

SAFETY AND EFFICACY OF ACECLOFENAC IN OSTEOARTHRITIS PATIENTS

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HOW TO CITE THIS ARTICLE:

Anand R Kanaki, Ravi D Mala, Jeevangi Santosh Kumar, Prasanna Jewargi, Srinivas Raikar. "Safety and efficacy of aceclofenac in osteoarthritis patients". Journal of Evolution of Medical and Dental Sciences 2013; Vol. 2, Issue 42, October 21; Page: 8048-8055.

ABSTRACT: OBJECTIVE: The objective of this study was to study safety and efficacy of Aceclofenac in osteoarthritis patients. **MATERIAL AND METHODS:** The study included 29 males and 36 females in the age group of 40-60 years suffering from osteoarthritis. Patients were received Aceclofenac 100 mg twice daily after food. Clinical assessment was done at screening, after 1 month, 2 months and 3 months of treatment by calculating Western Ontario Mac Master (WOMAC) scores, time taken to walk 100 feet, Visual Analogue Scale Scores for pain, investigator's assessment on a LIKERT Scale and joint tenderness. Safety assessment was based on adverse effects. **RESULTS:** Aceclofenac was found significant improvement in their efficacy parameters of WOMAC scores, investigator's assessment and joint tenderness. Aceclofenac was found to be well tolerated in terms of G.I adverse effects. Compliance was also better with Aceclofenac. **CONCLUSIONS:** Aceclofenac is a safe, well tolerated and effective drug in osteoarthritis.

KEY WORDS: Aceclofenac, osteoarthritis, WOMAC Score, LIKERT Scale, VAS Score.

INTRODUCTION: Osteoarthritis (OA) is one of the most common, chronic, musculoskeletal disorder particularly affects the knee and hip joints in elderly people¹. OA rarely occurs before the age of 40 but by the age of 75 at least 85% of the populations have either clinical or radiographic evidence of osteoarthritis². Its prevalence after the age of 65 is about 60% in men and 70% in women³. OA is a disease of synovial joints characterized by cartilage loss with accompanying peri-articular bone response⁴. Cartilage is a protein substance that serves as a "Cushion" between the bones of the joints⁵. Osteoarthritis is also known as degenerative arthritis⁶. The term osteoarthritis implies an inflammatory disease⁷. OA is associated with pain and inflammation of the joint capsule, impaired muscular stability, reduced range of motion and functional disability⁸.

Risk factors for OA include advanced age⁹, female gender¹⁰, genetic predisposition¹¹, obesity¹², and joint injury including trauma, repetitive use, and prior inflammation. Genes that encode Collagen type II have been proposed as candidate genes for familial OA^{13, 14}. Radiographs can help confirm OA when the diagnosis is uncertain from clinical examination. It is usually not difficult to differentiate OA from a systemic rheumatic disease, such as rheumatoid arthritis, because joint involvement in the latter disease is usually symmetric and polyarticular, with arthritis in wrists and metatarsophalangeal joints (sites not usually involved in OA) and constitutional features such as prolonged morning stiffness, fatigue, weight loss, or fever may be seen¹⁵. Synovial fluid analysis reveals mild leukocytosis is i.e. with a predominance of mononuclear cells. Synovial fluid analysis is of particular value in excluding other conditions, such as calcium pyrophosphate dehydrates deposition disease, gout or septic arthritis¹⁶.

The 2000 American College of Rheumatology (ACR) Subcommittee on osteoarthritis Guidelines recommends that pharmacologic interventions be used only as adjuncts to Non-

Pharmacologic measures. The evidence supporting Non-Pharmacological therapies is sparse and is mainly limited to the treatment of knee osteoarthritis¹⁷. A Cochrane review from 2001¹⁸ concluded that land-based therapeutic exercise seemed to reduce pain and improves function in symptomatic osteoarthritis of the knee. Orally administered NSAIDs play an important role in the symptomatic management of osteoarthritis. It is estimated that more than 30 million people worldwide take NSAIDs¹⁹.

While NSAIDs are effective in the management of pain and inflammation in a large number of conditions including osteoarthritis, it is now well established that they are associated with the development of upper gastrointestinal (GI) damage including mucosal erosions, ulcers and life-threatening conditions like perforations and hemorrhage²⁰. This led to the development of cyclooxygenase-2 (COX-2) inhibitors. The potential advantage of COX-2 inhibitors is that they have fewer adverse effects on the gastrointestinal tract as a result of having less inhibitory effect on the gastro protective prostaglandins produced by COX-1 enzymes in the gastrointestinal tract. This advantage of COX-2 selective NSAIDs has been demonstrated in many trials^{21, 22}.

