

Efficacy and Safety of Nimesulide in the Complex Treatment of Patients with Knee and Hip Osteoarthritis

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Abstract

Aim: Evaluate the effectiveness and tolerability of nimesulide in osteoarthritis knee and hip patients- divided in subgroups based on the standard of care treatment received.

Methods: In this open label, phase IV study conducted in the knee and hip osteoarthritis outpatients between March 2011 and August 2013, patients with knee/hip pain ≥ 40 mm on visual analogue scale were enrolled. Patients were divided into five subgroups and each group of patients were administered nimesulide 100 mg twice daily for up to 3 weeks in addition to the standard of care treatment. Patients were evaluated at baseline, Day 7 \pm 2, Day 14 \pm 2, and at Day 21 \pm 2 for severity of pain at rest and movement by visual analogue scale, Lequesne index, and degree of joint dysfunction and stiffness by Western Ontario and Mc master Universities Arthritis index.

Results: Of the 182 knee osteoarthritis outpatients, 161 patients and all 20 hip osteoarthritis patients completed the study. Reduction in pain intensity was observed in all the groups from baseline to post treatment. A statistically significant decrease in mean visual analogue score was observed. Functional indices scores also improved during the treatment. The total treatment effectiveness was evaluated as "good" in 79.8%, as "satisfactory" in 17.8%, and "unsatisfactory" in 2.4% patients. Overall tolerability was defined as "good" in 85.3%, as "satisfactory" in 5.7%, and "unsatisfactory" in 9% patients.

Conclusion: Nimesulide 100 mg twice daily for three weeks is effective and well tolerated in osteoarthritis knee and hip patients.

Keywords: Osteoarthritis; Knee; Hip; Anti-Inflammatory Agents; Non-Steroidal; Standard of Care; Pain

Abbreviations

ACR: American College of Rheumatology; AE: Adverse Event; BC: Base Complex; BD: Twice Daily; COX: Cyclooxygenase; GCP: Good Clinical Practice; GI: Gastrointestinal; NHWS: National Health and Wellness Survey; NSAIDS: Non-Steroidal Anti-Inflammatory Drugs; OA: Osteoarthritis; SOC: Standard of Care; VAS: Visual Analogue Scale; WOMAC: Western Ontario and Mc Master Universities Arthritis Index

Introduction

Osteoarthritis (OA), a common degenerative joint disease affects 85% patients above 70 years and 20% of the general population [1]. As per the 2011 national health and wellness survey (NHWS), 7.8% of the total urban Russian adult population suffers from OA [2].

Osteoarthritis is a progressive disease with gradual increase in pain, functional limitation, and joint deformity [3].

Knee and hip OA are the most common causes of musculoskeletal disability [4]. There is an immense burden on society as there is an impairment in patients' quality of life, work/productivity loss, and socio-economic impact.

According to the current treatment algorithm, non-steroidal anti-inflammatory drugs (NSAIDS) are recommended for the treatment of OA [5-7]. Simple analgesics like paracetamol is effective in mild OA, however NSAIDS are comparatively more effective in severe cases and are generally preferred by the clinicians. Nevertheless, traditional NSAIDS are commonly associated with gastrointestinal toxicity and nimesulide, being a gastro sparing agent has a place in OA management [8].

Nimesulide is a non-acidic NSAID with an excellent cyclooxygenase-1/cyclooxygenase-2 (COX1/COX2) inhibitory ratio. It has a potent analgesic, anti-pyretic, and anti-inflammatory activities and comparatively better gastrointestinal (GI) profile as compared to other drugs in the same class [3].

It has been approved worldwide- in over 50 countries for the treatment of acute pain, osteoarthritic pain, and primary dysmenorrhoea [8].

The available evidence indicates that nimesulide is as effective as other NSAIDs such as piroxicam [9], diclofenac [9], ketoprofen [10], naproxen [11], etodolac [12], and coxibs [13] in the short-term treatment of OA pain and inflammation. Safety data from clinical trial and post-marketing survey has shown good safety profile of the drug [11].

We have studied the efficacy and safety of nimesulide in the treatment of knee and hip OA in different subgroups of patients based on the standards of care received by the patients in addition to nimesulide.

Materials and Methods

Participants and Study Design

This was an open label, phase IV trial to evaluate the efficacy, safety, and tolerability of nimesulide in the treatment of patients with knee and hip osteoarthritis.

The study was conducted in the period between March 2011 and August 2013 in Russia.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). All patients provided signed informed consent prior to the start of the study in accordance with local regulations and standards of Bioethics. This trial is registered with <http://clinicaltrials.gov>, number NCT02922712.

