ORIGINAL RESEARCH

Effectiveness of aceclofenac, diclofenac and paracetamol in osteoarthritis

[1]Dr. Prakash Gundagatti, [2]Dr. Sareetha AV

[1]Associate Professor, Department of General Medicine, SSIMS & RC, Davangere, Karnataka, India
[2]Assistant Professor, Department of Pharmacology, Ambedkar Medical College, Bangalore, Karnataka, India

Corresponding Author
Dr. Sareetha AV
Assistant Professor, Department of Pharmacology, Ambedkar Medical College, Bangalore, Karnataka, India

Received: 02 Sept, 2023 Accepted: 25 Sept, 2023

Abstract
NSAIDs are the cornerstone effective anti-inflammatory and analgesics recommended to alleviate persistent osteoarthritic pain and inflammation. NSAIDs such as Ibuprofen, Diclofenac, Aceclofenac, Celecoxib are in wide use and frequently available in over the counter formulations. A detailed history, complete physical examination and routine investigations were done for all the subjects. The subjects who met the eligibility criteria were randomized in 1:1:1 into 3 groups of 80 each, to receive standard dose of either Aceclofenac, Diclofenac, or Paracetamol as per the age and weight respectively for 6 weeks after obtaining their informed consent. On 6th week, the percentage of subjects responded to study medication with regards to pain and movement was higher in Aceclofenac group (48.8%) than compared to subjects treated with Diclofenac (37.5%) and Pracetamol (12.5%). Both Aceclofenac (53%) and Diclofenac (53%) treated subjects equally showed extreme response to the treatment with score 4 by Likert scale on 10th week compared to Paracetamol group (20%).

Keywords: Aceclofenac, diclofenac, paracetamol, osteoarthritis

Introduction

The American College of Rheumatology (ACR) states guidelines for the treatment of OA which include non-pharmacological methods like patient education, physical & occupational therapy and other therapies for mild symptomatic OA.[1]

The pharmacological therapy includes various classes of drugs for oral, topical and intra-articular administration. Commonly prescribed are Non-steroidal anti-inflammatory drugs (NSAIDs). A corticosteroid injection is recommended when evidence of inflammation with joint effusion are present. Narcotics are reserved for severe cases.

Paracetamol is the initial analgesic of choice for pain management in OA. Paracetamol, a metabolite of phenacetin, is in use since 19th century. It selectively inhibits cyclo-oxygenase enzyme (COX-3) in central nervous system (CNS) and elicits potent analgesic property[16] although there is evidence of risk of hepatotoxicity with higher doses.[2]

Alternatively, NSAIDs are the cornerstone effective anti-inflammatory and analgesics recommended to alleviate persistent osteoarthritic pain and inflammation. NSAIDs such as Ibuprofen, Diclofenac, Aceclofenac, Celecoxib are in wide use and frequently available in over the counter formulations. However, the use of non-selective NSAIDs is in question due to the appearance of significant upper gastrointestinal (GI) and cardiovascular (CV) adverse events (AEs).[3]

Diclofenac, an NSAID, a phenyl acetic acid derivative, inhibits COX 2 with greater potency; is in use since 1973. It has extended tissue penetrability and greater distribution in synovial joint, proven to be effective and well tolerated in OA. However, its gastric toxicities like epigastric pain, gastric ulceration and bleeding limits its long term use.

Aceclofenac, a prodrug of Diclofenac is widely used in OA. In contrast to Diclofenac, it enhances the glycosaminoglycan (GAG) synthesis and suppresses the metalloproteinase and proteoglycan release which results in chondroprotective benefit and has reliable gastro protective safety profile.[4]

An estimate of 40% of people aged more than 65 years are prescribed one or more NSAIDs per year. However, the availability of NSAIDs over the counter has increased the exposure of NSAIDs to larger population.

Since NSAIDs and Paracetamol are effective for short relief of OA pain, and are most commonly used in OA management, the ideal agent should have good efficacy and low propensity to cause adverse events. Hence, this study was carried out to compare the

effectiveness, safety and of Aceclofenac, Diclofenac and Paracetamol in osteoarthritis patients.

Results

Source of data: Confirmed Osteoarthritis patients in the Department of Orthopaedics.

Study design: Prospective, randomized, open-labelled active controlled study.

Study duration: 1 year.

Sample size: 240 patients.