However, the cardiovascular safety of these drugs was found to be controversial. Three independent randomized trials and a cumulative meta-analysis²³ confirmed excess cardiovascular risk as well as serious skin reactions were also seen with Rofecoxib and valdecoxib²⁴. A preferential COX-2 inhibitor is expected to be safer than a conventional NSAID in its propensity to cause GI adverse effects, and at the same time, unlike highly selective COX-2 inhibitors, it will not leave COX-1 activity unopposed and thus may have reduced propensity for cardiovascular adverse events²⁵.

Aceclofenac is an effective analgesic and anti-inflammatory agent provides symptomatic relief in a variety of painful conditions²⁶. Aceclofenac appears to be particularly well tolerated among the NSAIDs with a lower incidence of gastro intestinal adverse effects. This good tolerability profile results in a reduced withdrawal rate and greater compliance with treatment²⁷. Aceclofenac inhibits synthesis of the inflammatory cytokines like interleukin (IL)-1, Tumor necrosis factor (TNF), and Prostaglandin E2 (PGE2) production²⁸. Since long-term NSAID treatment is indicated for osteoarthritis, the ideal agent should have good efficacy and a low propensity to cause adverse events. Hence the present study was carried out in osteoarthritis patients to evaluate the safety and efficacy of Aceclofenac.

MATERIALS AND METHODS: The patients were recruited after obtaining their informed consent. The study protocol was approved by the Institutional Ethics Committee of M.R. Medical College, Gulbarga, Karnataka. The study recruited 65 osteoarthritis patients of which 29 were male and 36 female patients. The age of the patients were ranged between 40-60 years, suffering from the OA for at least 6 months. In this study demographic characteristic such as age, sex and diagnosis were recorded (Table 1). A thorough general physical examination was done. Laboratory investigations such as Complete blood count, LFT, Serum electrolytes, Serum creatinine, RBS, Urine analysis, Stool occult blood and X-ray of the knee joint were carried out before drug administration and after the completion of treatment.

Eligible Patients received Aceclofenac 100 mg twice daily were administered orally for 3 months.

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Inclusion criteria: 1. Male and female patients who were ≥ 40 years of age. 2. Radiological diagnosed with osteoarthritis of the knee. 3. With a minimum Western Ontario Mac Master (WOMAC) Index score of 40, Visual Analogue Scale (VAS) score of 4 mm. 4. Whose disease status worsened by at least one point on the 0-4 LIKERT Scale.

Exclusion criteria: 1. Patients with a history or showing the presence of other Rheumatic disease that would be responsible for secondary osteoarthritis. 2. Patients with a history of peptic ulcers. 3. Patient with a history of bleeding disorders. 4. Patients with renal impairment. 5. Alcoholic liver disease. 6. Pregnant or lactating woman. 7. Uncontrolled medical conditions like Severe Anemia, Hypertension, Congestive cardiac failure and Bronchial asthma. 8. History of hypersensitivity to Aceclofenac or other NSIADs. 9. Patient who had previously received Aceclofenac was also excluded from the study.

Clinical examination was done at screening after 1, month, 2 month and 3 month. The outcome of the therapy was based on the improvement of the clinical manifestations of osteoarthritis and tolerability of the drug.

Clinical Assessments: Clinical assessment was done by calculating WOMAC scores²⁹, time taken to walk a distance of 100 feet, Visual Analogue Scale Scores³⁰ for pain, investigator's assessment on a LIKERT scale³¹ and joint tenderness. Tolerability assessment was based on adverse events as well as compliance. Adverse events were monitored and noted at every visit.

Statistical Analysis: For parametric data, Student's t-test and Chi-square goodness-of-fit tests were used, whereas for non-parametric data RIDIT analysis was used.

RESULTS:

Parameters	Aceclofenac Group (n = 65)
No. of patients	65
Male: Female	29:36
Age (years)	53.63 \pm 5.23
Weight (Kg)	62.18 \pm 9.26
Pulse (Rate/min)	77.06 \pm 6.49
Systolic BP (mmHg)	117.81 \pm 10.99
Diastolic BP (mmHg)	78.21 \pm 7.12
Respiratory (Rate/min)	16.66 \pm 0.90
Patient with edema	0

Table 1: Demographic data (mean \pm SD)

Parameters	Aceclofenac
WOMAC score	52.1568 \pm 11.52588
Time taken to walk 100 feet (sec)	79.9570 \pm 44.9455
Symptom scores for pain on 0-10 VAS	
Weight bearing	5.4729 \pm 3.652
Pain at rest Active	4.379 \pm 1.763585
	5.2365 \pm 2.02

Table 2: Screening visit parameters (mean \pm SD)

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	Aceclofenac group
Baseline	50.65 ± 12.12
1 st Month	40.45 ± 10.38
2 nd Month	34.29 ± 9.74
3 rd Month	27.41 ± 9.91

Table 3: WOMAC scores at baseline and after 1, 2 and 3rd month treatment (mean ± SD)

	Aceclofenac
Baseline	96.69 ± 18.28
1 st Month	91.68 ± 16.70
2 nd Month	84.75 ± 20.03
3 rd Month	79.42 ± 15.93

Table 4: Time (in seconds) taken to walk 100 feet in distance baseline and after 1st month, 2nd month and 3rd month.

