

DOUBLE-BLIND RANDOMIZED COMPARATIVE EVALUATION OF EFFICACY AND SAFETY OF NIMULID (NIMESULIDE) AND DICLOFENAC IN OSTEOARTHRITIS

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ABSTRACT

The efficacy and safety of Nimulid (Nimesulide) and Diclofenac was evaluated in a double blind randomized diclofenac controlled trial in patients suffering from osteoarthritis of the knee joint. Out of 141 patients, 71 (42 males, 29 female) received Nimulid 100 mg. BD and 70 patients (40 male, 30 female) received Diclofenac 75 mg BD. There was no statistically significant difference in the age, sex, duration of illness distribution of patients in both the groups. Various parameters studied were: severity of pain on routine activity and on movement, morning stiffness and limitation of movement - Nimulid (Nimesulide) appeared to reduce limitation of movement more effectively than Diclofenac ($P < 0.05$). At the end of therapy there were more number of patients with mild limitation of movement in the Nimulid group than in the Diclofenac group. Requirement for paracetamol as rescue therapy was significantly lesser in Nimulid group compared to Diclofenac group. Six patients receiving Diclofenac and two patients receiving Nimulid experienced mild and transient gastrointestinal side effects. However, no patients in either of the groups discontinued the protocol therapy due to side effects.

Nimulid (Nimesulide) 100 mg BD is an effective and well tolerated analgesic and anti-inflammatory agent in osteoarthritis.

Key Words - Osteoarthritis -Drugs-Efficacy-Safety

INTRODUCTION

Osteoarthritis is a common condition affecting both males and females during their productive years of life. Knee joint is most commonly affected because of its weight bearing function. The commonly used modalities of the treatment include non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular steroids, physiotherapy. All treatment modalities are not uniformly successful and all of them carry certain potential side effects. In addition, there are significant drug interactions with some commonly used NSAIDs, like diuretics, beta adrenergic blocking agents, angiotensin converting enzyme inhibitors and other drugs used in cardiovascular diseases. Similarly, intra-articular injection of steroids is also not without local and systemic side effects. Therefore, the search for safe, effective and well tolerated drugs continues.

Nimulid (Nimesulide) is a newer nonsteroidal anti-inflammatory drug which has been used as an analgesic in variety of painful conditions. Unlike other NSAIDs, Nimulid selectively inhibits the formation of proinflammatory prostaglandins. Consequently, Nimulid is better tolerated by the gastrointestinal tract than other NSAID's (Davis & Brogden, 1994). Moreover, Nimulid at a therapeutic concentration (3mg/ L) reduced the degradation of the matrix by inhibiting the synthesis of metalloproteinases such as collagenase and stromelysin when added to human articular cartilage explant in vitro (Pelletier and Pelletier. 1993). These results suggest that Nimulid may reduce the breakdown of osteoarthritic human cartilage. Efficacy of Nimulid has been compared with piroxicam, naproxen, etodolac and ketoprofen. However, efficacy in comparison with Diclofenac sodium has not been reported in patients with osteoarthritis of the knee joint-Therefore. present multicentre, double blind randomized Diclofenac sodium controlled study was conducted to compare efficiency and safety of Nimulid (Nimesulide) in osteoarthritis of the knee joint.

MATERIAL AND METHODS

Present multicentre, double blind Diclofenac controlled, randomized, parallel trial was conducted at LNJP Hospital, New Delhi and KG Medical College, Lucknow from July 1994 to April 1995. This protocol was approved by hospital ethics committee.

All newly diagnosed patients with confirmed diagnosis of osteoarthritis of knee, for at least 6 months before the study and a Steinbrocker functional capacity of class I, II & III were included. Patients with osteoarthritis already receiving therapy with other NSAIDs were also included after a washout period of 15 days during which placebo was administered.

