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OSTEOARTHRITIS;

EFFICACY AND SAFETY OF ACECLOFENAC IN THE TREATMENT: A RANDOMIZED DOUBLE-BLIND COMPARATIVE CLINICAL TRIAL VERSUS DICLOFENAC"

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ABSTRACT… Objective: To assess the efficacy and safety of aceclofenac in the treatment of osteoarthritis. **Study design:** Randomized double blind Phase IV trial. **Place and Duration of study:** This study was conducted in the department of Orthopaedics & Spine Surgery, Ghurki Trust Teaching Hospital, Lahore. The duration was eight weeks. **Methodology:** A total of 90 subjects, fulfilling the inclusion criteria and willing to give free informed consent were enrolled in this trial. All these subjects were randomized into two treatment groups (A & B). Subjects either received Aceclofenac 100 mg twice daily or Diclofenac 75 mg twice daily for 08 weeks. During the screening visit, information on their demographic characteristics, medical history and previous and current medications were collected. A thorough physical examination and necessary laboratory investigations were carried out before drug administration and after the completion of treatment (end of week 8). Clinical examination was done at baseline visit, randomization and 2, 4 and 8 weeks. Gastrointestinal (GI) safety was assessed using adverse drug reaction (ADR) reports. WOMAC questionnaire was used to see improvement in activities of daily living and pain was assessed using visual analogue scale (VAS). All data was collected in the case report form (CRF). Statistical evaluation was performed at the end of the trial and results were analyzed using SPSS. **Results:** 70 subjects completed the study while 20 were lost in follow-up. There were 28 males and 34 females in the study with mean age of 56 years. There was a significant decrease in WOMAC and VAS scores in both groups. In group A (Diclofenac group) VAS decreased from 7.107 to 2.538 (p= 0.000) and WOMAC decreased from 32.75 to 7.38 (p=0.000). In group B (Aceclofenac group), VAS decreased from 7.912 to 6.0 (p=0.001) while WOMAC decreased from 37.29 to 21.50 (p=0.000) showing the efficacy of both drugs. There was also significant decrease in the disease severity in both groups at the end of treatment. But the safety profile of (Diclofenac) group A was not significant (p=0.767) as compared to (Aceclofenac) group B (p=0.022). **Conclusions:** Aceclofenac is efficacious and safe drug for the treatment of osteoarthritis in adults as compared to Diclofenac.

Key words: Aceclofenac. Diclofenac. Osteoarthritis. Visual analogue scale (VAS). WOMAC questionnaire.

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INTRODUCTION

NSAIDS are widely used for a variety of musculoskeletal disorders and their efficacy is well established. However, adverse events particularly upper gastrointestinal (GI), often lead to treatment withdrawl[1]. Since most patients with inflammatory pain require prolonged treatment, efficacious and well tolerated non steroidal anti-inflammatory drugs (NSAIDs) with favourable side effect profiles are required for successful patient management[2]. Because of their analgesic & anti-inflammatory properties, NSAIDs have long been the preferred therapy for relief of pain and stiffness of arthritic diseases[3]. NSAIDs are widely used in the treatment of acute and chronic low back pain. However, NSAIDs are associated with a high incidence of GI side effects which may lead to discontinuation of treatment[4]. NSAIDs are considered to be the first line symptomatic treatment for rheumatoid arthritis (RA) as well[5].