Patients

Patients ≥ 40 years of age referred to outpatient clinic and diagnosed with OA knee and hip and associated pain syndrome (based on American College of Rheumatology [ACR], criteria) [14] were included in the study. Patients with radiological abnormalities complying with I-III grades of Kellgren [15] and only those presenting with pain in the affected knee or hip joint not less than 40 points according to 100-point visual analogue scale (VAS) were enrolled.

Patients with acute peptic ulcer over several past years, any history of upper gastrointestinal (GI) bleeding, malignant neoplasms, patients with uncontrolled hypertension, severe heart failure, hematopoietic disorders, type I diabetes, patients with the presence of other rheumatic diseases except osteoarthritis, or patients treated with corticosteroids (systemic and/or intra-articular injection for 6 weeks prior to the study), warfarin and other coumarin derivatives were excluded from the study.

Study Design and Treatment

Patients who had taken NSAIDs (except nimesulide) without any beneficial effect prior to enrolment in the study were administered with nimesulide 100 mg twice daily orally for 3 weeks. Depending on the severity of pain, degree of joint dysfunction, and related diseases, each group of patients was assigned an appropriate set of treatment in addition to the study drug. Base complex (BC) of SOC treatment included nicotinic acid and/or vitamins B and cartilage protectors; remedial gymnastic (exercises aimed at decrease in pain, enhancement of muscular and capsular-ligamentous apparatus, increase in motion in affected joints); and physiotherapy (phonophoresis with hydrocortisone, electrophoresis with metamizole sodium, magnetotherapy, sinusoidal modulated current, laser treatment, pneumopulsation, cryotherapy, electro-neurostimulation) which was used in combination or successively.

The primary endpoint was reduction of pain intensity (on 100 mm VAS scale). The secondary endpoints were lequesne and WOMAC indices, assessment of the overall effectiveness of therapy (VAS, 0-100 mm), assessment of the overall tolerability, frequency and severity of any adverse effects.

Assessments

Study participants were evaluated at baseline (Visit 1, Day 0) and during the treatment visits on Day 7 \pm 2 (Visit 2), 14 \pm 2 (Visit 3), and Day 21 \pm 2 (Visit 4).

A detailed history of all patients was taken prior to enrolment. Physical examination and evaluation of articular syndrome was done at all the visits. Treatment efficacy was determined by severity of pain, degree of joint dysfunction, presence of synovitis, and the nature of co-morbidities.

The Lequesne index [16] (at baseline and visit 4) was used to assess the severity of OA for the following indicators: pain at rest, pain during walking, the most travelled distance without pain, and daily activities. The WOMAC index [17] (at baseline and visit 4) was used to assess the severity of pain, stiffness, and joint function.

Overall treatment effectiveness and treatment tolerability was assessed on visit 2, visit 3, and visit 4.

For pain at rest, analgesic effect was considered: Good = VAS < 10 points, Satisfactory: VAS 10 to 30 points and Unsatisfactory: VAS > 30 points. For pain on movement, analgesic effect was considered: Good: VAS < 20 points, Satisfactory: VAS 20 to 30 points and Unsatisfactory: VAS > 30 points.

Overall safety was evaluated by recording adverse events (AEs) and determining laboratory parameters.

Patients were discontinued from the study if there was the lack of analgesic effect of the study drug within a week's duration.

Results and Discussion

Results

Of the 182 osteoarthritis knee outpatients (167 women and 15 men, 41 to 80 years old), 161 completed the study. All 20 hip OA patients, 18 women and 2 men, 46 to 76 years old, completed the study.

Knee OA patients were divided into five groups based on the clinical features and SOC treatment modalities.

Group 1 (n = 61): These patients had unpronounced signs of local inflammation but with significant pain. Base complex of SOC was fully performed.

Group 2 (n = 14): This group comprised of patients with contraindications for physiotherapy or those who rejected physiotherapy and were not administered NSAIDs previously. All patients from other groups received NSAIDs (except for nimesulide), moreover, usually at full doses and for a long period of time.

Group 3 (n = 42): Patients with evident muscular hypotrophy who had massage added to the BC.

Group 4 (n = 41): In patients with evident local irritation reaction accompanied with synovitis, glucocorticosteroids were administered intra-articularly with BC in the beginning of the treatment course.

Group 5 (n = 3): This group of patients received single doses of hyaluronic acid products intra-articularly in addition to BC

Hip OA patients were divided into 3 groups:

Group 1 consisted of patients not previously taking NSAIDs who have contraindications and/or refuse to conduct physical therapy.

