|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
PubMed (National Library of Medicine ID: 101738825)
Index Copernicus Value 2018: 75.71
Original Research Article
Volume 3, Issue 8; August: 2019; Page No. 189-195

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

Dr. Sara Sultana[1], Dr. Braj Nandan Kumar Sah[1]
[1]Tutor, Department of Pharmacology, Jawahar Lal Nehru Medical College, Bhagalpur, Bihar, India.

Article Info: Received 28 July 2019; Accepted 21 August. 2019
DOI: https://doi.org/10.32553/ijmbs.v3i8.490
Address for Correspondence: Dr. Sara Sultana, Tutor, Department of Pharmacology, Jawahar Lal Nehru Medical College, Bhagalpur, Bihar, India
Conflict of interest: No conflict of interest.

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 ($p \leq 0.05$) 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 NSAIDsat the lowest effective dose [9] long-term use should be avoided [9]. The recent ACR recommendations list topical capsaicin, topical

NSAIDs, oral NSAIDs (includingCOX-2 inhibitors) and tramadol for initial pain treatment ofhand 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 ($p \leq 0.05$) 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.1. various parameters

Parameters	Tramadol(N=40)	Aceclofenac(N=40)	r	p
Age	64.750±6.159	63.975±6.411	0.506	0.001
Height	1.598±0.070	1.618±0.082	0.097	0.550
Weight	68.800±6.243	68.975±8.288	-.126	0.437
BMI	21.375±1.943	21.625±2.046	0.133	0.414
Systolic B.P.	124.050±6.388	122.975±8.666	0.230	0.154
Diastolic B.P.	79.500±5.519	81.050±5.271	0.053	0.746

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 2: WOMAC Osteoarthitis index

Variables	Tramadol group					Aceclofenac group				
	1st visit	Last day visit	r	p	Mean differences	1st visit	Last day visit	r	p	Mean differences
Pain questionnaire scoring	12.025±2.201	8.450±1.239	-.408	0.009	3.575	12.150±1.188	8.200±1.324	0.534	0.00	3.950
Stiffness questionnaire scoring	3.925±0.828	2.950±0.677	0.450	0.004	0.975	4.200±0.686	2.375±1.004	0.446	0.004	1.825
DPDA questionnaire scoring	40.275±1.739	30.825±1.152	0.716	0.000	9.450	41.075±1.700	29.250±1.613	-.362	0.022	11.825
WOMAC score (overall)	57.550±2.669	43.150±1.251	0.243	0.130	14.400	55.575±1.906	37.625±1.995	0.867	0.000	17.950

When WOMAC osteoarthritis index was compared between and within patients of tramodol (group A) and aceclofenac (group B). Pain questionare score of within group A patients of 1st day and last day visit was statistically significant differences (p=0.009). Similarly pain questionare 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

differences (p=0.000). Similarly DPDA questionnaire scores of within group B patients of first day and last visit was also significantly differences (p=0.022). But greater mean differences was seen group B patients (group A mean differences=9.450 and group B mean differences=11.825).

When over all WOMAC scores was compared within group A patients of first day and last day visit. It was not statistically significant differences (p=0.130). Similarly within group B, it was statistically significant differences (p=0.000). And greater mean differences was also seen in group B patients (group A= 14.400 and group B=17.950).

Table 3: Visual analogue score

Variables	Tramadol group					Aceclofenac group				
	1st visit	Last day visit	r	p	Mean differences	1st visit	Last day visit	r	p	Mean differences
During weight bearing	5.350±1.098	2.350±1.001	0.468	0.002	3.000	5.125±1.264	1.625±0.837	0.094	0.565	3.500
At rest	4.050±1.197	1.975±1.025	0.419	0.007	2.075	4.725±1.198	2.525±1.061	0.580	0.000	2.200
Active movement	5.625±0.925	2.650±1.387	0.075	0.646	2.975	5.250±1.315	1.875±1.583	0.733	0.000	3.375

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 4: Efficacy measures

Variables	Tramadol group					Aceclofenac group				
	1st visit	Last day visit	r	p	Mean differences	1st visit	Last day visit	r	p	Mean differences
Time taken to walk 100 ft	104.725±4.782	95.750±9.363	0.600	0.000	8.975	104.725±5.579	92.725±13.647	0.587	0.000	12.000
Joint tenderness score	1.800±0.686	0.825±0.500	0.343	0.030	0.975	1.975 ±0.973	0.800±0.686	0.529	0.000	1.175
Disease status score	1.850±0.483	2.425±0.594	0.317	0.046	-.575	1.725±0.784	2.925±0.797	0.746	0.000	-1.200

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).

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=0.046). Similarly, disease status score of first day and last day visit of group B patients was statistically extremely significant differences (p=0.000). And greater mean differences was also seen in group B patients (group A= -.575, group B= -1.200).

DISCUSIONS

Osteoarthritis is one of the most common, chronic and progressive musculoskeletal disorders. It usually occurs after the ages of 50 [11]. It particularly affects the knee and hip joints in elderly people [11]. Primary symptoms are joint pain, stiffness, limited movement, and impaired quality of life. Progression of disease can lead to joint failure with pain and disability [11]. Osteoarthritis is a degenerative joint disease that mainly involves the cartilage and many surrounding tissues. Osteoarthritis causes damage and loss of articular cartilage within the synovial joints, increases the thickness of the subchondral plate, and leads to remodeling of the subarticular bone, osteophyte formation, ligamentous laxity, weakening of periarticular muscles, synovial inflammation and cyst formation in the subchondral bone [12]. Synovial tissue cells and subchondral osteoblasts produce cytokines. IL-1 beta and the tumor necrosis factor (TNF)-alpha are key cytokines in the catabolic process of cartilage degradation [13]. Inflammatory cytokines provide essential biochemical signals that stimulate chondrocytes to release cartilage-degrading enzymes [14].Prevalence of osteoarthritis increases with age and it affects 60% of men and 70% of women after the age of 65 [15].In our present study, out of total 80 cases, osteoarthritis of knee was affected in 37.5% of men and 62.5% of women. Mean and standard deviation of age, height, weight, BMI, systolic blood pressure and diastolic blood pressure of tramadol group patients (group A) were not statistically significant differences with aceclofenac group patients (group B).