However, treatment with NSAIDs is associated with upper GI bleeding[6]. NSAIDs induced GI toxicity is among the most common serious adverse effects of these drugs. An estimated 1 in 600-2400 patients prescribed NSAIDs are admitted to hospital with clinically important GI complications as perforation and bleeding which entail approximately a death rate of 10%[7]. Gastroduodenal mucosal lesions caused by NSAIDs are also a major cause of death in patients with rheumatic disease[8]. More recently, overall safety profile of selective cyclo-oxygenase-2 (COX-2) inhibitors and traditional NSAIDs has come under intense debate. Therefore, it is essential to determine the actual risk of upper gastrointestinal (UGI) complications with COX-2 selective and traditional NSAIDs alone or combined with other compounds in a real life setting[6]. COX-2 is an enzyme expressed by cells involved in inflammation (macrophages, monocytes). It is responsible for the synthesis of prostanoids involved in acute and chronic inflammation. It has become increasingly clear that, apart from sensitizing peripheral nociceptors, prostaglandins (PGs) may also act in the central nervous system (CNS) to produce hyperalgesia. COX-2 is expressed constitutively in the dorsal horn of spinal cord and becomes upregulated briefly after a trauma, such as damage to a limb, in the corresponding sensory segments of spinal cord[9]. Aceclofenac appears to be particularly well tolerated among the NSAIDs, with a lower incidence of GI adverse effects. This good tolerability profile results in a reduced withdrawl rate and greater compliance with treatment which make it a unique NSAID. It has been suggested that aceclofenac blocks PGE2 production via COX-1 & 2 inhibition in human rheumatoid synovial and other inflammatory cells[10]. In rodents, the acute gastric ulcerogenic activity of aceclofenac was found to be 02, 04 & 07 fold less than naproxen, diclofenac or indomethacin, respectively[5]. Aceclofenac has therapeutic index four times greater than that of diclofenac[3]. Following oral administration, aceclofenac is rapidly and well absorbed, with a half life of 04 hours. It is an effective NSAID in the treatment of osteoarthritis (OA), rheumatoid arthritis (RA) & ankylosing spondylitis (AS) compared with Ketoprofen, Indomethacin, Diclofenac, Naproxen, Piroxicam & Tenoxicam[1]. We compared the efficacy and tolerability of aceclofenac with that of diclofenac resinate in patients with osteoarthritis in local population.

OBJECTIVES

1. The objective of this study was to assess the efficacy and safety of aceclofenac in the treatment of osteoarthritis.
2. Improvement in the clinical manifestations of osteoarthritis and gastrointestinal tolerability.

MATERIAL & METHODS

SETTING
Multi-centered study (03 centers).

STUDY DESIGN
Randomized, double blind, Phase IV trial.

SAMPLE TECHNIQUE
Non-probability (Purposive).

SAMPLE SIZE
A total of 90 subjects, 30 at each centre fulfilling the inclusion criteria and willing to give free informed consent were included this trial.

DATA COLLECTION
All these subjects were randomized into two treatment groups Group A and Group B. The randomization was done using blind chit pads in a box. Subjects either received Aceclofenac 100mg twice daily or Diclofenac 75mg twice daily for 8 weeks.

During the screening visit, information on their demographic characteristics, medical history and previous and current medications were collected.

A thorough physical examination and necessary laboratory investigations (including blood count, BT, CT, ESR, liver function tests, serum electrolytes, serum creatinine, serum albumin, blood sugar, urine analysis, stool occult blood and

X-ray of the knee) was carried out before drug administration and after the completion of treatment (end of week 8).

Clinical examination was done at baseline visit, randomization and 2,4 and 8 weeks. GI safety was assessed using adverse drug reaction (ADR) report and Western Ontario MacMaster (WOMAC) questionnaire and pain was assessed using visual analog scale (VAS) in the case report form (CRF). All data was incorporated into CRF accordingly.

SUBJECT INCLUSION CRITERIA

1. Male and female patients ≥ 40 years of age.
2. Radiologically diagnosed (grade 1-2) osteoarthritis of the knee or any other joints with a minimum Western Ontario MacMaster (WOMAC) index score of 40.
3. Minimum visual analogue scale (VAS) score of 4mm.

SUBJECT EXCLUSION CRITERIA

1. Patients with a history or showing the presence of other rheumatic disease responsible for secondary osteoarthritis.
2. Patients with a history of peptic ulcers, duodenal ulcers, gastrointestinal bleeding or bleeding disorders.
3. Patients with renal impairment (Creatinine clearance > 150ml/min/1.73/m^2).
4. Pregnant and lactating women.
5. Patients with a history of hypersensitivity to aceclofenac, diclofenac or any other NSAID, or those requiring aspirin, corticosteroids, warfarin, ticlopidine or any other drug that affects the platelet function.

