COMPARATIVE STUDY OF SAFETY, EFFICACY, AND TOLERABILITY OF ACECLOFENAC VERSUS DICLOFENAC IN OSTEOARTHRITIS PATIENTS.

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ABSTRACT: OBJECTIVE: The objective of this study was to compare safety, efficacy and tolerability of Aceclofenac verses diclofenac in osteoarthritis patients. **MATERIAL AND METHODS:** The study included 57 males and 70 females in the age group of 40-60 years suffering from osteoarthritis. Patients were received Aceclofenac 100 mg twice daily and diclofenac 75 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. Tolerability assessment was based on adverse effects. **RESULTS:** Aceclofenac was found to be statistically superior over diclofenac in efficacy parameters of WOMAC scores, investigator's assessment and joint tenderness. Aceclofenac was found to be statistically more superior to diclofenac in terms of G.I adverse effects. Compliance was also better with Aceclofenac. **CONCLUSIONS:** Aceclofenac is a safe, well tolerated and effective drug as compared to Diclofenac in Osteoarthritis.

INTRODUCTION: Osteoarthritis (OA) is one of the most common, chronic, musculoskeletal disorder particularly affects the knee and hip joints in elderly people[1].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 osteoarthritis[2]. Its prevalence after the age of 65 is about 60% in men and 70% in women[3].OA is a disease of synovial joints characterized by cartilage loss with accompanying peri-articular bone response[4]. Cartilage is a protein substance that serves as a "Cushion" between the bones of the joints[5]. Osteoarthritis is also known as degenerative arthritis[6]. The term Osteoarthritis implies an inflammatory disease[7].OA is associated with pain and inflammation of the joint capsule, impaired muscular stability, reduced range of motion and functional disability[8].

Risk factors for OA include advanced age[9], female gender[10], genetic predisposition[11], obesity[12], 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 seen[15]. 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 arthritis[16].

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-Pharmacologic therapies is sparse and is mainly limited to the treatment of knee osteoarthritis[17].A Cochrane review from 2001[18] 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 NSAIDs[19].

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 hemorrhage[20].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-analysis[23] confirmed excess cardiovascular risk as well as serious skin reactions were also seen with Rofecoxib and valdecoxib[24].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 events[25].

Aceclofenac is an effective analgesic and anti-inflammatory agent provides symptomatic relief in a variety of painful conditions[26].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 treatment[27].Aceclofenac inhibits synthesis of the inflammatory cytokines like interleukin (IL)-1, Tumor necrosis factor (TNF), and Prostaglandin E2 (PGE2) production[28]. 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, efficacy and tolerability of Aceclofenac verses Diclofenac.

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 127 osteoarthritis patients of which 57 were male and 79 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 physical examination and laboratory investigations including 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 were randomized into two treatment groups. Aceclofenac Group (n = 65) Diclofenac Group (n = 62). Patients received Aceclofenac 100 mg twice daily & Diclofenac 75 mg twice daily were administered orally for 3 months.

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. 3Patient 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, Diclofenac or other NSIADs.9.Patient who had previously received diclofenac / 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 scores[29], time taken to walk a distance of 100 feet, Visual Analogue Scale Scores[30] for pain, investigator's assessment on a LIKERT scale[31] 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:

Table 1: Demographic data in the treatment groups (mean ± SD)

Parameters	Aceclofenac Group (n = 65)	Diclofenac Group (n = 62)	Test statistics
No. of patients	65	62	----
Male: Female	29:36	28:34	----
Age (years)	53.63 ± 5.23	53.83 ± 4.92	P>0.05
Weight (Kg)	62.18 ± 9.26	64.11 ± 8.40	P>0.05
Pulse (Rate/min)	77.06 ± 6.49	78.62 ± 5.74	P>0.05
Systolic BP (mmHg)	117.81 ± 10.99	118.87 ± 9.45	P>0.05
Diastolic BP (mmHg)	78.21 ± 7.12	79.54 ± 6.59	P>0.05
Respiratory (Rate/min)	16.66 ± 0.90	16.70 ± 0.83	P>0.05
Patient with edema	0	0	----

Table 2. Screening visit parameters in the treatment groups (mean ± SD)

Parameters	Aceclofenac group	Diclofenac group
WOMAC score	52.1568 ± 11.52588	53.4342 ± 12.60159
Time taken to walk 100 feet (sec)	79.9570 ± 44.9455	89.3088 ± 43.05394
Symptom scores for pain on 0-10 VAS	5.4729 ± 3.652	5.4423 ± 20.09821
Weight bearing	4.379 ± 1.763585	4.4886 ± 1.74852
Pain at rest Active	5.2365 ± 2.02	5.4128 ± 2.128356

