

A COMPARATIVE STUDY OF EFFICACY AND TOLERABILITY OF TRAMADOL AND ACECLOFENAC IN TREATMENT OF OSTEOARTHRITIS

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ABSTRACT

Osteoarthritis (OA) is a leading cause of musculoskeletal disability in elderly patients. It is a slow evolving disorder causing degeneration of articular cartilage associated with symptoms of joint tenderness, stiffness and limitation of movement. These symptoms get more worsened with weight bearing and movement. Non-steroidal anti-inflammatory (NSAIDs) drugs and often Opioid analgesics offers a symptomatic relief in the management of osteoarthritis. So, the present study is conducted to compare the efficacy and tolerability of Tramadol and Aceclofenac in patients of osteoarthritis.

MATERIALS AND METHODS

The present study is a randomized, single centered, prospective clinical study and was conducted on 140 patients.

INCLUSION CRITERIA

Patients of sex, aged 40-60 years, suffering with symptoms of OA of knee who are radiologically diagnosed.

EXCLUSION CRITERIA

- Patients <40 and >60 years of age.
- Patients with a history of peptic ulcers and hypersensitivity to NSAIDs/Opioids.
- Patients with history of bleeding tendencies, cirrhosis and oesophageal varices.
- Patients who have previously received Tramadol or Aceclofenac for treatment of osteoarthritis.

After initial clinical assessment and baseline investigations, Aceclofenac tablet was given to 70 patients and Tramadol tablet was given orally to another 70 patients for 8 weeks. At the follow up, the results were analysed and compared statistically by paired t- test, unpaired t-test, Fischer's exact test.

RESULTS

Aceclofenac has shown significant change than Tramadol in efficacy parameters like Western Ontario Mac Master (WOMAC) scores ($p < 0.0001$), joint tenderness ($p < 0.0001$), investigator assessment for disease status ($p = 0.01$) and response to therapy ($p = 0.038$). Incidence of adverse effects is significant with Tramadol ($p = 0.02$).

DISCUSSION

Aceclofenac was found superior than Tramadol in improving the patient's clinical condition. Aceclofenac was found to be well tolerated than Tramadol in terms of nausea, dyspepsia, epigastric distress, drowsiness.

CONCLUSION

Aceclofenac is efficacious and safer drug than Tramadol in treatment of osteoarthritis of knee.

KEYWORDS

Aceclofenac, Tramadol, WOMAC osteoarthritis index, Visual Analogue Scale.

HOW TO CITE THIS ARTICLE: Sridhar G, Jyothirmai J, Anuradha P, et al. A comparative study of efficacy and tolerability of tramadol and aceclofenac in treatment of osteoarthritis. J. Evid. Based Med. Healthc. 2016; 3(14), 462-467.

DOI: 10.18410/jebmh/2016/107

Submission 25-01-2016, Peer Review 09-02-2016,

Acceptance 15-02-2016, Published 18-02-2016.

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DOI: 10.18410/jebmh/2016/107

INTRODUCTION: Osteoarthritis (OA) is one of the most common, chronic musculoskeletal disorders. It is the most common cause of musculoskeletal disability in elderly patients.¹ WHO estimates worldwide as 9.6% in men and 18% in women aged more than 60 years.²

Combination of orally administered Non-steroidal anti-inflammatory drugs (NSAIDs) and Non pharmacological intervention play an important role in the symptomatic

management of osteoarthritis. As NSAIDs are effective in management of pain and inflammation in osteoarthritis, the ideal agent should have good efficacy and low propensity to cause adverse effects.^{3,4,5}

Aceclofenac is a novel Non-steroidal anti-inflammatory drug with analgesic and antipyretic properties. It inhibits cyclo-oxygenase activity with reduction in the tissue production of prostaglandins and is used in the treatment of rheumatoid arthritis and osteoarthritis, reduces joint swelling and relieves pain.^{6,7}

Tramadol is a synthetic, centrally acting analgesic used to treat moderate to severe pain. It appears to have actions at the μ -opioid receptor as well as in the noradrenergic and serotonergic system. Tramadol is increasingly used in osteoarthritis. But studies on Tramadol has shown increased incidence of adverse effects similar to other opioids and include nausea, vomiting, constipation, headache, dizziness, dry mouth, sedation, asthenia, fatigue and sweating.^{8,9,10,11} "There is a huge unmet medical need for good drugs to halt osteoarthritis progression and the search for a safe and effective option is still on". So, now, the present study is carried out to compare the efficacy and tolerability of Tramadol and Aceclofenac for the treatment of osteoarthritis.