Pain on weight bearing	Aceclofenac group	
	Left Knee	Right Knee
Baseline	5.29 ± 1.83	5.11 ± 1.90
1 st month	4.30 ± 1.76	4.15 ± 1.89
2 nd month	3.53 ± 1.55	3.32 ± 1.64
3 rd month	2.57 ± 1.40	2.43 ± 1.41

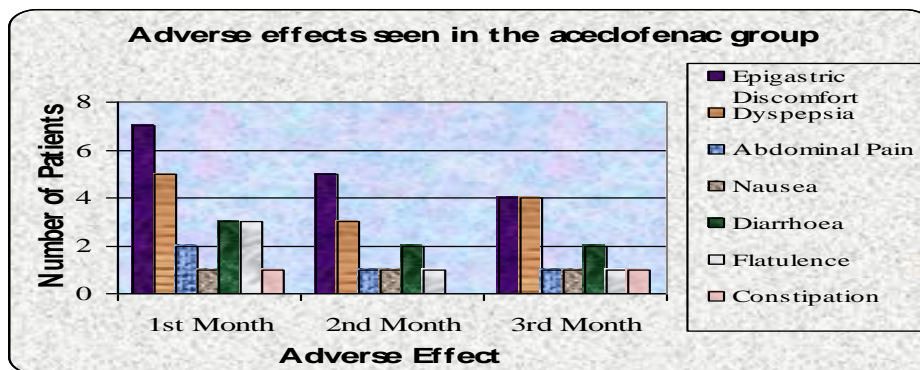
Table 5: Visual analogue scale (VAS) scores for pain at baseline and after 1st month, 2nd month and 3rd month treatment (mean ± SD)

		Aceclofenac n [%]
Efficacy*	High	41 (63%)
	Moderate	18(27%)
	Mild	2(3%)
Safety*	Good	44(67%)
	Moderate	17(26%)
	Poor	0(0%)

Table 6: Outcome of therapy (efficacy and safety) as assessed by the Physician after 3rd month of treatment.

Adverse effects: Less common adverse events were cough, constipation, headache and rhinorrhea. No clinically significant biochemical changes were observed in any of the patients.

Adverse effects seen with the Aceclofenac



Safety: With regard to safety, Aceclofenac was found to be safe in terms of Epigastric discomfort, dyspepsia and abdominal pain. Patient's compliance was also better with Aceclofenac. Physician rating of treatment showed Aceclofenac was statistically safe and well tolerated.

DISCUSSION: Until recently the new COX-2 selective inhibitors have been increasingly used. They have equal efficacy to standard NSAIDs. However the cardiovascular safety of these drugs was found to be controversial^{32, 33}. Aceclofenac has been evaluated in international studies and is indicated for

the relief of pain and inflammation associated with rheumatoid arthritis, osteoarthritis or Ankylosing spondylitis³⁴. This study evaluates its efficacy and safety in patients with osteoarthritis. Aceclofenac has also shown stimulatory effects on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL-1. IL-1 suppresses various growth factors. Inhibition of IL-1 thus stimulates synthesis of cartilage matrix. There is also evidence that Aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human articular chondrocytes subjected to inflammatory stimuli³⁵ and that 4'-hydroxyaceclofenac has chondro protective properties attributable to suppression of IL-1 mediated promatrix metalloproteinase production and proteoglycan release^{36,37}. Thus Aceclofenac may prevent the degradation of articular connective tissue in patients with rheumatoid arthritis and osteoarthritis, and should be classified as a unique NSAID.

Based on the findings of the study provides evidence that Aceclofenac is effective in the treatment of osteoarthritis. However, Aceclofenac was found to be statistically significant in certain aspects of efficacy such as WOMAC scores, investigator's assessment and joint tenderness. Aceclofenac was found to be statistically significant in terms of epigastric discomfort, dyspepsia, abdominal pain and compliance.

There is no significant change in the parameters of laboratory investigations including complete blood count, serum creatinine, blood urea, Serum electrolytes, RBS, LFT, RFT, urine analysis, stool occult blood before and after the treatment.

Whether Aceclofenac may have less propensity to cause cardiovascular adverse events due to its preferential COX-2 inhibition^{38, 39}, will need further evaluation. Aceclofenac may be an alternative to non-selective NSAIDs as well as to selective COX-2 inhibitors for the treatment of patients with osteoarthritis or rheumatoid arthritis.

CONCLUSION: Aceclofenac has anti-inflammatory, analgesic properties and gastrointestinal damage is less. This may be due to preferential inhibition of COX-2. This study shows that Aceclofenac is a safe, effective and well tolerated drug for osteoarthritis.

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Date of Submission: 18/09/2013.

Date of Peer Review: 19/09/2013.

Date of Acceptance: 09/10/2013.

Date of Publishing: 15/10/2013