A HOSPITAL BASED COMPARATIVE STUDY OF TOLERABILITY AND EFFICACY OF TRAMADOL VERSUS ACECLOFENAC ON PATIENTS WITH OSTEOARTHRITIS OF KNEE JOINT.

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Abstract

Objectives: This present study was done to compare the tolerability and efficacy of tramadol versus aceclofenac in terms of WOMAC Osteoarthritis Index and Visual Analogue Scale of patients with osteoarthritis of knee joint.

Methods: A detail history, clinical examinations and relevant investigations were performed to all cases of osteoarthritis of knee joint. Group A patients were advised to receive tramadol 75 mg twice daily for 8 weeks, and group B patients were advised to receive aceclofenac 100 mg twice daily for 8 weeks. And we had evaluated the WOMAC Osteoarthritis Index and VAS score of first day and last day visit of patients with osteoarthritis of knee joint.

Results: Data was analyzed by using SPSS (version 26) software. Paired sample statistical methods were used. Mean and standard deviation was observed and mean differences were compared. P value was taken less than or equal to 0.05 (p≤0.05) for significant differences.

Conclusions: This present study concluded that the WOMAC Osteoarthritis Index score and VAS score of patients who had received aceclofenac medication had statistically significant differences as well as greater mean differences than patients who received tramadol. Hence, aceclofenac is effective drugs than tramadol in terms of efficacy and tolerability of patients with osteoarthritis of knee joint.

Key words: Osteoarthritis of knee, WOMAC osteoarthritis index, Visual Analogue Scale.

Introduction:

Osteoarthritis (OA) is universally known as one of most common musculoskeletal disorder. It normally implicates as pain involving several joints [1], mainly occurring in the elderly with a radiographic prevalence of nearly 70% in persons over age 65. The burden of the disease is mainly related to pain occurrence leading to functional disability that varies from mild to moderate difficulties in movement of normal daily living activities. Therefore, pain relief portrays a key role in the treatment of OA [2]. The treatment of the OA is greatly dependent based on the specific site [3].

Paracetamol is effective in treating certain types of OA. The drug is considered as first-line treatment for mild to moderate pain [4]. However OA patients often prefer NSAIDS for better pain relief [5]. NSAIDs are targeted therapy for pain management in RA patients, but are not appropriate for long-term disease control [6]. Fixed-dose combination products are seldom mentioned in available OA and RA guidelines [7]. The NICE guideline initially recommends paracetamol for all OA pain or topical NSAIDs for hand and knee OA ahead of oral NSAIDs, COX-2 inhibitors or opioids [8]. Topical capsaicin should be considered an adjunct to core treatment for hand and knee OA, and intra-articular corticosteroid injections an adjunct in all OA pain. The OARSI guideline recommends the initial administration of paracetamol for mild to moderate knee or hip OA, and topical NSAIDs and capsaicin as adjuvant or alternatives to oral analgesics in knee OA pain [9]. Weak opioids and narcotic analgesics can be considered for refractory pain but stronger opioids should only be used for severe pain in exceptional circumstances. The evidence presented included fixed-dose combinations of opioids and paracetamol. Both the NICE and OARSI guidelines recommend the use of oral NSAIDs at the lowest effective dose [9] long-term use should be avoided [9]. The recent ACR recommendations list topical capsaicin, topical
NSAIDs, oral NSAIDs (including COX-2 inhibitors) and tramadol for initial pain treatment of hand OA, and advice against intra-articular therapies and opioid analgesics [10].

Drug utilization research was defined as the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences. Periodic evaluation of drug utilization patterns needs to be done to enable suitable modifications in the prescription of drugs to increase the therapeutic benefit and decrease the adverse effects. Objectives of our study were to compare the tolerability and efficacy of tramadol and aceclofenac of patients with osteoarthritis of knee joint.