AIMS AND OBJECTIVES:

1. To compare the efficacy of Tramadol and Aceclofenac in osteoarthritis patients in terms of improvement in the
 1. WOMAC Osteoarthritis Index score for;
 - Pain Stiffness.
 - Difficulty performing daily activities.
 - WOMAC score (overall).
 2. Visual analogue scale score for;
 - Pain during weight bearing.
 - Pain at rest.
 - Pain during active movement.
 3. Time taken to walk 100 feet distance.
 4. Patient's overall response of OA to study medications.
 5. Investigator's assessment of disease status.
 6. Investigator's assessment on response of the patient's OA to study medication.
 7. Joint tenderness.
2. To compare the tolerability of Tramadol and Aceclofenac in osteoarthritis patients in terms of incidence of adverse effects.

MATERIAL AND METHODS:

Selection of Patients: The present study is a randomized (systematic), open labelled (non-blinded), comparative clinical study between Tramadol and Aceclofenac in osteoarthritis of knee patients conducted in a single centre. The study was conducted on 140 patients (54 males and 86 females in the age group of 40- 60), suffering from osteoarthritis of knee attending the orthopaedic outpatient clinic, Karimnagar.

A. Inclusion Criteria:

- Male and female patients who were 40-60 years of age.
- Patients with symptoms and signs of osteoarthritis, radiologically diagnosed with osteoarthritis of knee with a minimum Western Ontario MacMaster (WOMAC) Index of 40 and Visual Analogue scale (VAS) score of 4mm.
- Normal haematology, renal function test, liver function test values.

B. Exclusion Criteria:

- Patients <40 and >60 years of age.
- Patients with a history of peptic ulcers and hypersensitivity to NSAIDs /Opioids.
- Patients with history of bleeding tendencies, cirrhosis and oesophageal varices.
- Patients who have previously received Tramadol or Aceclofenac.
- Pregnant or lactating women.
- Patients with uncontrolled medical conditions like severe anaemia, hypertension and asthma were excluded from the study.

Study Design: 140 patients who participated in the present study were divided into two groups after systematic randomization. Informed consent was taken from all the patients participated in the study after explaining the expected advantages and known side effects of Tramadol / Aceclofenac.

Randomization: Randomization is done by computer generated random numbers (done online: www.randomization.com).

Group Allocation: These patients were divided into two groups:

- **Aceclofenac Group:** 70 patients were in this group who received Aceclofenac tablet 100 mg, twice daily for 8 weeks.
- **Tramadol group:** 70 patients were in this group who received Tramadol tablet 75mg twice daily for 8 weeks.

During the screening visit, information on their demographic characteristics, medical history and previous/current medications was collected. A thorough physical examination and necessary laboratory investigations (including blood count, ESR, liver function test, serum electrolytes, serum creatinine, blood sugar, urine analysis, stool occult blood and X-ray of the knee) were carried out. X-ray of the chest and ECG were carried out if required.

Follow-up: 12 patients in Tramadol and 10 patients in Aceclofenac lost to follow-up.

Analysis: Finally 58 patients in Tramadol and 60 patients in Aceclofenac were analysed. (Figure 1).