Method of collection of data

The study was initiated after obtaining approval from the Institutional Ethics Committee. A total of 240 patients with confirmed OA were recruited for the study. Informed, written consent was obtained from all subjects.

Procedure

A detailed history, complete physical examination and routine investigations were done for all the subjects. The subjects who met the eligibility criteria were randomized in 1:1:1 into 3 groups of 80 each, to receive standard dose of either Aceclofenac, Diclofenac, or Paracetamol as per the age and weight respectively for 6 weeks after obtaining their informed consent.

After randomization, each subject received the allotted drug with instructions as per the scheduled dosage and all the subjects were also instructed to continue the physical activity and physical therapy.

If the treatment response was found to be inadequate at any time point, subjects would be withdrawn from the study and will be switched to another suitable treatment. Patients were assessed at 3 visits i.e., at base line, 6 weeks and 10 weeks.

Inclusion Criteria

Patients aged > 40 years of either sex with confirmed osteoarthritis involving any joint.

Exclusion criteria

1. Patients with co-morbidities like renal / hepatic/ coagulation disorder.
2. Patients with hypersensitivity to NSAIDs.
3. Patients who require concomitant therapy with drugs (such as Warfarin, Aspirin, Corticosteroids, and Antiepileptics).
4. Pregnant and lactating women.
5. Patients with Rheumatic arthritis (RA), Gout.
6. All unstable patients suffering from any serious ailments.
7. Patients scheduled for Knee replacement therapy.

Clinical Assessment: Efficacy was assessed by evaluating subjects for Visual Analogue Score (VAS) for pain, Western Ontario McMaster (WOMAC) score for functionality of the joint and overall response to the study medication was rated by investigator on Likert scale at every clinical visit.

Results

Table 1: Comparison of pain by VAS

VAS Score	Aceclofenac Group I	Diclofenac Group II	Paracetamol Group III	p value
Base line	53.25±13.85	57.00±14.27	58.50±13.42	
6th week	40.25±12.92	43.00±11.95	22.75±13.02	<0.001**
10th week	10.38±10.49	9.00±10.98	10.53±6.69	
p value	<0.001**	<0.001**	<0.001**	-

p<0.001**: Strongly significant

Significantly greater reduction of mean pain score was reported in Paracetamol treated patients at 6 weeks compared to those treated on Aceclofenac and Diclofenac (22.75±13.02 vs. 40.25±12.92 and 43.00±11.95 respectively; *p*<0.001).

On 10th week, the mean VAS score was similar in all the groups of Aceclofenac, Diclofenac and Paracetamol with mean score of 10.38±10.49, 9.00±10.98 and 10.53±6.69 respectively. There was no statistical difference between the groups.

The results proclaim that statistical significance with VAS score of pain prevailed on 6th week. On 10th week, the mean VAS score was more or less equal in all the groups without any statistical significance.

Table 2: Comparison of WOMAC SCORE on pain domain

Pain Domain	Aceclofenac Group I	Diclofenac Group II	Paracetamol Group III	p value
Base line	13.18±0.67	12.21±1.27	13.21±0.87	-
6th week	9.28±0.91	8.16±0.99	7.43±1.17	-
10th week	4.05±1.02	4.56±4.70	6.98±1.12	<0.001**
p value	<0.001**	<0.001**	-	-

The reduction in mean WOMAC score in pain domain was similar in 3 groups of Aceclofenac, Diclofeanc and Paracetamol with Mean scores of (9.28±0.91, 8.16±0.99, 7.43±1.17) respectively. There was no statistical significant difference between the groups on 6th week.

The effect was evident on 10th week with a mean score of (4.05±1.02), (4.56±4.70) versus (6.98±1.12)

in Aceclofenac group, Diclofenac group versus Paracetamol group respectively (p= <0.001).

Analysis of mean change in WOMAC score in pain domain from base line gives statistically significant improvement to treatment on 6th week and on 10th week (p<0.001) in the Aceclofenac group and Diclofenac group.

