (30 nimesulide, 40 piroxicam). Two patients each receiving nimesulide or piroxicam were withdrawn from the study because of adverse drug reactions. The total number of dropouts from the study were 16.

After 8 weeks of therapy an improvement in all the efficacy parameters was seen with both the drugs (Table 2). However, the decrease in the joint circumference and joint swelling with both the treatments was not significant statistically.

At baseline significantly more patients receiving nimesulide had tender joints (grades 1,2,3) in comparison to piroxicam ($p < 0.05$) (Table 2). The articular index of joint tenderness improved with both the treatments. However, this was statistically significant only in patients receiving nimesulide ($p < 0.05$). A significantly greater percentage of patients reported their handicap as severe to unbearable in the group receiving nimesulide compared to piroxicam at baseline, which improved significantly at 4 weeks, and continued till 8 weeks. No significant difference in patients self-assessment of global efficacy of the treatment was observed in both the groups. In the physicians assessment of the arthritic condition, within groups a significant improvement was seen with both the treatments at 4 weeks which was maintained till 8 weeks ($p < 0.01$).

Paracetamol was used as rescue therapy in 14.6% patients receiving nimesulide and 24.7% patients receiving piroxicam. The paracetamol requirement ranged from 1-2 tablets a day in patients receiving nimesulide and 1 - 4 tablets in patients receiving piroxicam. The functional capacity either improved or showed no change in 98% patients receiving nimesulide and 94-5% patients receiving piroxicam (Table 2). No statistically significant difference was observed in any of the parameters when the two treatments were compared.

Table 1 — Characteristics of Patients

	Group A*	Group B*

		B**
(1) Patients who received the treatment for 8 weeks —		
Total number of patients enrolled	41	49
Total number of dropouts	9	7
Total number of patients withdrawn	2	2
Total number of patients who completed the study	30 (93.8%)	40 (95.2%)
Sex :		
Male	7 (21.8%)	25 (78.2%)
Female	10 (23.8%)	32 (76.2%)
Age (years) Mean±S.D :	46.7±4.1	47.3±5.2
Duration of disease (months):		
Mean±S.D	33.2±25.9	44.9±21.6
(2) Patients who received the treatment for 24 weeks —		
Total number of patients	5	5
Sex :		
Male	1	4
Female	1	4
Age (years) Mean±S.D	48.0±4.9	53.6±6.4
Duration of disease (months) :		
Mean±S.D	44.0±24.1	45.2±20.9
Severity of disease :		
Mild	3	2
Moderate	2	3
* Nimesulide 100 mg twice daily, **Piroxicam 20 mg once daily		

Table 2 — Changes in Efficacy Parameters in Patients Suffering from Osteoarthritis of the Knee Joint, after 8 weeks of Therapy with Nimesulide (100mg twice daily) or Piroxicam (20mg once daily)

Parameters	Nimesulide (n=30) (In Weeks)					Piroxicam (n=40) (In Weeks)				
	0	2	4	6	8	0	2	4	6	8
OSI	14.6	12.6**	11.0**	11.4**	10.7**	13.3	12.6**	10.4**	10.4**	9.3**
Mean±SD	5.4	4.9	5.1	5.0	5.6	6.3	6.4	6.5	6.6	6.6
% of patients										
AIJT:										
0 Not tender	35.5*	42.0	47.4	51.6	51.7*	57.9	63.6	62.7	67.5	67.5
1 Tender	41.9	46.0	42.1	35.5	48.3	28.9	25.5	27.5	20.9	17.5
2 Winced	21.0	12.0	10.5	12.9	0.0	13.2	10.9	9.8	11.6	15.0
3 Withdrew	1.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SAH:										
1. Mild	4.8	-	10.5*	-	20.0*	15.5	-	13.7	-	32.5
2. Moderate	24.2	-	50.0	-	36.7	41.6	-	49.2	-	30.0
3. Severe	67.8	-	39.5	-	40.0	29.9	-	25.5	-	37.5
4. Unbearable	3.2*	-	0.0	-	3.3	13.0	-	11.7	-	15.0
PAGAC:										
1. Excellent	3.0	6.0	5.3**	3.2**	6.7**	0.0	10.9	11.7**	14.6**	12.5**
2. Good	0.0	8.0	23.6	38.7	33.3	2.6	18.2	21.6	24.4	30.0
3. Fair	29.3	34.0	31.6	29.0	20.0	54.6	30.9	31.4	24.4	20.0
4. Poor	67.7	50.0	39.5	29.0	33.3	41.6	36.4	31.4	34.1	17.5
5. V.Poor	0.0	2.0	0.0	0.0	6.7	1.2	3.6	3.9	2.5	10.0
Rescue therapy:										
required	-	14.6	-	-	-	24.7	-	-	-	-
FC:										