Group 2 and 3 patients received various NSAIDs (except nimesulide) at full doses and for a longer period of time.

All patients were on nimesulide, vitamins, chondroprotectors, and physiotherapy; 15 patients were on additional physiotherapy in group 2 and 3; and 8 patients were on massage.

Efficacy Analysis

Knee Osteoarthritis

Primary Analysis

Pain intensity by VAS: At baseline, overall mean VAS score of pain intensity were 71.8 ± 1.2 mm on movement and 35.0 ± 1.7 mm at rest (Group 1 to 4). This indicates a severe disease and a poor quality of life. The difference in VAS score in the 5th group, cannot be considered significant due to smaller sample size (n = 3). Thus, we did not compare it with other groups. The reduction in pain intensity was observed in all the studied groups during the treatment. There was a statistically significant ($P < 0.05$) decrease in mean VAS score (both in movement and at rest) from baseline to post-treatment (Table 1 and Figure 1).

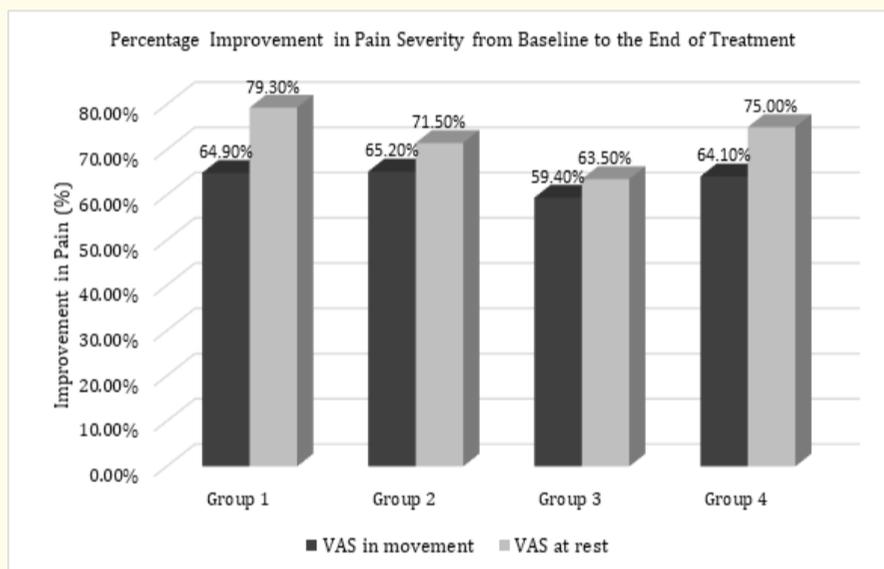


Figure 1: Improvement in the Pain Severity (by VAS Score) from Baseline to the End of Treatment.

Parameters	Group 1* n = 61 (37.8%)			Group 2* n = 14 (8.7%)			Group 3* n = 42 (26.1%)			Group 4* n = 41 (25.5%)		
	Before treatment	After treatment	Improvement (%)	Before treatment	After treatment	Improvement (%)	Before treatment	After treatment	Improvement (%)	Before treatment	After treatment	Improvement (%)
VAS in movement (mm)	70.8 ± 2.0	24.9 ± 2.2	64.9	68.3 ± 3.8	23.8 ± 4.6	65.2	75.5 ± 2.7	30.7 ± 3.0	59.4	74.9 ± 2.5	26.9 ± 2.9	64.1
VAS at rest (mm)	36.1 ± 3.1	7.5 ± 1.3	79.3	29.4 ± 5.8	8.4 ± 3.2	71.5	34.9 ± 3.7	12.7 ± 2.4	63.5	33.9 ± 3.9	8.5 ± 2.0	75.0
Lequesne index (Points)	15.3 ± 0.5	10.3 ± 0.5	32.8	16.6 ± 1.3	11.0 ± 1.2	33.9	20.5 ± 4.2	13.8 ± 1.6	32.8	15.7 ± 0.6	11.2 ± 0.6	29.1
WOMAC (Points)	132.3 ± 6.3	73.6 ± 5.2	44.4	120.9 ± 11.3	77.2 ± 12.4	36.1	132.1 ± 7.4	85.2 ± 6.8	35.5	145.6 ± 6.0	88.0 ± 6.0	39.3

Table 1: Evaluation of Efficacy of the Treatment Performed (Mean Values in Points) in Knee Osteoarthritis.

* $p < 0.05$, within group before and after treatment

Secondary Analysis

The patients showed improvement in the scores of functional indices such as Lequesne index and WOMAC index from baseline to the end of treatment in all four groups (Figure 2).

