Original Article

A Comparative Study of Efficacy and Safety of Piroxicam and Naproxen in the Management of Pain in Osteoarthritis of the Knee

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Abstract

Introduction: Osteoarthritis (OA) is a degenerative joint disease and cause for functional disability. OA is characterized by the insidious onset of pain and limited range of movements. Piroxicam and naproxen are used in OA, rheumatoid arthritis, acute gouty arthritis, migraine, dysmenorrhea, and postoperative pain. The aim of this study was to compare the efficacy and safety of these drugs in patients with OA of the knee. **Materials and Methods:** This was a randomized, open-label, comparative, parallel group study conducted in patients with OA of knee joints. They received either oral piroxicam 20 mg or naproxen 500 mg twice daily for 6 weeks. The pain was assessed using Visual Analog Scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores at baseline, 2nd, 4th, and 6th week. Patient satisfaction score (PSS) and quality of life were assessed at follow-up. Adverse effects were assessed using the World Health Organization causality scale. Descriptive and inferential statistics were used. **Results:** A total of 110 patients were recruited, 47 males and 63 females, 100 completed the study (51 in Group P and 49 in Group N). Both piroxicam and naproxen significantly reduced VAS and WOMAC scores at the 2nd, 4th, and 6th week ($P = 0.001$) compared to baseline, but this was not significant between the groups. PSS was significantly ($P = 0.03$) high at 4th and 6th week when compared to week 2 with both medications, but between the medications, it was insignificant ($P = 0.10$). The adverse effects such as epigastric discomfort, nausea, and vomiting were observed with both the drugs, but it was more with naproxen. **Conclusion:** Piroxicam was as effective as naproxen in relieving pain and improving the range of movements with less adverse effects.

Keywords: Knee joints, naproxen, osteoarthritis, piroxicam

Introduction

Pain is the most common complaint in osteoarthritis (OA), which restricts the physical activity of the patients as well as decreases work performance.[1] In OA of the knee, pain may arise from periosteal elevation, trabecular microfractures, capsular distension, and/or synovial inflammation. Factors complicating determination of the source of pain may include varus or vagus deformity, weight issues, and the emotional impact of chronic pain. Once the cause of pain is identified, treatment plan can be formulated.[2] Pain is the most common reason in patients with OA to seek medical help.[3] The current treatment strategies for OA aim to educate the patient about OA, alleviate pain, optimize and maintain joint function and prevent or suppress the progression of adverse structural change affecting the joint tissues.[4]

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Commonly used pharmacological agents for pain management are nonsteroidal anti-inflammatory drugs (NSAIDs).[5] Most of the patients with OA take medication for a long period and have a number of comorbidities, which requires concomitant medication, increasing the likelihood of adverse events including gastrointestinal (GI) injury.[6] There is an increasing demand for more effective and safer treatment for OA. Piroxicam is an NSAID, an oxicam derivative, which are enolic acids that inhibit cyclooxygenase (COX) enzyme non

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selectively. It results in inhibition of prostaglandin production, which is the main mediator of pain. It has a long half-life (t½) of approximately 50 h and available as oral formulation, and hence, it is suitable for use in OA.[5] It is also used in the management of postoperative pain, musculoskeletal disorders, and dysmenorrhea.[7] It has shown clinical efficacy in relieving pain associated with OA and rheumatoid arthritis, especially where there is an associated inflammatory component.[8] It also suppresses primary and secondary lesions of adjuvant arthritis.[9] Naproxen is an NSAID, a propionic acid derivative and is a nonselective COX enzyme inhibitor. It is well-absorbed orally and has a t½ of 14 h.[5] It has clinically proven efficacy with regard to analgesia and relief of morning stiffness.[10] It has side effects such as abdominal pain, gastritis, drowsiness, nausea, vomiting, dizziness, and pruritis.