The diagnosis of osteoarthritis was made if at least three criteria were present, namely: pain aggravated by motion and at least partly relieved by rest; limitation of the range of motion; Inactivity stiffness; tenderness on pressure; synovitis indicative of osteoarthritis by joint fluid analysis when effusion is present. and radiologically at least one of the following was present Joint space narrowing; Subchondral Bony sclerosis (eburnation): Bone cysts; Gross deformity and subluxation and/ or loose bodies.

The following classification of functional impairment was recommended as an adjunct to the criteria for the stages of osteoarthritis: Class I: Complete functional capacity with ability to carry on all usual duties without handicaps. Class II: functional capacity adequate to conduct normal activities despite handicap or discomfort or limited mobility of one or more joints. Class III: Functional capacity adequate to perform only little or none of the duties of usual occupation or of self care. Class IV : Largely or wholly incapacitated with patient bedridden or confined to wheel chair, permitting little or no self care.

Patients receiving antineoplastic agents, corticosteroids, gold salts, penicillamine, colchicine and anticoagulants, hydantoin, antidiabetic drugs or anti malarial within one month preceding the study at the time of inclusion were excluded. Patients with other types of arthritic conditions or scheduled for hospitalization or bed rest or for joint replacement surgery because of arthritis with evidence of active gastro intestinal disease as well as pregnant and nursing women were excluded from the study.

All adult patients between the age group of 20-80 years of both sexes who satisfied above mentioned criteria not suffering from other serious illness were included in the study. Informed consent was obtained from patients before inclusion in the study. Nimulid was given in the dose of 100 mg BD and Diclofenac sod 75 mg BD. Paracetamol was given as rescue drug if patient felt that pain relief by the study medication was inadequate. No other medication was permitted during the study period. These patients received either Nimulid or Diclofenac as per randomisation protocol. Neither patient nor doctor were aware of the nature of the drugs. Compliance was ensured by counting number of tablets at each visit. If patient did not take medicine for more than three days he was considered as drop out from the study.

The clinical assessment included following indicators of efficacy: pain and discomfort at rest and on movements, maximum distance walked, activity of daily living, joint movements and swelling, morning stiffness and adverse events. These symptoms were graded as mild, moderate or severe by the investigator.

X-ray of the affected joint, hemogram, rheumatoid factor, antinuclear factor, kidney and liver function tests were examined before and 2 months after therapy.

All clinical parameters as well as investigations to confirm diagnosis were recorded at the time of entry. These patients were followed up two weekly for two months. At each visit data on clinical parameters, adverse effects along with number of paracetamol tablets consumed during the last week was recorded. Number of paracetamol tablets consumed was recorded as (< 7 per week, 8-15 per week, >15 per week).

The differences from baseline in various parameters were compared between treatment using appropriate two tailed T test. $P < 0.05$ was considered as statistically significant.

RESULTS

Total of 141 patients, 70 in Diclofenac group 71 in Nimulid were enrolled in the study. The two groups had similar demographic and baseline characteristic (Table 1).

Table 1: Patient characteristics

Patient Characteristics	Diclofenac (n=70)	Nimulid (n=71)
Mean Age (Y)	61.4	61.2
Male	40.0	42.0
Female	30.0	29.0
Duration of illness (y)	06.8	07.5
Joint involvement		
Unilateral	53.0	56.0
Bilateral	17.0	15.0

There was no difference in duration of illness and number of joints (Table 1). Table 2 shows the influence of drug treatment on the pain intensity and limitation of range of movement. These result showed that similar degree of pain existed in both the groups at baseline. Both Nimulid and Diclofenac relieved pain effectively and there was no statistically significant difference between the two drugs in relation to severity of pain after 8 weeks of therapy. However, Nimulid improved range of movements of the joint more effectively than Diclofenac ($P < 0.05$). Number of patients who showed improvement was similar for the two treatment groups after 8 weeks of the treatment with either Nimulid (Nimesulide) or Diclofenac. The assessment of range of joint movement before starting protocol therapy indicated that a greater proportion of patients (86-90%) complained of moderate to severe limitation of joint movement in both the study groups (29.41 % in Diclofenac and 47.9% in Nimulid group). However, there were significantly more number of patients with mild limitation of range of movement in the Nimulid group (63.38%) after treatment at 8 weeks than in the (44.28%) Diclofenac group (Table 2).