Table 3: Comparison of WOMAC SCORE on stiffness domain

Stiffness Domain	Aceclofenac Group I	Diclofenac Group II	Paracetamol Group III	p value
Base line	1.93±0.98	2.15±1.01	2.10±0.91	0.304
6th week	0.66±0.62	0.86±0.57	0.65±0.62	0.045*
10th week	0.26±0.50	0.35±0.48	0.33±0.47	0.499
p value	<0.001**	<0.001**	<0.001**	-

At base line, there was no statistically significant difference in WOMAC score in stiffness between the three groups (1.93±0.98, 2.15±1.01, 2.10±0.91; p=0.304). Improvement in stiffness was highest in Aceclofenac group on 10th week (0.26±0.50 vs. 1.93±0.98) when compared to the baseline. However, on 10th week, all the drugs were found to be equal in reducing the stiffness (p=0.499).

Table 4: Comparison of WOMAC SCORE on difficulty in performing physical activity domain

Difficulty in performing physical activity domain	Aceclofenac Group I	Diclofenac Group II	Paracetamol Group III	p value
Base line	47.28±1.60	46.33±2.30	45.44±2.97	-
6th week	36.20±2.52	38.14±2.98	37.08±5.07	-
10th week	25.29±2.12	30.23±3.67	32.30±2.70	<0.001**
p value	<0.001**	<0.001**	-	-

The WOMAC score on difficulty in performing physical activity domain showed significant improvement on 10th week in comparison to base line in all the three groups (p<0.001). The reduction in WOMAC score in this domain was highest in the Aceclofenac group when compared to Diclofenac and Paracetamol groups at 10th week. (25.29±2.12 vs. 30.23±3.67, 32.30±2.70; p< 0.001).

The effect in reducing WOMAC score was evident on 6th week, almost all three groups were similar and there was no statistically significant difference.

The procured results for WOMAC score on difficulty in performing the physical activity domain shows statistically significant improvement to treatment in Aceclofenac group and Diclofenac group (p<0.001) on 10th week.

Table 5: Investigator assessment to pain and movement by Likert scale at 6th week

Overall response to study medication	Aceclofenac Group I	Diclofenac Group II	Paracetamol Group III
0	0 (0%)	0 (0%)	2 (2.5%)
1	0 (0%)	3 (3.8%)	12 (15%)
2	5 (6.3%)	15 (18.8%)	25 (31.3%)
3	36 (45%)	32 (40%)	31 (38.8%)
4	39 (48.8%)	30 (37.5%)	10 (12.5%)

On 6th week, the percentage of subjects responded to study medication with regards to pain and movement was higher in Aceclofenac group (48.8%) than compared to subjects treated with Diclofenac (37.5%) and Paracetamol (12.5%).

Table 6: Investigator assessment to pain and movement by Likert scale at 10th week

Overall response to study medication	Aceclofenac Group I	Diclofenac Group II	Paracetamol Group III
0	0 (0%)	0 (0%)	3 (3.8%)
1	0 (0%)	0 (0%)	5 (6.3%)
2	0 (0%)	1 (1.3%)	17 (21.3%)
3	27 (33.8%)	26 (32.5%)	19 (48.8%)
4	53 (66.3%)	53 (66.3%)	16 (20%)

Both Aceclofenac (53%) and Diclofenac (53%) treated subjects equally showed extreme response to the treatment with score 4 by Likert scale on 10th week compared to Paracetamol group (20%).

Discussion

In the present study, primary outcome of reduction of pain intensity by VAS score at 10 weeks as shown statistically significant reults in all the three groups (p <0.001). The greater reduction was reported in Diclofenac group (9.00±10.98) compared to Aceclofenac group (10.38±10.49) and Paracetamol group (10.53±6.69).

In the Verkleji SPJ *et al*., study showed the similar results as that of the our study. There was no significant difference between the Diclofenac group

and Paracetamol group on follow up at 2, 4 and 12 weeks in reducing the pain severity with the mean score of 5.4 vs 5.1 in Diclofenac group and Paracetamol group respectively.[5]

Our study results are in contrast to a prospective study conducted by Ward *et al.* where 200 patients received 100mg of Aceclofenac and 197 patients received 50 mg of Diclofenac in OA of knee and 71% of the patients in the Aceclofenac group reported improvement in pain intensity as compared to 59% treated with Diclofenac. Greater improvement in knee movement, reduced pain on movement was observed with Aceclofenac than Diclofenac.[6]

According to present study results, the reduction of mean WOMAC score in pain domain was statistically significant in both groups, Aceclofenac and Diclofenac compared to Paracetamol. [4.05±1.02, 4.56±4.70, vs 6.98±1.12 respectively (p<0.001)].