Materials And Methods

A randomized, open-label, comparative, parallel group, prospective study was conducted in patients diagnosed with OA of knee joints. This study was carried out by the Departments of Pharmacology and Orthopaedics in R. L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar, from January 2015 to June 2016. Patients of either gender, aged between 40 and 70 years with symptomatic idiopathic OA of bilateral knee joint involvement for a minimum period of 6 months, radiological evidence of OA of knee joints and morning stiffness of <30 min duration with crepitus on motion were included in the study. Exclusion criteria were: patients with a history of surgery or acute trauma to the knee joint within 6 months, history of peptic ulcer, GI bleeding, psychiatric illness and bronchial asthma, acute inflammatory arthritis, pseudogout, or severe osteoporosis, those with deranged hepatic or renal parameters and also who were hypersensitive to piroxicam or naproxen. Patients with pain due to OA of knee joints were recruited, randomized by simple randomization in a 1:1 ratio into two groups of 55 each, with Group P receiving piroxicam 20 mg and Group N receiving naproxen 500 mg, both medications given orally twice daily for 6 weeks. Patients were followed up at 2nd, 4th, and 6th week. The patients recruited in both groups were matched in terms of age, gender, weight, and body mass index (BMI). They were instructed to perform the mild exercise (knee flexion and hamstring stretch), apply hot fomentation, and use Indian style toilet.

Demographic details and relevant history were collected from the patient at the time of recruitment. Clinical examination including general physical examination and knee joints examination (inspection, palpation, the range of movements and measurements) was performed. Routine laboratory investigations such as complete hemogram, random blood sugar, blood urea, serum creatinine, liver function test, and urine routine were carried out at baseline. X-rays of knee joints were taken at baseline for diagnosis. Rheumatoid factor was done when required. The Visual Analog Scale (VAS)[6] and Western Ontario and McMaster Universities Arthritis Index (WOMAC)[1] scores were assessed at baseline and at each follow-up. The VAS score was graded from 0 to 10 according to patient's response. WOMAC is a subjective score consisting of subscales in terms of pain, stiffness, and physical function. All the parameters were graded on a scale of 0–4 depending on the severity, from none to severe. The reduction in WOMAC score indirectly indicates improvement in the quality of life (QOL). If the VAS score was >3 after initiating the treatment with study drugs, oral tramadol 50 mg was used as rescue analgesic. Patients' satisfaction with respect to pain relief was assessed using patient's satisfaction score (PSS) at each follow-up. PSS was graded as 1 = poor, 2 = fair, 3 = good, and 4 = excellent. During the follow-up, the safety of the drugs was monitored using the World Health Organization causality scale.

Statistical methods

To detect a mean difference of VAS score of 0.98 at the end of 1 month with an effect size of 0.564, power of 80%, alpha error of 5%, and dropout rate of 10%, the required sample size was 55 patients per group. The demographic data were analyzed using descriptive statistics. The VAS and WOMAC scores were assessed using repeated measure analysis of variance followed by Bonferroni *post hoc* test within the group and unpaired *t*-test between the groups. Adverse events were analyzed using Chi-square test. Patient's satisfaction score was analyzed using Wilcoxon and Mann–Whitney U-test. QOL was analyzed using descriptive statistics. The value of $P < 0.05$ was considered as statistically significant.

Results

Patients with OA of both the knee joints recruited were 110 but 100 patients completed the 6 weeks study period [Figure 1]. The analysis was performed for patients who have completed the study. The demographic parameters such as age, gender-wise distribution, BMI, and occupation were comparable in both the groups. Among 110 patients, the majority of patients in both groups were females (57.3%). Housewives constituted for >40% in both the groups [Table 1].

The VAS score within the groups and between both medications is represented in Table 2.

The reduction in mean VAS score was statistically significant at each follow-up compared to baseline in both groups ($P = 0.001$). By week 6, there was significant ($P = 0.001$) decrease in VAS score with both the medications. The reduction in mean VAS score was not significant ($P = 0.20$, $P = 0.81$, $P = 0.38$) between the treatments at any point of time [Table 2]. The area under the curve for a reduction in pain in patients receiving medications in both the groups [Figure 2] was calculated by trapezoid method. The decrease in the area of trapezoid over a period indicates the reduced intensity of pain with both medications. When this area was compared between medications, it was less with piroxicam (5.33) compared to naproxen (5.45) at week 6.