Table 3 demonstrates the number of paracetamol consumed as rescue drug in case of inadequate pain relief by either of the study drugs. Number of patients needing 8-15 paracetamol tablets per week to control pain progressively decreased from about 60% at week 2 to 35.71% at the end of therapy in Diclofenac group and 54% to 14% in the Nimulid group. Greater number of patients (43.66) in the Nimulid group were consuming > 15 paracetamol tablets per week at week 2 compared to 20% in the Diclofenac group. However, at the end of therapy, requirement for paracetamol tablets declined in both the groups but it reached significant level only in the patients receiving >7 paracetamol tablets per week in the Nimulid group (78.87%) compared with 57.14% in Diclofenac group.

Two patients out of 71 in Nimulid group and 6 out of 70 patients in Diclofenac group experienced transient and mild gastritis. None of the patients in either of this study group discontinued protocol therapy because of side effects. The overall tolerance of both the drugs was very good as rated by both patients and the investigating physician.

Table 2 : Effect of Diclofenac 75 mg BD and Nimulid (Nimesulide) 100 mg BD on pain intensity on Visual Analogue Score (VAS)

Parameter	Diclofenac (n = 70)		Nimulid (Nimesulide) (n = 71)	
	Before	After	Before	After
Pain intensity				
Mild	7 (10)	22 (31.42)	5 (7.04)	20 (28.16)
Moderate	28 (40)	39 (55.71)	30 (42.25)	40 (56.33)
Severe	36 (51.42)	9 (12.85)	34 (47.88)	11 (15.49)
Limitation of range of movements				
Mild	9 (1.28)	31 (44.28)	7 (9.85)	45* (63.38)
Moderate	32 (45.71)	20 (28.57)	30 (42.25)	20 (28.16)
Severe	29 (41.42)	19 (27.14)	34 (47.88)	6 (8.45)
* P <0.05				
Figure in parenthesis denote percentage				

Table 3 : Consumption of paracetamol (500 mg) as a rescue drug in patients treated with Diclofenac and Nimulid (Nimesulide)

Paracetamol intake	Diclofenac		Nimulid (Nimesulide)	
	Week 2	Weeks	Week 2	Weeks
<7 per week	4 (5.71)	40 (57.14)	2 (2.81)	56 (78.87)
8-15 per week	42 (60)	25 (35.71)	38 (53.52)	10 (14.08)
>15 per week	14 (20)	5 (7.14)	31 (43.66)	5* (7.04)
*P <0.05				
Figure in parenthesis denote percentage				

DISCUSSION

In the present, medium term study of patient with osteoarthritis, treatment with Nimulid clearly produced prompt and sustained control of pain. The efficacy of Nimulid (Nimesulide) was judged to be comparable with that of Diclofenac. However, Nimulid improved range of movement of the joints more effectively as compared to Diclofenac sodium. The tolerability of Nimulid was good and did not differ statistically from Diclofenac sodium. The principal adverse effects reported were those relating to the gastro intestinal tract but these adverse events were self limiting and mild in nature. These results and reports from various studies which compared efficacy of Nimulid with piroxicam, ketoprofen, naproxen, and etodolac demonstrate that Nimulid is equivalent to piroxicam and etodolac (Dreiser and Riebenfeld, 1993; Fossaluzza and Montagnani, 1989; Lucker 1994).

In conclusion, osteoarthritis is a persistent and progressive degenerative disorder characterised by pain and increasing functional limitation. Nimulid has combined analgesic and anti-inflammatory properties with greater gastrointestinal tolerability. In addition, Nimulid has been shown to inhibit metallopeptidase synthesis and proteoglycan degradation in vitro explants. These findings, together with the results of the above clinical studies suggest Nimulid to be an adequate and appropriate therapy in either short or medium term management of osteoarthritis.

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