The mean WOMAC score for reduction in stiffness between the three groups was not statistically significant at end of the study. All the three groups were found to be equally efficacious in reducing the stiffness. (p= 0.499).

The reduction in WOMAC score for difficulty in performing the physical activity domain was highest for the Aceclofenac group when compared to Diclofenac and Paracetamol groups at the end of the study [25.29±2.12 vs. 30.23±3.67, 32.30±2.70; p <0.001)].

The procured results for WOMAC score in all the domains conclude that, Aceclofenac and Diclofenac were equally efficacious in reducing pain score and in improving the physical activity compared to Paracetamol (p<0.001) but greater improvement observed with Aceclofenac group compared to Diclofenac and Paracetamol groups (p<0.001).

Out study results are in similar to a prospective study conducted among 355 osteoarthritis patients by Diaz *et al.* The study results showed that there was no statistical significant difference between the Aceclofenac and Diclofenac treated subjects. However, the incidences of GI side effects were more in Diclofenac (27) when compared to Aceclofenac (14). The results concluded that Aceclofenac better the Diclofenac.[7]

Gaulda *et al.* in his study observed that there was significant improvement in pain and functional capacity of knee joint with Aceclofenac when compared to Paracetamol (p= 0.004) which approximates the results of present study.[8]

Similar results were obtained by a study done by Anand RK *et al.* The results showed that Aceclofenac statistically superior over Diclofenac (p<0.0001) in the efficacy parameter like VAS and WOMAC and investigator assessment of pain and movement on Likert scale.[9,10] Study limitations open labelled study assesed for single knee joint no radiological report to support the same.

Conclusion

Based on the findings of our study, there is evidence that Aceclofenac is as effective as Diclofenac in the treatment of osteoarthritis. Both Aceclofenac and Diclofenac were found to be statistically superior to Paracetamol in certain aspects of efficacy such as WOMAC score and investigators assessment to pain and movement by Likert scale.

References

1. Manyanga T, Froese M, Zarychanski R, Abou-setta A, Friesen C, Tennenhouse M *et al.* Pain management with acupuncture in osteoarthritis: a systematic review and meta-analysis. BMC Complementary and Alternative Medicine. 2014;14:312.
2. Bhatia D, Bejarano T, Novo M. Current interventions in the management of knee osteoarthritis. J Pham Bioall Sci. 2013;5(1):30-38.
3. Turkiewicz A, Petersson IF, Bjork J, Hawker G, Dahlberg LE, Lohmander LS *et al.* Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032. Osteoarthritis and cartilage. 2014;20:1826-1832.
4. Hochberg MC. Osteoarthritis year 2012 in review: clinical. Osteoarthritis and cartilage. 2012;20:1465-69.
5. Verkleij SPJ, Luijsterburg PAJ, Bohnen AM, Koes BW, Bierma-Zeinstra SMA. NSAIDs vs acetaminophen in knee and hip osteoarthritis: a systematic review regarding heterogeneity influencing the outcomes. Osteoarthritis and Cartilage. 2011;19:1-8
6. Tripathi KD. Non-steroidal anti-inflammatory drugs. Essentials of Medical Pharmacology. 7th Ed. New Delhi. Jaypee brothers medical publishers Ltd; 2013. p.192-209.
7. Diaz C, Rodrigue de-la SA, Geli C, Belmonte MA, Olmedo J, Bltran J. Efficacy and tolerability of Aceclofenac versus Diclofenac in the treatment of knee arthritis: a multi center study. Eur J Rheumtol inflamm. 1996;16(1):17-22.
8. Gualda EB, Ivorra JC, Abello JC, Molina JT and Busquets JF. Aceclofenac vs Paracetamol in the management of symptomatic osteoarthtitis of knee: a double blind 6 week randomized controlled trial. Osteoarthritis and cartilage. 2007;15:900-908.
9. Anand RK, Patil RS, Kumar JS, Mala RD. Comparative study of safety, efficacy, and tolerability of Aceclofenac versus Diclofenac in osteoarthritis patients. Journal of evolution of Medical and Dental sciences. 2013;2(15):2432-2439.
10. Pareek A, Chandanwale AS, Oak J, Jain UK, Kapoor S. Efficacy and safety of aceclofenac in the treatment of osteoarthritis: A randomized double-blind

11. comparative clinical trial versus diclofenac-an Indian experience. Curr Med Res opin. 2006;22:977-88.