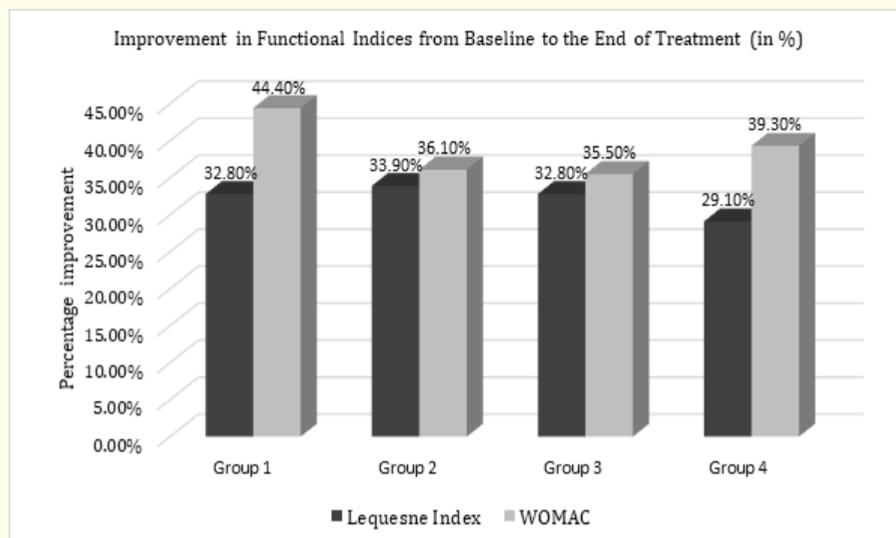


Figure 2: Improvement in the Functional Indices from Baseline to the End of Treatment.

The total treatment effectiveness was evaluated as “good” in 130 patients (79.8%), as “satisfactory” in 29 (17.8%) patients, and “unsatisfactory” in 4 (2.4%) patients.

Overall tolerability was defined as “good” in 151 (85.3%) patients, as “satisfactory” in 10 (5.7%) patients, and “unsatisfactory” in 16 (9%) patients.

Total 21 patients were withdrawn from the study, of which 16 patients were withdrawn due to epigastric pain (6), edema of face, upper, and lower extremities (5), episodes of increased blood pressure (2), atrial fibrillation (2), and skin rash on the legs (1). Two patients were withdrawn due to lack of analgesic effect and 3 patients were withdrawn due to soft tissue injury shoulder or urgent business trip. There were no clinically significant changes in the biochemical laboratory parameters.

Hip osteoarthritis

The results for hip OA patients are shown in table 2. All the parameters- pain intensity by VAS and functional indices showed significant reduction ($P \leq 0.05$) from baseline to end of treatment, except pain at rest in group 1.

Parameters	Group 1 (n = 5)			Group 2 (n = 7)			Group 3 (n = 8)		
	Before treatment	After treatment	Improvement (%)	Before treatment	After treatment	Improvement (%)	Before treatment	After treatment	Improvement (%)
VAS in movement (mm)	70 ± 8	39 ± 19 *	44	77 ± 5	31 ± 9 *	60	76 ± 5	19 ± 7 *	75
VAS at rest (mm)	43 ± 13	27 ± 17	39	44 ± 9	13 ± 5 *	70	45 ± 8	6 ± 1 *	87
Lequesne index, points	18 ± 1	15 ± 2 *	16	14 ± 1	10 ± 2 *	27	16 ± 1	8 ± 2 *	50
WOMAC points	156 ± 17	109 ± 17 *	30	138 ± 15	99 ± 19 *	28	137 ± 12	73 ± 12 *	47

Table 2: Evaluation of Efficacy of the Treatment Performed (Mean Values in Points) in Hip Osteoarthritis.

* $p \leq 0.05$

Discussion

Our study was the first study in Russia which compared the effectiveness and tolerability of nimesulide in OA patients, particularly in subgroups based on their category of standard of care in Russia.

The primary goal of OA management is the control of pain, disability, and quality of life. Nimesulide, with its favourable pharmacokinetic profile and a shorter plasma half-life, provides rapid pain relief. This may improve patients’ satisfaction, adherence to therapy, and also contribute to OA patients for carrying out their everyday activities [18].

Nimesulide is associated with lesser side effects of GI, renal, skin, or cardiovascular systems than other non-selective NSAIDs [19].