The WOMAC score within the groups and between both medications is represented in Table 3. The reduction in pain,

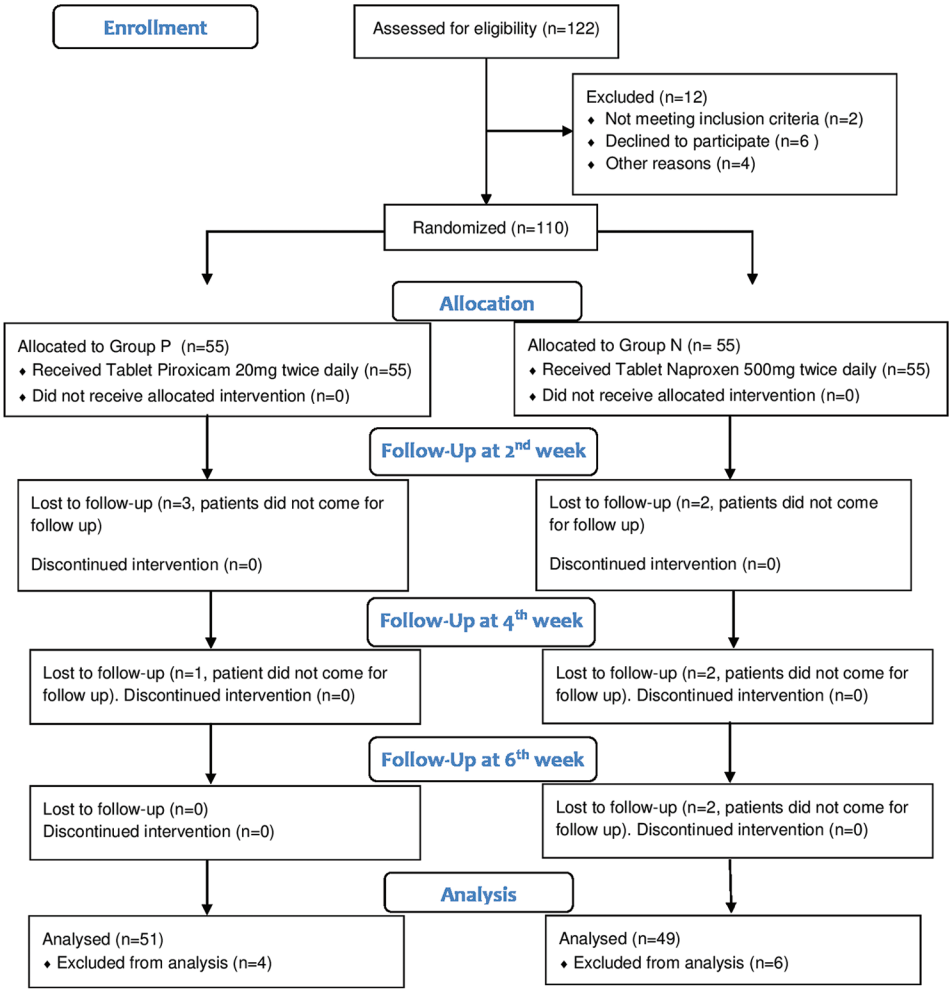

Figure 1: Consort flow chart representing recruitment, randomization and follow-up

Table 1: Comparison of demographic parameters between Group P and Group N

Variables	Group P (n=55)	Group N (n=55)
Age (years), mean±SD	55.24±9.80	52.03±9.00
Male/female	23/32	24/31
BMI (kg/m^2), mean±SD	25.80±4.32	26.00±4.57
House wife	24	22
Farmer	16	18
Teacher	8	9
Tailor	7	6

BMI: Body mass index, SD: Standard deviation

stiffness, and physical function scores were statistically significant (P = 0.001) at weeks 2, 4, and 6 compared to baseline with both the medications [Table 3]. Based on the physical function subscale of WOMAC, reduction in score indicates gradual improvement in the QOL at 2nd, 4th, and 6th week. When the scores of subcales were compared between groups, the reduction was insignificant at each follow-up. The reduction in WOMAC score was statistically significant (P = 0.001) at weeks 2, 4, and 6 compared to baseline with both the medications. More than 75% decrease in the score was observed at week 6. The reduction in mean WOMAC score was insignificant between piroxicam and naproxen at all the follow-up visits.

In piroxicam group, 64.7% of patients graded their satisfaction as good at both 4th and 6th week. Nearly 5.9% of patients expressed their satisfaction as excellent at week 6. This increase in PSS at both weeks was statistically significant as compared to week 2 (P = 0.03). At 4th week, 60.7% of patients graded their satisfaction as good, whereas 63.2% at 6th week in group N. PSS was significantly improved at 4th and 6th week compared to week 2 with naproxen (P = 0.03). PSS was insignificant between the medications (P = 0.10) [Figure 3]. Adverse effects with piroxicam and naproxen were epigastric discomfort (19.2% vs. 32%), nausea (15.3% vs. 18.8%), and vomiting (15.3% vs. 24.5%). These symptoms were treated with omeprazole 20 mg once daily till they subsided.