Parameters for Efficacy Measurement:

- 1. WOMAC Osteoarthritis Index:** The Index is self-administered and assesses the three dimensions of pain, disability and joint stiffness in knee and hip osteoarthritis using a battery of 24 questions. It is a valid, reliable and responsive measure of outcome, and has been used in diverse clinical and interventional environments. It is available in both 5-point Likert and 100mm Visual Analogue scale format. Every question is rated from 'none (0)', 'mild (1)', 'moderate (2)', 'severe (3)' and 'very severe (4)'.
- 2. Visual analogue scale (VAS):** A visual analog scale like this lets you bypass the cognitive level of your brain and give a true representation of your pain. Symptom score for pain on 0-10 VAS is calculated for Weight bearing, Pain at rest and active movement.
- 3.** The patient was made to walk a distance of 100 ft. and the time taken was assessed in seconds.
- 4.** The patient rated the overall response of his or her OA to study medications on a 0-4 Likert scale ('none', 'Poor', 'moderate', 'good', and 'excellent').
- 5.** The investigator rated the overall assessment of disease status on a 0-4 Likert scale ('very poor', 'poor', 'moderate', 'well' and 'very well').
- 6.** The investigator rated the response of the patient's OA to study medication on a 0-4 Likert scale ('none', 'Poor', 'moderate', 'good', and 'excellent').
- 7.** Study of joint tenderness, i.e. pain on palpation to passive motion. It was graded on a 0-3 scale ('no pain', 'pain', 'pain and wincing' and 'withdrawal')

Parameters for Tolerability Measurement: Tolerability was assessed on the basis of the adverse events reported. All reported adverse drug reactions were graded according to Common Toxicity Criteria (CTC) and compared between the groups.

STATISTICAL ANALYSIS: Interval data have been expressed as Mean±SD and categorical data in percentage. P value <0.05 was considered statistically significant. Statistical Tools used for Data Analysis are Paired t-test, Unpaired t-test and Fisher's exact test. Statistical package for Social Sciences (SPSS) statistics version 18.0 software was used for analysing the data.

RESULTS: The baseline demographic data and clinical characteristics of all 140 patients participated in this study have been compared in the Table 1 and p values suggests the homogeneity of our study subjects in two groups.

At follow up, 22 were lost and finally 118 patients (60 in Aceclofenac group and 58 in Tramadol group) completed the study. Among 140 patients, 86(61.42%) patients were female and 54(38.58%) patients were male. The mean age was 52.80+4.55 in Tramadol group and 53.61+5.64 in Aceclofenac group.

The changes in WOMAC osteoarthritis scores, joint tenderness score, investigators assessment of disease status score and response to therapy and patient's response to drug in both Tramadol and Aceclofenac groups were statistically significant within groups by paired t-test. When the same parameters were compared at 2nd visit between Tramadol and Aceclofenac by unpaired t-test, there was a significant difference between the groups.

VAS scores for pain during weight bearing, at rest, and during active movement were also significantly reduced with both Tramadol and Aceclofenac.

In both study groups, the adverse effects reported are of grade- I, as per CTC grading of adverse drug reactions (ADR). The incidence of ADR in Tramadol and Aceclofenac was 29.4% and 11.7% respectively. On comparison of incidence of two groups by Fischer's exact test, it was found statistically significant in Tramadol group (p=0.02).

DISCUSSION: Ensuring the symptom free and good quality of life to OA patients is the therapeutic challenge to treating physicians. In this study, improvement was seen in WOMAC osteoarthritis index score in both groups, but change was better in Aceclofenac group. Both Tramadol and Aceclofenac are equal in efficacy in reducing pain score during weight bearing, at rest, and on active movement on Visual Analogue Scale. Aceclofenac is superior in reducing the time taken to walk 100ft, joint tenderness score and disease status score compared to Tramadol. Patient's response to drug is better with Aceclofenac than Tramadol.

Aceclofenac has been recently clarified in that the compound was shown to elicit preferential inhibition of COX-2. The drug also inhibits synthesis of inflammatory cytokines like interleukin (IL)-1 β and Tumour Necrosis Factor (TNF) and inhibits prostaglandin E2 (PGE2) production thus preventing the degradation of articular connective tissue in patient with rheumatoid arthritis and osteoarthritis and should be classified as a unique NSAID.¹²

The efficacy of Aceclofenac has been attributed to the following effects, viz. its stimulatory effect on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL- β . Inhibition of IL- β thus stimulates synthesis of cartilage matrix. In vitro data shows that, there is stimulation of glycosaminoglycan synthesis in human osteoarthritic cartilage by Aceclofenac. There is also evidence that Aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human articular chondrocyte subjected to inflammatory stimuli and that 4-hydroxyAceclofenac has chondroprotective properties attributed to suppression of IL-1 β mediated pro-matrix metalloproteinase production and proteoglycan release.^{13,14,15}

Aceclofenac appears to be particularly well tolerable among the NSAIDs, with a lower incidence of gastrointestinal side effects. This good tolerability profile results in a reduced withdrawal rate and greater compliance with treatment.^{16,17}

CONCLUSION: Analysis of the study results of all the efficacy and tolerability measures proves that Aceclofenac is better drug for treating osteoarthritis than Tramadol.