DATA ANALYSIS

All data was collected at the end of 8th week and analyzed using SPSS software.

RESULTS

A total of 90 patients were included in the study. They were divided in 2 groups of 45 patients each. 28 patients were lost in follow-up (17 from group A and 11 from group B). So 28 patients from group A and 34 from group B completed the study. Group A was given Tab. Diclofenac sodium 75 mg BD for 08 weeks while group B was given Tab. Aceclofenac 100 mg BD for the same period. Out of these 62 patients, 28 were males and 34 were females. The mean age of these patients was 56 years (Table I).

	Mean±SD
AGE	56.21±9.52
Age in GROUPS	
A	56.04±10.78
B	56.35±8.51
SEX	n (%)
Male	28(45.2%)
Female	34(54.8%)
Number of patients in Groups	n (%)
A	28(45.2%)
B	34((54.8%)

Table-I. Descriptive Statistics: Baseline characteristics of patients

The mean visual analogue scale (VAS) for pain in group A was 7.1 and in group B 7.9. The mean Western Ontario Mac Master (WOMAC) index score for osteoarthritis knee in group A was 32.75+14.42 (>40) and in group B, it was 37.29+11.51(>40). After 08 weeks of medication, VAS dropped to 2.5 in group A and 6 in group B showing significant reduction in pain especially in group A. Similarly, WOMAC dropped to 7.38 in group A and 21.50 in group B showing significant reduction in difficulty in performing daily activities specially in group A (Table II).

Regarding the status of disease on follow up visits, 27 patients in group A started medication with moderate/severe symptoms and after 8 weeks of treatment, only 1 patient had moderate symptoms. In group B, 33 patients had moderate/severe symptoms to start with and 10 patients had moderate symptoms at the end of treatment. But the safety profile is not statistically significant in group A as compared to group B (Table III).

GROUP A	BASELINE	WEEK 2	WEEK 4	WEEK 8	p-value
N	28	25	14	13	
VAS	7.107+1.499	6.2+1.633	4.786+1.424	2.538+0.877	0.000*
WOMAC	32.75+14.42	21.20+9.57	17.57+6.66	7.38+1.61	0.000*
GROUP B					
N	34	30	16	12	
VAS	7.912+1.545	6.633+1.712	6.875+1.5	6.0+1.595	0.001*
WOMAC	37.29+11.51	28.97+12.95	27.50+6.78	21.50+6.52	0.000*

Table-II. Severity of disease on follow-up visits
**= Significantly different*

GROUP A	BASELINE	WEEK 2	WEEK 4	WEEK 8	p-value
N	28	25	14	13	
MILD	1	1	2	12	0.000*
MODERATE	18	17	11	1	0.000*
SEVERE	9	7	1	0	0.000*
SAFETY	26	24	13	13	0.767 NS
GROUP B					
N	34	30	16	12	
MILD	1	1	1	2	0.005*
MODERATE	10	16	9	10	0.005*
SEVERE	23	13	6	0	0.000*
SAFETY	26	28	16	12	0.022*

Table-III. Status of disease on follow-up visits of patients

The gradual drop in number of patients from 28 at the start of treatment to 13 at the end of treatment in group A and from 34 to 12 in group B shows that number of patients requiring further treatment kept on decreasing with the passage of time.

Results of group B only

If we look at the results of group B alone, out of total 34 patients of this group, 12 were males and 22 females with a mean age of 56 years (Table-IV).