Discussion

OA is one of the most common degenerative disease particularly affecting the knee joints, and it is the major cause

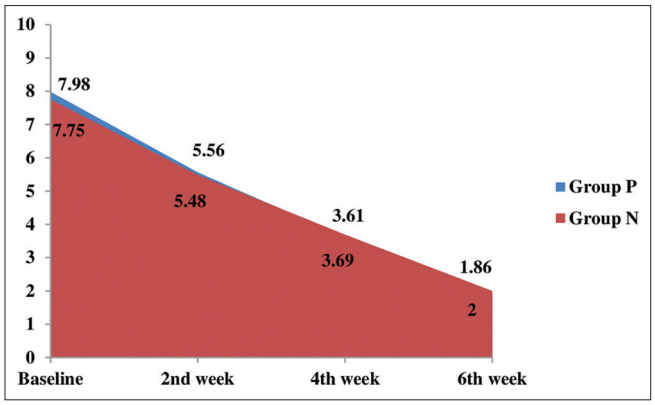

Figure 2: Area under curve – piroxicam and naproxen

Table 2: Comparison of mean visual analog scale scores within and between the groups at all evaluation points

	Mean±SD		*P* (between groups)
	Group P	Group N	
Baseline	8.00±1.51	7.78±1.45	0.40
2nd week	5.52±1.35*	5.45±1.32*	0.20
4th week	3.53±1.10*	3.55±1.12*	0.81
6th week	1.80±0.70*	1.90±0.60*	0.38

*P=0.001 when comparing the evaluation points with baseline.
SD: Standard deviation

Table 3: Comparison of subscales of Western Ontario and McMaster Universities Arthritis Index within and between the groups at all evaluation points

	Mean±SD		*P* (between groups)
	Group P	Group N	
Pain subscale			
Baseline	13.25±2.25	13.27±1.95	0.42
2nd week	09.92±1.74*	09.81±1.62*	0.36
4th week	07.03±1.34*	07.00±1.41*	0.28
6th week	04.35±0.82*	04.41±0.86*	0.17
Stiffness subscale			
Baseline	04.73±0.50	04.58±0.53	0.26
2nd week	03.51±0.50*	03.55±0.54*	0.41
4th week	02.51±0.50*	02.55±0.54*	0.74
6th week	02.00±0.00*	02.02±0.14*	0.32
Physical function subscale			
Baseline	39.63±3.34	39.56±2.92	0.54
2nd week	29.66±3.57*	30.40±2.85*	0.40
4th week	19.47±3.08*	20.07±3.25*	0.12
6th week	09.52±2.28*	09.89±1.99*	0.20

*P=0.001 when comparing the evaluation points with baseline.
SD: Standard deviation

of disability in elderly. OA is a disease of synovial joints characterized by inflammation of the joint capsule, cartilage loss along with periarticular bone damage. It is associated with pain, impaired muscular stability, reduced range of movement, and functional disability. OA rarely occurs before the age of

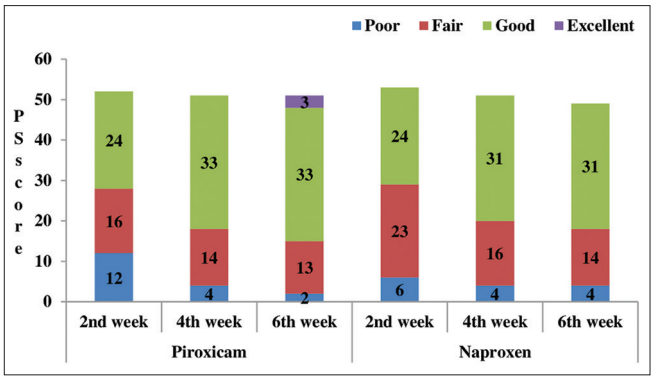

Figure 3: Patient's satisfaction score

40 years but by 75 years at least 85% of the population have either clinical or radiographic evidence of the disease. OA is an appropriate model to assess the efficacy of new analgesics at repeated doses.[5] NSAIDs are widely used for the treatment of pain in patients with OA. However, they are associated with adverse effects mainly GI, such as epigastric discomfort, dyspepsia, abdominal pain, nausea, and vomiting. Thus, the decision to prescribe NSAIDs is based on their effectiveness to reduce pain with less adverse effects.