Parameters	Tramadol group (n=70)	Aceclofenac group (n=70)	P value
Female Sex (%)	60	62.8	0.86
Age (years)	52.80±4.55	53.61±5.64	0.349
Height (meters)	1.68±0.81	1.68±0.71	0.786
Weight (Kgs)	64.94±6.53	64.86±5.98	0.936
BMI (Kg/ meter ²)	22.86±2.29	22.89±1.80	0.930
Systolic BP (mm of Hg)	124.89±15.12	122.66±11.11	0.152
Diastolic BP (mm of Hg)	73.83±13.84	73.97±14.75	0.953
Edema	0	0	-

Table 1: Baseline demographic data and clinical characteristics of the 140 patients of OA patients participated in the study

Data are in Mean±SD.

Variable	Tramadol group				Aceclofenac group				Difference between the groups Ψ
	1 st Visit	2 nd Visit	Mean difference	p value \$	1 st Visit	2 nd Visit	Mean difference	P value \$	
Pain questionnaire scoring	12.33±3.13	8.76±1.09	3.57	<0.0001*	12.00±1.08	7.60±1.18	4.4	<0.0001*	<0.0001*
Stiffness questionnaire scoring	4.21±0.58	3.26±0.76	0.95	<0.0001*	4.17±0.61	2.73±0.75	1.44	<0.0001*	<0.0001*
DPDA questionnaire scoring	39.91±2.14	30.66±1.78	9.25	<0.0001*	40.67±2.17	29.03±02.06	11.64	<0.0001*	<0.0001*
WOMAC score (overall)	56.48±3.59	42.67±01.99	13.81	<0.0001*	56.83±2.31	38.0±2.29	18.83	<0.0001*	<0.0001*

Table 2: Change in WOMAC osteoarthritis index score in study groups

Data are in Mean ± SD, \$ Paired t-test, Ψ- unpaired t- test.

Variable	Tramadol group				Aceclofenac group				Difference between the groups Ψ
	1 st Visit	2 nd Visit	Mean difference	p value \$	1 st Visit	2 nd Visit	Mean difference	P value \$	
During weight bearing	5.29±0.95	2.88±1.09	2.41	<0.0001*	5.30±0.83	2.77±0.92	2.53	<0.0001*	0.547
At rest	4.72±0.93	2.71±1.02	2.01	<0.0001*	4.83±1.02	2.38±0.84	2.45	<0.0001*	0.064
Active movement	5.40±0.93	3.65±1.25	1.75	<0.0001*	5.20±0.86	2.87±1.21	2.33	<0.0001*	0.207

Table 3: Changes in visual analogue scale scores for pain in study groups

Data are in Mean±SD, \$ Paired t-test, Ψ- unpaired t- test.

Variable	Tramadol group				Aceclofenac group				Difference between the groups Ψ
	1 st Visit	2 nd Visit	Mean difference	p value \$	1 st Visit	2 nd Visit	Mean difference	P value \$	
Time taken to walk 100ft	102±3.59	84.93±9.028	17.07	<0.0001*	101.45±11.65	82.8±9.35	18.57	<0.0001*	0.230
Joint tenderness score	1.48±1.06	0.81±0.57	0.67	<0.0001*	1.58±0.94	0.53±0.50	1.05	<0.0001*	0.006
Disease status score	2.36±0.66	2.52±0.62	0.16	0.028*	2.20±0.65	2.82±0.62	0.62	<0.0001*	0.011

Table 4: Changes in efficacy measures in study groups

Data are in Mean ± SD, \$ Paired t-test, Ψ- unpaired t- test.

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