Table 3.WOMAC scores in the two treatment groups at baseline and after 1, 2 and 3rd month treatment (mean ± SD)

	Aceclofenac group	Diclofenac group	Unpaired t-test p-value
Baseline	50.65 ± 12.12	51.77 ± 12.75	> 0.05
1st Month	40.45 ± 10.38	46.74 ± 10.66	< 0.0001
2nd Month	34.29 ± 9.74	41.38 ± 11.78	< 0.0001
3rd Month	27.41 ± 9.91	34.97 ± 12.64	< 0.0001

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

	Aceclofenac group	Diclofenac group	Unpaired t-test
Baseline	96.69 ± 18.28	98.77 ± 18.18	0.371 (NS)
1st Month	91.68 ± 16.70	91.80 ± 14.65	0.948 (NS)
2nd Month	84.75 ± 20.03	86.60 ± 14.07	0.4011 (NS)
3rd Month	79.42 ± 15.93	82.10 ± 14.58	0.2339 (NS)

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

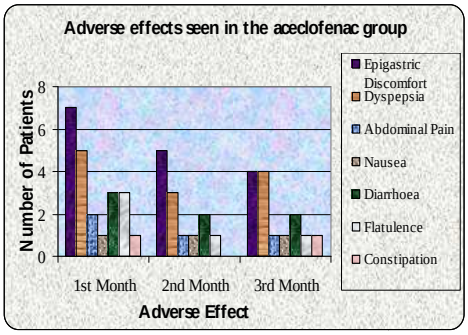
	Aceclofenac group		Diclofenac group	
	Left Knee	Right Knee	Left Knee	Right Knee
Pain on weight bearing				
Baseline	5.29 ± 1.83	5.11 ± 1.90	5.43 ± 2.04	5.12 ± 1.97
1st month	4.30 ± 1.76	4.15 ± 1.89	4.97 ± 1.87	4.69 ± 1.94
2nd month	3.53 ± 1.55	3.32 ± 1.64	4.34 ± 1.71	4.22 ± 1.83
3rd month	2.57 ± 1.40	2.43 ± 1.41	3.62 ± 1.55	3.42 ± 1.65

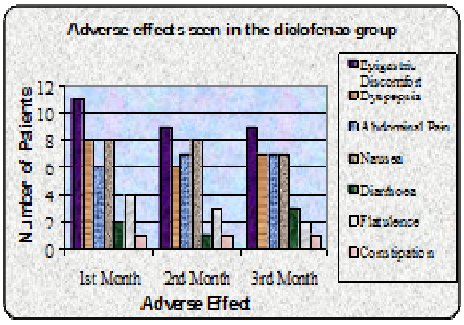
Table 6. Outcome of therapy (efficacy and tolerability) as assessed by the Physician in the two treatment groups after 3rd month of treatment.

		Aceclofenac n [%]	Diclofenac n [%]
Efficacy*	High	41 (63%)	18(29%)
	Moderate	18(27%)	23(37%)
	Mild	2(3%)	18(29%)
Tolerability*	Good	44(67%)	22(35%)
	Moderate	17(26%)	26(41%)
	Poor	0(0%)	11(17%)

ADVERSE EFFECTS: One patient in the Diclofenac group reported skin rash and one patient had severe gastrointestinal symptoms. 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 in the Aceclofenac group Adverse effects seen in the Diclofenac group





Tolerability: With regard to tolerability, Aceclofenac was found to be superior to diclofenac in terms of epigastric discomfort, dyspepsia and abdominal pain, whereas no statistically significant difference was observed in terms of diarrohea, nausea, flatulence or constipation. Patient's compliance was also better with Aceclofenac. Physician rating of treatment showed Aceclofenac was statistically superior to diclofenac.

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 spondylitis[34]. This study not only evaluates its efficacy and tolerability in patients but also compare it with diclofenac which is of the widely used drug for chronic pain[35].

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. In vitro data show stimulation by Aceclofenac of glycosaminoglycan synthesis in human osteoarthritic cartilage. There is also evidence that Aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human articular chondrocytes subjected to inflammatory stimuli[36] and that 4'-hydroxyaceclofenac has chondro protective properties attributable to suppression of IL-1 mediated promatrix metalloproteinase production and proteoglycan release[37,38].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 as effective as diclofenac in the treatment of osteoarthritis. However, Aceclofenac was found to be statistically superior to diclofenac certain aspects of efficacy such as WOMAC scores, investigator's assessment and joint tenderness. The main difference is in terms of tolerability, wherein Aceclofenac was found to be statistically superior to diclofenac in terms of epigastric discomfort, dyspepsia, abdominal pain and Compliance.