In the present study, 110 patients diagnosed with moderate to severe OA of both the knee joints were recruited and randomized as shown in Figure 1. They received piroxicam 20 mg in Group P or naproxen 500 mg in group N twice daily for 6 weeks. One hundred patients completed the study period. Most of the patients (70%) were in the fifth decade of life which substantiates that OA occurrence increases as age advances. Some of the factors contributing to OA in elderly could be degenerative changes in the menisci, joint ligaments, increased bone turnover as well as calcification of joint tissues.[11]

The female patients were more in both the groups. A study by Rugstad *et al*., comparing piroxicam 20 mg with naproxen 750 mg once daily in OA of the knee also had more female patients.[12] This could be because in women, tendons are more elastic and knee joints are not aligned straight as in men which lead to injuries and may manifest as OA in the later part of their life. In addition, female patients whose mothers had OA might develop this disease in the same joint and at the same age. Estrogen protects cartilage from inflammation, but during and after menopause, the decreased estrogen level leads to high risk of OA.[13] Obesity contributes to extra stress on knees, which leads to cartilage breakdown, and in this study, most patients were overweight.

We observed that both piroxicam and naproxen significantly reduced the VAS scores at 2nd, 4th, and 6th week compared to baseline [Table 2]. The reduction in pain was significant in patients receiving either medication, and also there was a good clinical response. Between the groups, reduction in VAS score was not statistically significant at any of the follow-up visits. In a study by Richy *et al*., piroxicam was similar in efficacy compared to other NSAIDs in reducing pain in patients with OA of the knee.[14] Allegrini *et al*. have reported that piroxicam

patch was effective compared to placebo in reducing pain due to OA of the lumbar vertebra.[15] Alho *et al*. study showed that piroxicam and naproxen were similar in efficacy when used for OA of the hip joint.[16] In this study, the intensity of pain experienced by the patients over 6 weeks is represented by the area under the curve and those receiving piroxicam (5.33) had marginally better pain relief compared to naproxen (5.45) at week 6 as shown in Figure 2.

The parameters of WOMAC depicting pain, stiffness, and physical function were significantly reduced in both groups at each follow-up compared to baseline [Table 3]. In this study, both the drugs significantly reduced WOMAC score at 2nd, 4th, and 6th week compared to baseline. Reduction in WOMAC score implies a reduction in pain, improvement in flexibility of joints, and range of movements. This helps the patient in carrying out day-to-day activities independently, thus reduction in this score indicates improvement in the QOL of the patients. There was no significant reduction in WOMAC scores between the groups during the follow-up period. In a study by Smith *et al*., it was observed that NSAIDs such as piroxicam and naproxen reduced pain similar to opioids in patients with OA of the knee.[17] Reduction in VAS and WOMAC scores to the same extent by both the drugs in our study implies that they are equally efficacious in reducing the symptoms and signs of OA.

We also assessed the PSS at 2nd, 4th, and 6th week. In both the groups, more number of patients expressed satisfaction as "Good" with the study medications. There was an improvement in PSS in both the groups from 2nd week to 4th and 6th week [Figure 3]. There was no significant difference in the satisfaction score between piroxicam and naproxen ($P = 0.10$). This shows that patients in both the groups had pain relief and were able to perform their regular activities with less dependence. Most of our patients were in the fifth decade of life during which they have to depend on their family members for support, since they could carry out their activities independently, their satisfaction scores improved.

In this study, both medications were well-tolerated, and adverse effects were mild in nature. The adverse effects such as epigastric discomfort, nausea, and vomiting, were observed with both the drugs, but the number was more with naproxen than piroxicam, and these manifestations were treated symptomatically. In the study done by Richy *et al*., patients with OA of knee observed that piroxicam caused lesser adverse effects compared to other NSAIDs except meloxicam. The adverse effects were less even with twice daily administration of piroxicam compared to once daily intake of other NSAIDs.[14]

Conclusion

The pain relief and patient satisfaction were similar with both the drugs but a number of adverse effects were less with piroxicam, suggesting it to be a better alternative to naproxen in patients with OA of knee joints.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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