MATERIALS AND METHODS

This present study was conducted in Department of Pharmacology with the collaboration of Department of Orthopaedics, Jawahar Lal Nehru Medical College, Bhagalpur, Bihar, India during a period from March 2019 to July 2019. Entire subjects signed an informed consent, and approval by institutional ethical committee of Jawahar Lal Nehru Medical College, Bhagalpur, Bihar was sought.

Samples: A random sampling methods was used. A total of 80 osteoarthritis of knee joint were enrolled in this study. These total cases were categorized into two groups (group A and group B). Group A had 40 cases of osteoarthritis of knee received tramadol. Group B had 40 cases of osteoarthritis of knee received aceclofenac. A detail history, clinical examinations and relevant investigations were performed to all cases of osteoarthritis of knee joint. 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.

Inclusion Criteria: Male and female patients who were 35-65 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, and patients with normal haematology, renal function test, liver function test was taken.

Exclusion Criteria: Patients who were age <35 and >65 years. Patients with a history of peptic ulcers and hypersensitivity to NSAIDs/Opioids and with history of bleeding tendencies, cirrhosis and oesophageal varices. Patients who had previously received Tramadol or Aceclofenac. Pregnant or lactating women. And Patients with uncontrolled medical conditions like severe anaemia, hypertension and asthma were excluded from this study.

Methods:

Group A patients were advised to receive tramadol 75 mg twice daily for 8 weeks, and group B patients were advised to receive aceclofenac100 mg twice daily for 8 weeks.

Parameters:

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)’.

Visual analogue scale (VAS): A Visual Analog Scale 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 was calculated for Weight bearing, Pain at rest and active movement.

Procedure: The patient was made to walk a distance of 100 ft. and the time taken was assessed in seconds. 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’). The investigator rated the overall assessment of disease status on a 0-4 Likert scale (‘very poor’, ‘poor’, ‘moderate’, ‘well’ and ‘very well’). 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’). 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**

Data was analyzed by using SPSS (version 26) software. Paired sample statistical methods were used. Mean and standard deviation was observed and mean differences were compared. P value was taken less than or equal to 0.05 (p≤0.05) for significant differences.

**OBSERVATIONS**

In this present study, a total of 80 cases of osteoarthritis of knee with irrespective of sex were enrolled. These patients were categorized into two groups (group A and group B): Each group had 40 cases of osteoarthritis. Males and females were 37.50%(30) and 62.50%(50) respectively.

<table>
<thead>
<tr>
<th>Table 1. various parameters</th>
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<tr>
<td>Parameters</td>
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<tr>
<td>Age</td>
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<td>Weight</td>
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<td>BMI</td>
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<tr>
<td>Systolic B.P.</td>
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<tr>
<td>Diastolic B.P.</td>
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</table>

When we were compared mean and standard deviation of age, height, weight, BMI, systolic pressure and diastolic pressure of patients of tramadol group (group A) with of patients on aceclofenac group (group B), p value was found to be 0.001, 0.550, 0.437, 0.414, 0.154 and 0.746 respectively. Which is greater than 0.05. Hence it is not statistically significant differences.

<table>
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<th>Table 2: WOMAC Osteoarthritis index</th>
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<tr>
<td>Variables</td>
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<tr>
<td>Pain questionnaire scoring</td>
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<td>Stiffness questionnaire scoring</td>
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<td>DPDA questionnaire scoring</td>
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<td>WOMAC score (overall)</td>
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When WOMAC osteoarthritis index was compared between and within patients of tramadol (group A) and aceclofenac (group B). Pain questionnaire score of within group A patients of 1st day and last day visit was statistically significant differences (p=0.009). Similarly pain questionnaire of within group B patients of first day and last visit was also significantly differences (p=0.00). But greater mean differences was seen group B patients (group A mean differences=3.575 and group B mean differences=3.950).

Stiffness questionnaire score of within group A patients of first day and last visit was significant differences (p=0.004). Similarly stiffness questionnaire score of within group B patients of first day and last visit was also significant differences (p=0.004). But greater mean differences was seen group B patients (group A mean differences=0.975 and group B mean differences=1.825).