A significant improvement was observed in pain intensity from baseline to end of treatment in all the groups. The decrease in mean parameters of the pain was most evident for pain at rest, while it somehow differed in the groups. In the 2nd observation group with no physiotherapy performed, pain reduction was less. Eight patients who did not receive prior NSAIDs significantly affected the mean parameter in the group. Their mean pain index at rest improved by 71.5% and that in movement improved by 65.2%. In the 3rd group, pain reduction was worse due to evident muscular hypotrophy, which was difficult to correct with massage and remedial gymnastic for 3 weeks; these patients needed longer rehabilitation course. The pain reduction in the 4th group was comparable to the 1st group: in spite of the fact that evident inflammatory reaction was reported in these patients. Intra-articular administration of steroids assured good analgesic effect in the beginning of the treatment course (Table 1).

Comparative evaluation of the changes in mean functional indices demonstrated that the parameters were improved by > 25% in all the groups. However, the best result was achieved in the group 1 patients.

A non-comparative study with OA showed nimesulide 100 to 400 mg/day for 5 to 21 days produced significant improvements in the degree of spontaneous pain, morning stiffness, and global efficacy. Reduction in pain and morning stiffness was reported in > 80% patients and global efficacy of treatment was rated as good or excellent by > 70% patients and physicians [20].

A placebo controlled study showed consistent results with our study with reduction in spontaneous pain by 70.1% and movement induced pain by 67% at the end of treatment [21].

Earlier reported studies have demonstrated comparable efficacy of nimesulide with other NSAIDs in the short term management of pain and inflammation in OA [9-13].

In a comparative 3 weeks study, nimesulide and piroxicam showed improvement in pain intensity with reduction in VAS score from baseline to end of treatment and the difference in efficacy between the two groups was not statistically significant ($p = 0.1$). Similarly, the observed difference in pain improvement between nimesulide and ketoprofen was not statistically significant ($p = 0.6$) [10].

A double blind trial demonstrated superiority of nimesulide over diclofenac with 70.6% patients in nimesulide group vs 50% patients in diclofenac group reporting mild pain in the affected joint on treatment completion. About 50% patients in the diclofenac group had breakthrough pain as compared to 17.6% patients in the nimesulide group [9].

As compared to rofecoxib, nimesulide provided rapid pain relief and was more effective in terms of overall pain improvement and quality of life [3].

In an open label study by Famaey, et al. [22], the global efficacy and tolerability was rated as satisfactory or excellent by 87.1% and 93.1% patients respectively and by 90.1% and 94.7% of the investigators respectively.

In our study, total treatment effectiveness as evaluated by physician, was good in 79.8%, satisfactory in 17.8%, and unsatisfactory in 2.4% patients. Overall tolerability was good in 85.3%, satisfactory in 5.7%, and unsatisfactory in 9% patients.

In a dose finding study by Bourgeois, et al. nimesulide 100 mg twice daily (BD) had been confirmed to be the most favourable dosage regimen- 50 mg BD was insufficient to produce prompt analgesic effect while 200 mg group had higher adverse effects within first week of treatment than the 100 mg group [23]. Therefore, we have used 100 mg BD nimesulide in our study.

Nimesulide is a well-tolerated drug. In a comparative study with diclofenac, drug related GI events with nimesulide were 10.9% lower than diclofenac. Three gastroscopic studies have shown either no difference between nimesulide and placebo after 1 week or diclofenac after 1 month, or a lower incidence of gastric erosions with nimesulide versus indomethacin after 2 weeks. The global evaluation was rated as good to excellent in 90.5% and 89% patients with regard to efficacy and good to excellent in 77% and 73% patients with regard to tolerability by investigators and patients respectively [22].

An Italian post-marketing survey in OA patients, confirmed the good tolerability profile of short term (1 to 3 weeks) nimesulide therapy. Our study results are in concordance with side effects reported in this study. Common AEs belonged to gastrointestinal, body as a whole, skin, and CNS which was consistent with our study [24].

Two non-comparative studies evaluated the long term tolerability (3 and 12 months) of oral nimesulide 100 mg BD. Majority of reported AEs were mild to moderate and no serious GI AEs was associated with long term administration of nimesulide [25].

We have not studied the rapid onset of action of nimesulide in our study. This would have been an additional advantage to study this in subgroups.

Conclusion

Our study has confirmed the effectiveness and tolerability of nimesulide 100 mg twice daily for three weeks in OA knee and hip patients; patients being divided in subgroups based on standard of care. Its short term tolerability especially with regard to GI tolerability has been advantageous [13].

Conflict of Interest

Research funding provided by Dr Reddy's Laboratories Ltd. Hyderabad, India. Amit Garg, Namita Gupta, Suhas Khandarkar and Shyam Akku are employees of Dr. Reddy's Laboratories.

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