FC:										
1. Improved		64.0					74.5			
2. Unchanged		34.0					20.0			
3. Worsened		2.0					5.5			

OSI - Osteoarthritis Severity Index; **AIJT** - Articular Index of Joint Tenderness; **SAH** - Self-Assessment of Handicap; **PC** - Functional Capacity; **PAGAC** - Physician's Assessment of Global Arthritic Condition

*p<0.05; **p<0.01

[\(TOP^\)](#)

An overall improvement in all the efficacy parameters was observed (Table 3). However, statistically significant difference was observed only in osteoarthritis severity index at 12 weeks and maintained till 24 weeks with both the treatments (p<0.05) (Fig.,1). Rescue therapy ranged from 1-2 tablets of paracetamol and was started earlier at 4 weeks in patients receiving piroxicam and at 8 weeks in patients receiving nimesulide.

The changes in the cartilages of the tibiofemoral joints before starting treatment ranged from normal (grade 0) to severely denuded cones (grade 4) using MRI. Only 1 patient receiving nimesulide had normal cartilages. Degenerative changes in the medial menisci were observed in 3 patients receiving nimesulide and all the 5 patients receiving piroxicam. Osteophytes were observed in all the 10 patients.

Table 3 – Changes in Efficacy Parameters in Patients with Osteoarthritis of the Kee joint, after 24 weeks of Therapy with Nimesulide (100mg twice daily) or Piroxicam (20mg once daily).

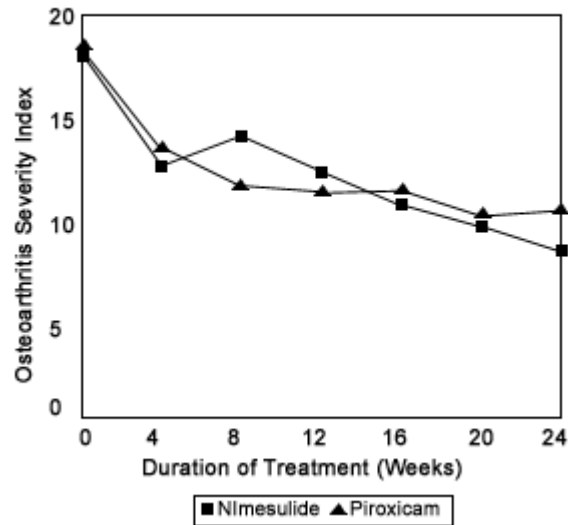
Parameters	Nimesulide (n=5) (In weeks)			Piroxicam (n=5) (In weeks)		
	0	12	24	0	12	24
OSI	18.0	12.2*	8.3*	18.3	11.2*	10.3*
Mean±SD	4.1	5.2	2.7	3.2	4.4	4.4
JC (cm)	35.9	34.7	34.6	37.5	37.4	37.1
Mean±SD	4.6	5.2	5.31	3.7	3.6	3.6
Number of patients						
AIJT						
0 Not tender	0	6	4	0	6	4
1 Tender	6	2	6	0	4	6
2 Winced	4	2	0	4	0	0
3 Withdrew	0	0	0	6	0	0
SAH						
1. Mild	0	2	2	0	2	2
2. Moderate	2	6	8	8	8	4
3. Severe	8	2	0	2	0	4
4. Unbearable	0	0	0	0	0	0
PAGAC						
1. Excellent	0	0	2	0	0	2
2. Good	2	4	4	0	6	2
3. Fair	6	2	2	4	2	4
4. Poor	2	2	2	6	2	2
5. V. poor	0	2	0	0	0	0
Paracetamol tablets Consumed day						
0	10	4	6	10	6	4
1	0	6	4	0	4	6
2	0	0	0	0	0	0
FC						
1. Improved	-	8	10	-	8	10
2. Unchanged	-	2	0	-	2	0
3. Worsened	-	0	0	-	0	0

OSI - Osteoarthritis Severity Index; **JC** - Joint Circumference; **cm** - Centimetre, **AIJT** - Articular Index of Joint tenderness; **SAH** - Self Assessment of handicap; **FC** - Functional Capacity; **PAGAC** -