	Mean±SD
Age	56.35±8.51
SEX	n (%)
Male	12(35.29%)
Female	22(64.71%)
Number of patients in Group	n
B	34

Table-IV. Descriptive statistics: Baseline characteristics of patients

GROUP B	BASELINE	WEEK 2	WEEK 4	WEEK 8	p-value
N	34	30	16	12	
VAS	7.912+1.545	6.633+1.712	6.875+1.5	6.0+1.595	0.001*
WOMAC	37.29+11.51	28.97+12.95	27.50+6.78	21.50+6.52	0.000*

Table-V. Severity of disease on follow-up visits

** = Significantly Different*

GROUP B	BASELINE	WEEK 2	WEEK 4	WEEK 8	p-value
N	34	30	16	12	
MILD	1	1	1	2	0.005*
MODERATE	10	16	9	10	0.005*
SEVERE	23	13	6	0	0.000*
SAFETY	26	28	16	12	0.022*

Table-VI. Status of disease on follow-up visits of patients

** = Significantly Different NS = Not Significant*

VAS dropped from 7.9 to 6.0 and WOMAC dropped from 37 to 21 showing significant reduction in pain and disability in knee osteoarthritis to perform daily activities (Table V). Similarly, 33 patients had moderate/severe symptoms at the start of treatment and 10 patients had moderate symptoms at the end of 8 weeks treatment. The most important aspect of treatment in group B was the statistically significant safety profile (p=0.022) (Table VI).

DISCUSSION

The results of this study clearly highlight the safety profile of Aceclofenac group against Diclofenac group (p=0.022) though the efficacy of Diclofenac group was superior to that of Aceclofenac group. Aceclofenac was associated with a significantly better gastrointestinal tolerance than diclofenac. A recent endoscopic study has shown that diclofenac significantly impairs gastric mucosal hexosamine content and blood flow. In contrast, gastric mucosal hexosamine was significantly increased and gastroduodenal blood flow remained unchanged with aceclofenac[1]. Several randomized, double-blind, placebo-controlled studies have established that aceclofenac is effective, safe and well tolerated in the treatment of dental pain, post episiotomy pain and knee pain. Aceclofenac shows a trend towards superiority in its efficacy and tolerability compared with diclofenac[4]. G. Pasero et al; also carried out a similar but long term comparative study of aceclofenac and diclofenac in RA and confirmed that the therapeutic efficacy of aceclofenac was comparable to that of diclofenac. But the main disadvantage of long term therapy with NSAIDs was the risk of gastrointestinal disturbances[5]. Akira Yanagawa et. al carried out endoscopic evaluation of NSAID induced gastroduodenal mucosal damage and showed that gastric mucosal lesions occurred in 02 of 10 subjects (20%) receiving aceclofenac versus 05 of 10 subjects (50%) receiving diclofenac, including one who developed ulcer. This suggests that it possesses a therapeutic advantage over conventional NSAIDs[8]. M J Llorente Melero et. al also showed that upper gastrointestinal bleeding (UGIB) is more likely to develop in subjects with traditional NSAID use, than in subjects who use new COX-2 inhibitors such as aceclofenac[7]. D E Ward et. al also conducted their study on the comparison of aceclofenac with diclofenac in the treatment of

osteoarthritis and concluded that there was both objective (assessment of knee flexion) and subjective (patient's assessment of pain intensity) evidence that aceclofenac was more effective than diclofenac. Finally, 71% of patients in the aceclofenac group reported improvement in pain intensity compared to 59% in the diclofenac group. Moreover, tolerability of aceclofenac was very good and there was some evidence that the incidence of gastrointestinal adverse effects was lower than for diclofenac[3]. Several other studies confirm aceclofenac as an efficacious therapy which patients are highly satisfied with. Ernst Martin Lemmel et. al extensively evaluated aceclofenac in clinical trials and proved it to be effective in the treatment of both chronic and acute inflammatory and degenerative diseases, with significantly lower adverse events compared with other NSAID therapies[2].

CONCLUSIONS

On the basis of observations made in this study, we can safely conclude:

1. Aceclofenac is effective and reliable drug for the treatment of Osteoarthritis in the Pakistani population.
2. Aceclofenac is safe and posesses an excellent gastrointestinal tolerability profile.

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