Whether Aceclofenac may have less propensity to cause cardiovascular adverse events due to its preferential COX-2 inhibition[39, 40], will need further evaluation. Aceclofenac may be an

alternative to non-selective NSIADs as well as to selective COX-2 inhibitors for the treatment of patients with osteoarthritis or rheumatoid arthritis.

CONCLUSION: Since long term NSAID treatment is indicated for osteoarthritis, the ideal agent should have good efficacy and a low propensity to cause adverse events. Aceclofenac has anti-inflammatory and analgesic properties similar to those of diclofenac and gastrointestinal damage is less than that of diclofenac. 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.

BIBLIOGRAPHY:

1. Walker-Bone K, Javaid K, Arden N, et al. Regular review: medical management of osteoarthritis. BJM 2000; 321: 936-40.
2. Jämsen E, Jäntti P, Puolakka T, et al. Primary knee replacement for primary osteoarthritis in the aged: gender differences in epidemiology and preoperative clinical state.Aging Clin Exp Res. 2012 Dec;24(6):691-8.
3. Sarzi-Puttini P, Cimmino MA, Scarp R, et al. Osteoarthritis: an overview of the disease and its treatment strategies. Semin Arthritis Rheum 2005; 35: 1-10.
4. Kumar & Clerk. 5th Edition, M. Shipley, CM Black, J Compston & D O Gradiagh. Clinical Medicine. Page No. 533.
5. Medicinenet.com/ Osteoarthritis/ article.html.2007. William C., Shiel J., MD.
6. Liu-Bryan R Synovium and the innate inflammatory network in osteoarthritis progression. Curr Rheumatol Rep. 2013 May;15(5):323. doi: 10.1007/s11926-013-0323-5.
7. Fadda SM, Gamal SM, Elsaid NY et al . Resistin in inflammatory and degenerative rheumatologic diseases: Relationship between resistin and rheumatoid arthritis disease progression.Z Rheumatol. 2013 Mar 9. 18.
8. Bjordal JM, Ljunggren AE, Klovning A, et al. Non-steroidal anti-inflammatory drugs, inciding cyclo-oxygenase-2 inhibitors, in osteoarthritis knee pain: meta-analysis of randomized placebo controlled trials. BMJ 2004; 329: 1317.
9. Hagen ND, Olson T, Millett P. Comprehensive post-arthroscopic management of a middle-aged adult with glenohumeral osteoarthritis: a case report.Int J Sports Phys Ther. 2013 Feb;8(1):54- 61.
10. Macrini TE, Coan HB, Levine SM, Lerma T et al. Reproductive status and sex show strong effects on knee OA in a baboon model. Osteoarthritis Cartilage. 2013 Mar 11.
11. Haseeb A, Haqqi TM. Immunopathogenesis of osteoarthritis. Clin Immunol. 2013 Mar;146(3):185-96.
12. Koonce RC, Bravman JT. Obesity and osteoarthritis: more than just wear and tear. J Am Acad Orthop Surg. 2013 Mar; 21(3):161-9.
13. Seki K, Fujimori T, Savagner P et al. Mouse Snail family transcription repressors regulate chondrocyte, extracellular matrix, type II collagen, and aggrecan. J Biol Chem. 2003 Oct 24; 278(43):41862-70.
14. 14.Li G, Han N, Li Z, Lu Q. Identification of transcription regulatory relationships in rheumatoid arthritis and osteoarthritis. Clin Rheumatol. 2013 Jan 8.
15. Duncan AE, Colman RJ, Kramer PA. Longitudinal study of radiographic spinal osteoarthritis in a macaque model. J Orthop Res. 2011 Aug; 29(8):1152-60.