Physician's Assessment of Global Arthritic Condition

*p<0.05

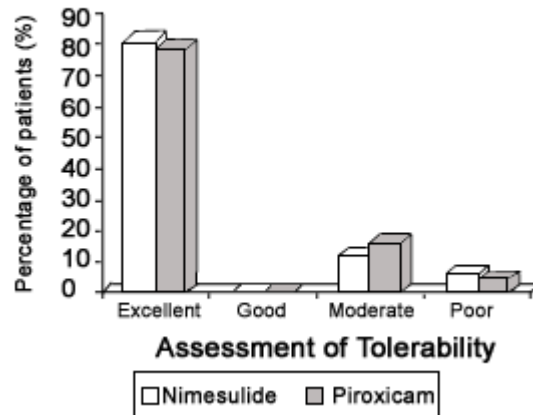
Figure 1: Improvement in Osteoarthritis severity index with Nimesulide or Piroxicam after 24 weeks of therapy



In all the 10 patients no significant change was observed either in the cartilages of the tibiofemoral joints or in any other associated Joint structures after six months of therapy, except in one patient receiving nimesulide in whom a decrease in fluid was observed.

Adverse effects were observed in 6 patients receiving nimesulide and 9 patients receiving piroxicam. Gastrointestinal disturbances specifically heart burn was the commonest adverse drug reaction (12.5% nimesulide, 19.0% piroxicam). However, upper gastrointestinal endoscopy was normal in all these patients. This was followed by dermatological reactions (6.3% nimesulide, 2.4% piroxicam) with both the drugs. The causal relationship of the adverse drug reaction to the drug was certain in all cases. Global tolerance was rated as excellent by 81.2% patients receiving nimesulide and 78.6% patients receiving piroxicam (Fig 2). Four patients, two each receiving nimesulide and piroxicam were withdrawn from the study due to adverse effects. These were pruritus (2 cases) with nimesulide and fixed drug reaction (1 case) with piroxicam, for which the patients were withdrawn at two weeks. One case of gastralgia with piroxicam was withdrawn at four weeks. The hepatic function tests and renal function tests did not show any significant changes with either of the treatments at 8 or 24 weeks.

Figure 2: Assessment of drug tolerability after 8 weeks of therapy with Nimesulide or Piroxicam



DISCUSSION

Both nimesulide and piroxicam were found to be comparable with regard to the outcome of therapy. The osteoarthritis severity index which is an indicator of degree of functional impairment improved significantly with both the treatments leading to overall functional improvement. These results are similar to those observed by Dreiser and Riebenfeld⁶.

The functional capacity improved in 74.5% of patients receiving piroxicam and in only 64% of patients receiving nimesulide. This could be attributed to the baseline value of articular index of joint tenderness and self assessment of handicap which was significantly more in patients receiving nimesulide and to the greater amount of paracetamol consumed by a larger percentage of patients in the group receiving piroxicam.

Both nimesulide and piroxicam were well tolerated. Gastrointestinal and dermatological side effects were commonly seen, more so with Piroxicam. It is considered amongst the most toxic of NSAIDs that cause GIT adverse effects with incidence as high as 28.1%^{16,17}. It appears that nimesulide has a slightly lower potential for gastric mucosal toxicity than piroxicam as has been reported earlier also^{5,18}. Consistent with previous data, no significant change in hepatic and renal functions was observed with nimesulide or piroxicam^{19,20,21}.

In the last decade there has been increasing interest in the possibility that available NSAIDs may "modify" the disease process by influencing various aspects of cartilage metabolism. In this study, we have attempted to study the influence of nimesulide and piroxicam on the osteoarthritic process when used for a duration of 6 months, in terms of global outcome, and their effects on joint cartilages and associated structures.

All the patients who received treatment for 6 months progressively showed an improvement in their clinical outcome measures, but no change in the joint structures including the cartilage as observed by magnetic resonance imaging.

A clinical study of longer duration with larger number of patients is required, to show any macroscopic changes in cartilage integrity.

CONCLUSION

To conclude, the results of this study suggests that nimesulide and piroxicam are comparable in efficacy and tolerability in patients suffering from osteoarthritis of the knee joint. Statistically insignificant minor differences observed can only be delineated when the study is conducted in a larger number of patients. Magnetic resonance imaging carried out in a few patients gives us a lead that this technique may be useful for assessing changes in joint structures including cartilage.

Whether these drugs have chondroprotective action or reverse the osteoarthritic changes in the joint cartilages and associated structures, however, remains to be established.

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MAM College, New Delhi

* Department of Pharmacology

** Institute of Human Behaviour & Allied Sciences, Shahdara, Delhi

*** Department of Orthopaedics

**** Department of Medicine

***** MRI Centre, Green Park, New Delhi