DPDA questionnaire scores of within group A patients of 1st day and last day visit was statistically significant
When visual analogue score during weight bearing was compared between and within group of patients of tramadol (group A) and aceclofenac (group B). Patients of first day and last day visit of visual analogue score of group A was statistically significant differences (p=0.002). But first day and last day visit of VAS of group B patients was not statistically significant (p= 0.565). But greater mean differences was seen in group B patients (group A=3.000, group B=3.500).

When VAS during at rest was compared within and between group A and group B patients, First day and last day visit of group A patients was statistically significant differences (p=0.007). Similarly VAS of First day and last day visit of group B was also statistically significant differences (p=0.000). But greater mean differences was seen in group B patients (group A=2.075, group B= 2.200).

When VAS during active movement was compared within and between group A and group B patients, First day and last day visit of group A patients was not statistically significant differences (p=0.646). But VAS during active movement of first day and last day visit of group B patients was statistically significant differences (p=0.000). And greater mean differences was seen in group B patients (group A mean differences=2.975, group B mean differences=3.375).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tramadol group</th>
<th>Aceclofenac group</th>
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<tbody>
<tr>
<td></td>
<td>1st visit</td>
<td>Last day visit</td>
</tr>
<tr>
<td>During weight bearing</td>
<td>5.350±1.098</td>
<td>2.350±1.001</td>
</tr>
<tr>
<td>At rest</td>
<td>4.050±1.197</td>
<td>1.975±1.025</td>
</tr>
<tr>
<td>Active movement</td>
<td>5.625±0.925</td>
<td>2.650±1.387</td>
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</tbody>
</table>

When efficacy at time taken to walk 100 ft was compared within and between group (group A and group B), time taken to walk 100 feet of first day and last day visit of group A patients was statistically significant differences (p=0.000). Similarly, time taken to walk 100 of first day and last day visit of group B patients was also statistically significant differences (p=0.026). But greater mean differences was seen in group B patients (group A=8.975, group B=12.000).

<table>
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<tr>
<th>Variables</th>
<th>Tramadol group</th>
<th>Aceclofenac group</th>
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<tbody>
<tr>
<td></td>
<td>1st visit</td>
<td>Last day visit</td>
</tr>
<tr>
<td>Time taken to walk 100 ft</td>
<td>104.725±4.782</td>
<td>95.750±9.363</td>
</tr>
<tr>
<td>Joint tenderness score</td>
<td>1.800±0.686</td>
<td>0.825±0.500</td>
</tr>
<tr>
<td>Disease status score</td>
<td>1.850±0.483</td>
<td>2.425±0.594</td>
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</tbody>
</table>

When efficacy at joint tenderness score was compared within and between group A and group B, first day and last day visit of group A patients was not statistically significant differences (p=0.904). But efficacy at joint tenderness score of first day and last day visit of group B patients was statistically significant differences (p=0.000). And greater mean differences was seen in group B patients (group A=0.975, Group B=1.175).
When efficacy at disease status score of within and between group A and group B was compared, First day and last day visit of group A patients was statistically significant differences (p=0.004). But a greater mean difference was seen in group B patients (1.825) than group A patients (0.975). DPDA questionare score was extremely statistical significant differences in group A patients (p=0.000) than group B patients (p=0.022). But a greater mean difference was seen in group B patients (11.825) than group A patients (9.450). And over all WOMAC score of group B patients was extremely statistical significant differences (p=0.000) than group A patients (0.130). And a greater mean difference was also seen in group B patients (17.950) than group A patients (14.400). Hence, we had seen that patients who had received aceclofenac have got more improvement.

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 [16]. 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 [17]. 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 stimuli [18] and that 4'-hydroxyaceclofenac has chondro protective properties attributable to suppression of IL-1 mediated promatrix metalloproteinase production and proteoglycan release [19].

