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Original Article

# Comparative study of efficacy and safety of tapentadol versus etoricoxib in mild to moderate grades of chronic osteorthritis of knee

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ABSTRACT

*Objectives:* Chronic osteoarthritis of knee is very commonly encountered in clinical practice. Pain relief and restoration of physical function are the targets of therapy. This study aims to compare the efficacy and safety of tapentadol with etoricoxib in the management of osteoarthritis of knee.

*Methods:* This is a randomised, open labelled, controlled study in which patients received either tablet tapentadol (100 mg twice daily) or etoricoxib (30 mg twice daily) for 12 weeks. Follow-up was done after 2nd, 4th, 8th and 12th weeks of initiation of treatment and also after 2 weeks of treatment completion. Assessment of improvement in pain perception on Visual Analogue Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) sub-score for stiffness and physical function were performed.

*Results:* 108 patients receiving tapentadol and 110 patients receiving etoricoixb were analysed on Intention to Treat basis. Steady improvement was seen in VAS and WOMAC scores in both the groups, though there was no significant difference between the groups. Clinical Global Impression measured by physician showed significant difference between groups with greater number of patients experiencing at least satisfactory response at the end of the study in the tapentadol group ($p = 0.036$). The total number of adverse events was less with tapentadol than etoricoxib.

*Conclusions:* Tapentadol is as effective as etoricoxib in the management of mild to moderate grades of chronic osteoarthritis of knee with lower incidences of adverse effects.



## 1. Introduction

Osteoarthritis is a common type of arthritis, in which almost all structures of the joint undergo pathologic change. Hyaline articular cartilage loss is the most important pathologic feature, accompanied by increasing thickness and sclerosis of subchondral bony plate, outgrowth of osteophytes at the joint margin, stretching of articular capsule and mild synovitis. Joint vulnerability and joint loading are the two major risk

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factors for the development of osteoarthritis. Increasing age, female gender and genetic predisposition are other risk factors. Chronic osteoarthritis commonly affects cervical, lumbosacral spine, hip and knee joints.[1]

The goal of treatment in chronic osteoarthritis of knee is to minimise pain and loss of physical function. Therapy includes both non-pharmacological and pharmacologic measures. Weight reduction and exercise constitute an important part of therapy. Commonly prescribed medications for chronic osteoarthritis are acetaminophen, NSAIDs and cyclooxygenase-2 (COX-2) inhibitors.[1] Etorocoxib is a selective COX-2 inhibitor with better gastro-intestinal tolerability than non-selective NSAIDs. However, COX-2 inhibitors are associated with increased rate of cardiovascular events on long-term treatment. NSAIDs lead to salt and water retention in patients with cardiac, renal or hepatic co-morbidities.[2] Studies have shown etoricoxib as an efficacious alternative in the management of arthritis and pain, with the potential advantages of convenient once-daily administration and superior gastrointestinal tolerability compared with traditional NSAIDs.[3]

Tapentadol is a novel, centrally acting analgesic with μ-opioid receptor agonist and norepinephrine reuptake inhibitor activity within the pain pathways in the central nervous system. It is being used in chronic osteoarthritic pain of moderate to severe degree.[4,5]

Although both etoricoxib and tapentadol are used as analgesics in the treatment of chronic osteoarthritis, comparative data are sparse. The primary objective of our study is thus aimed to compare the efficacy and safety of tapentadol versus etoricoxib in chronic osteoarthritis of knee. The secondary objective was to assess the quality of life in the recruited patients.

## 2. Methods

Screening and recruitment of patients were carried out at the Rheumatology and Orthopaedics outpatient department of a tertiary care hospital during the period July 2012 to June 2013. Adult men and women within 40–60 years of age with primary, symptomatic osteoarthritis of tibio-femoral compartment of knee joint and fulfilling the American College of Rheumatology criteria[6] for diagnosis of knee osteoarthritis were recruited for the study. In patients having bilateral involvement, the more symptomatic knee was taken as the 'signal knee'. Radiographic examination in those included, showed presence of osteophytes in at least one tibio-femoral compartment in a radiograph taken not more than 6 months prior to the baseline visit.

Subjects with a history of hypersensitivity to tapentadol or etoricoxib, secondary osteoarthritis or accompanying osteoarthritis of hip and non-osteoarthritic causes of knee pain (e.g. bursitis, fibromyalgia, osteonecrosis, etc.) were excluded from the study. Also excluded were those suffering from serious or uncontrolled concomitant disease of liver, kidney, heart, thyroid, gastro-intestinal system, diabetes, HIV, malignancy. Patients using disease DMOADs (disease modifying osteoarthritis drug), corticosteroids or those, who had participated in any other clinical trial within the past 1 month were also not included. Secondary and non-osteoarthritic causes of knee pain were excluded by history, clinical examination and investigations such as ESR and CRP, plain radiograph of knee joints in all cases and MRI of knee joints in selected cases.

The study was conducted in accordance with the principles of the Declaration of Helsinki for Biomedical Research Involving Human Subjects. Also, every effort was made to adhere to the Good Clinical Practice Guidelines of the Government of India.[7] Written informed consent was mandatory for the recruitment of trial subjects. The study protocol, case record form and the patient informed consent form received clearance from the Institutional Ethics Committee.

A total number of 244 patients were enrolled for the study. For the purpose of sample size calculation, changes in a 100 mm Visual Analogue Scale (VAS) scores for 'pain on movement' during last 48 h was taken as the primary efficacy criteria. The study was designed to detect a difference of 1 mm in the VAS score between the two groups. The pooled standard deviation was calculated by a pilot study on 10 patients and was found to be 7. Assuming significance level ($\alpha$) of 0.05 and power of the study ($1 - \beta$) as 80%, the target sample size was found to be 222 (using WINPEPI version 11.39). Considering a 10% drop out rate, 244 subjects were to be recruited in total. They were randomised into two groups, 119 patients in group A and 125 patients in group B.

The study was designed as a unicentric, prospective, open label, randomised, controlled trial with two parallel treatment arms. Group A received tablet tapentadol 100 mg twice daily orally after meal for 12 weeks. Group B received tablet etoricoxib 30 mg twice daily orally after meal for 12 weeks. Provisions were made for up and down titration of the drugs depending on the symptoms.

The first visit (Visit 0) was the one during which, the patient was screened, which also served as the baseline visit, if he/she was not receiving any interacting drug. Otherwise a separate baseline visit was considered after a wash-out period of 2 weeks following withdrawal of the interacting drug. The treatment duration was for 12 weeks starting from the date of selection and recruitment of individual patient. Patient was investigated six times during the study. Visit 0 was the baseline visit on the day of recruitment. Thereafter Visit 1 was done on 2nd week, Visit 2 on 4th week, Visit 3 on 8th week and Visit 4 on 12th week. A follow-up visit was done 2 weeks after of stoppage of treatment to know the after-effect of the drugs. The total duration of the study was of 14 weeks for the individual patient.

Patients were asked to take commercially available study medications at the scheduled time points. As patients had to buy their medications, blinding could not be done. A trial diary was maintained by every patient. Patients enrolled in the study were not permitted to use any other analgesics, corticosteroids, 5-HT3 receptor antagonists or any other medication known to interact with or potentially alter the response to the study drugs.

At screening a thorough medical history was taken, and clinical examination of the subjects was performed to assess their suitability for participation in the study. Informed consent was obtained. Body weight, height, BMI, baseline resting pulse rate, respiratory rate and blood pressure were recorded on day 1 (Visit 0). Baseline Laboratory tests such as Hb%, TC, DC, ESR, platelet count, blood glucose (fasting), urea,