16. Liao W, Li Z, Wang H, Wang J, et al. Proteomic analysis of synovial fluid: insight into the pathogenesis of knee osteoarthritis. Int Orthop. 2013 Mar 28.
17. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Arthritis Rheum 2000; 43: 1905-15.
18. Fransen M, McConnell S, Bell M. Exercise for osteoarthritis of the hip or knee. In: The Cochrane Library, Issue 3. Chichester, UK: John Wiley and Sons; 2004.
19. McCarberg B, Tenzer P. The complexities in the pharmacologic management of osteoarthritis pain. Curr Med Res Opin. 2013 Mar 14.
20. Essex MN, Bhadra P, Sands GH. Efficacy and tolerability of celecoxib versus naproxen in patients with osteoarthritis of the knee: a randomized, double-blind, double-dummy trial. J Int Med Res. 2012; 40(4):1357-70.
21. Goldstein JL, Correa P, Zhao WW, et al. Reduced incidence of gastroduodenal ulcers with celecoxib, a novel cyclooxygenase-2 inhibitors, compared to naproxen in patients with arthritis. Am J Gastroenterol 2001; 96: 1019-27.
22. Hawkey C, Laine L, Simon T, et al. Comparison of the effect of rofecoxib (a cyclooxygenase-2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. The Rofecoxib Osteoarthritis Endoscopy Multinational Study Group. Arthritis Rheum 2000; 43: 370-7.
23. Juni P, Nartey L, Reichenbach S, et al. Rosk of cardiovascular events and refecoxib: cumulative meta-analysis. Lancet 2004; 364: 2021-9.
24. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005; 352: 1081-91.
25. Donnelly MT, Hawkey CJ. Review article: COX-II inhibitors--a new generation of safer NSAIDs? Aliment Pharmacol Ther. 1997 Apr; 11(2):227-36.
26. Dooley M, Spencer CM, Dunn CJ. Aceclofenac: a reappraisal of its use in the management of pain and rheumatic disease. Drugs. 2001; 61: 1351-78.
27. Legrand E. Aceclofenac in the management of inflammatory pain. Expert Opin Pharmacother 2004; 5: 1347-57.
28. Maneiro E, López-Armada MJ, Fernández-Sueiro JL,et al. Aceclofenac increases the synthesis of interleukin 1 receptor antagonist and decreases the production of nitric oxide in human articular chondrocytes. J Rheumatol. 2001 Dec; 28(12):2692-9.
29. Torres-Claramunt R, Leal J, Hinarejos P et al. Correlation Study Between KSS, WOMAC and SF-36 Scores in Patients Undergoing Total Knee Arthroplasty in a Spanish Speaking Population. J Arthroplasty. 2013 Mar 21. S0883-5403(13)00071-5.
30. Hutchison AM, Pallister I, Evans RM, et al. Intense pulsed light treatment of chronic mid-body Achilles tendinopathy: A double blind randomised placebo-controlled trial. Bone Joint J. 2013 Apr 1; 95-B (4):504-9.
31. Parmigiani L, Furtado RN, Lopes RV, et al. Joint lavage associated with triamcinolone hexacetonide injection in knee osteoarthritis: a randomized double-blind controlled study. Clin Rheumatol. 2010 Nov; 29(11):1311-5.
32. Bäck M, Yin L, Ingelsson E. Cyclooxygenase-2 inhibitors and cardiovascular risk in a nation-wide cohort study after the withdrawal of rofecoxib. Eur Heart J. 2012 Aug; 33(15):1928-33.

33. Carman WJ, Su S, Cook SF, et al. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiol Drug Saf. 2011 Jul; 20(7):754-62.
34. Pareek A, Chandurkar N, Gupta A, et al. Efficacy and safety of Aceclofenac-cr and Aceclofenac in the treatment of knee osteoarthritis: a 6-week, comparative, randomized, multicentric, double-blind study. 2011 May; 12(5):546-53.
35. Pareek A, Chandurkar N, Sharma VD et al. A randomized, multicentric, comparative evaluation of Aceclofenac-paracetamol combination with Aceclofenac alone in Indian patients with osteoarthritis. Expert Opin Pharmacother. 2009 Apr; 10(5):727-35.
36. Maneiro E, Lopez-Armada MJ, Fernandez-Sueiro JL, et al. Aceclofenac increases the synthesis of interleukin 1 receptor antagonist and decreases the production of nitric oxide in human articular chondrocytes. J Rheumatol 2001; 28: 2692-9.
37. Akimoto H, Yamazaki R, Hashimoto S, et al. 4-Hydroxy-aceclofenac suppresses the interleukin-1 induced production of promatrix metalloproteinases and release of sulfated-glycosaminoglycans from rabbit articular chondocytes. Eur J Pharmacol 2000; 401: 429-36.
38. Yamazaki R, Kawai S, Mizushima Y, et al. A major metabolite of Aceclofenac, 4-hydroxyaceclofenac, suppresses the production of interstitial pro-collagenase/ ProMMP-1 and prostro-melysin-1/ proMMP-3 by human rheumatoid synovial cells. Inflamm Res 2000; 49: 133-8.
39. Pavelka K. A comparison of the therapeutic efficacy of diclofenac in osteoarthritis: a systematic review of randomised controlled trials. Curr Med Res Opin. 2012 Jan; 28(1):163-78.
40. Paul S, Das N, Ghosh S. The effects of Aceclofenac and nabumetone in osteoarthritis. JNMA J Nepal Med Assoc. 2009 Apr-Jun; 48(174):121-5.