In this present study, Visual analogue score during weight bearing of group A patients was statistically significant differences (p=0.002) than group B patients (p=0.565). But a greater mean difference was seen in group B patients (3.500) than group A patients (3.000). VAS at rest of group B patients was statistically significant in both group patients (p=0.000). A greater mean difference was also seen in group B patients (3.575) than group A patients (3.500). Hence, pain was greater relieved by using aceclofenac. Stiffness questionare score was statistically significant in both group patients (p=0.004). But a greater mean difference was seen in group B patients (1.825) than group A patients (0.975). DPDA questionare score was extremely statistical significant differences in group A patients (p=0.000) than group B patients (p=0.022). But a greater mean difference was seen in group B patients (11.825) than group A patients (9.450). And over all WOMAC score of group B patients was extremely statistical significant differences (p=0.000) than group A patients (0.130). And a greater mean difference was also seen in group B patients (17.950) than group A patients (14.400). Hence, we had seen that patients who had received aceclofenac have got more improvement.

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relieved by the use of aceclofenac with respect to tramadol.

When efficacy was measured within and between group A and group B patients, Time taken to walk 100 feet, joint tenderness score and disease status score of group B patients was extremely statistical significant difference (p=0.000) than group A patients (p=0.000, 0.030 and 0.046 respectively). And a greater mean differences was also seen in group B patients (12.000, 1.175 and -1.200) than group A patients (8.975, 0.975, -0.575 respectively).

Tramadol is considered a weak opioid on the WHO pain ladder [20]. Due to its differences to other opioids. Tramadol’s analgesic effect derives from a combination of an agonist action at mu-opioid receptors (low affinity of parent drug, much higher affinity of its M1, O-desmethyl, metabolite) and inhibition of neuronal reuptake of serotonin (5-HT, 5-hydroxytryptamine) and norepinephrine [21].

Tramadol has been shown to decrease pain intensity in OA patients and to improve function; active-controlled studies show that tramadol provides analgesic benefits similar to diclofenac and superior to paracetamol [22]. Extended-release formulations of tramadol have been shown effective in treating chronic pain associated with OA as well as offering improvement in pain related sleep disorders [23].

Tramadol may be associated with a risk of dependence or abuse; the prevalence of abuse/dependence over a 12-month period in patients with chronic non-cancer pain was, however, equivalent for tramadol and NSAIDs, and significantly less than for hydrocodone [24]. In patients prone to convulsive disorders, the risk of convulsions may increase if tramadol is taken concomitantly with medication that lowers the seizure threshold. Some cases of serotonergic syndrome have been reported with the therapeutic use of tramadol in combination with other serotonergic agents such as selective serotonin re-uptake inhibitors (SSRIs) [25]. Recommended dosing should not exceed 400 mg/d, and should be reduced or closely supervised in geriatric patients (75 years) and those with cirrhosis or renal dysfunction [26].

Aceclofenac inhibits synthesis of the inflammatory cytokines like interleukin (IL-1), Tumor necrosis factor (TNF) and prostaglandin E2 (PGE2) production. Aceclofenac is an effective analgesic and anti-inflammatory agent provides symptomatic relief in a variety of painful conditions. Aceclofenac appears to be particularly well tolerated among the NSAIDS with a lower incidence of gastrointestinal adverse effects, this good tolerability profile results in a reduced withdrawal rate and greater compliance with treatment. Since long-term NSAIDS treatment is indicated for osteoarthritis, the ideal agent should have good efficacy and a low propensity to cause adverse events.

CONCLUSIONS

This present study concluded that the WOMAC osteoarthritis Index score and VAS score of patients who had received aceclofenac medication had statistically significant differences as well as greater mean differences than patients who had received tramadol. Hence, aceclofenac is effective drugs than tramadol in terms of efficacy and tolerability of patients with osteoarthritis of knee joint.

REFERENCES