When WOMAC osteoarthritis index was compared within and between groups A and groups B. Pain questionare score of group B patients was extremely statistically significant differences(p=0.000) than group A patients (p=0.009).A greater mean difference was also seen in group B patients (3.950) than group A patients (3.575). 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 (p=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 forthe 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 extremely statistically significant differences (p=0.000) than group A patients (p=0.007).And a greater mean difference was also seen in group B patients (2.200) than group A patients (2.075). VAS during active movement of group B patients was extremely statistical significant differences (p=0.000) than group A patients (p=0.646). And a greater mean difference was also seen in group B patients (3.375) than group A patients (2.975). Hence, it shows that pain in osteoarthritis of knee patients was greatly

relieved by the using 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 differences(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, -.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-monthperiod 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

1. Jain Shirpa, Khan Yab Zafar, Upadhyaa Prerna, Abhijeet Kumar. Assessment ofPrescribing Pattern in a Private Teaching Hospital in India. International Journal ofPharma Sciences, 2012; 3(3): 219-222.
2. Ahmed Mohamed, Ali Nahid, Rahman Ur Zia, Khan Misbahullah. A study on prescribing patterns in the management of Arthritis in the department of Orthopaedics. Scholars Research Library, 2012; 4(1): 5-27.
3. McCarberg Bill, Tenzer Penny. Complexities in the pharmacologic management of Osteoarthritis pain. Current Medical Research and Opinion, 2013; 29(5): 539-548.
4. Magliano M, Morris V, Eds. Use of analgesics in rheumatology. London: Arthritis Research Campaign 2002.
5. Wolfe F, Zhao S, Lane N. Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic diseasepatients: a survey of 1,799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. Arthritis Rheum 2000; 43(2): 378 85.
6. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007; 66(1): 34-45.
7. Luqmani R, Hennell S, Estrach C, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (the first two years). Rheumatology 2006; 45(9): 1167-9.
8. NICE. Osteoarthritis: the care and management of osteoarthritis in adults. London: National Institute for Health and Clinical Excellence; 2008; Available from:

http://www.nice.org.uk/ nicemedia/pdf/CG59 NICEguideline.pdf [cited 2011 May 13]

9. Zhang W, Moskowitz R, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008; 16(2): 137-62.
10. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012; 64(4): 455-74.
11. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology anvd burden of osteoarthritis. Br Med Bull 2013; 105: 185-99.
12. Mukherjee P, Rachita C, Aisen PS, Pasinetti GM. Non-steroidal anti-inflammatory drugs protect against chondrocyte apoptotic death. Clin Exp Rheumatol 2001; 19: 7-11.
13. Berenbaum F. Osteoarthritis year 2010 in review: pharmacological therapies. Osteoarthritis Cartilage 2011; 19: 361-5.
14. Brizuela NY, Montrull HL, Demurtas SL, Meirovich CI. Articular cartilage in osteoarthritic patients: effects of diclofenac, celecoxib and glucosamine sulfate on inflammatory markers. Rev Fac Cien Med Univ Nac Cordoba 2007; 64: 9-15.
15. Pareek A, Chandurkar N, Sharma VD, Desai M, Kini S, Bartakke G. A randomized, multicentric, comparative evaluation of aceclofenac–paracetamol combination with aceclofenac alone in Indian patients with osteoarthritis flare-up. Expert Opin Pharmacother 2009; 10: 727-35.
16. Bäck M, Yin L, Ingelsson E. Cyclooxygenase-2 inhibitors and cardiovascular risk in a nation-wide cohort study after the withdrawal of Rofecoxib. Europe Heart J. 2012 Aug; 33(15):1928-30.
17. 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, multicentre, double-blind study. 2011 May; 12(5):546-53.
18. 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.
19. Akimoto H, Yamazaki R, Hashimoto S, et al. 4-Hydroxy-aceclofenac suppresses the interleukin-1 induced production of promatrix metalloproteinase and release of sulfated-glycosaminoglycans from rabbit articular chondocytes. Europ J Pharmacol 2000; 401: 429-36.
20. WHO. WHO's pain ladder. Geneva, Switzerland: World Health Organization; 1986 [updated 2011; cited 2012 June 15]; Available from: http://www.who.int/cancer/palliative/painladder/en/ .
21. Raffa R, Friederichs E. The basic science aspect of tramadol hydrochloride. Pain Rev 1996; 3: 249-71.
22. Cepeda M, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. Cochrane Datab Syst Rev 2006; (3): CD005522.
23. Rosenberg M. The role of tramadol ER in the treatment of chronic pain. Int J Clin Pract 2009; 63(10): 1531-43.
24. Adams E, Breiner S, Cicero T, et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. J Pain Symptom Manage 2006; 31(5): 465-76.
25. Tramadol hydrochloride 50mg capsules. Surrey, England: Datapharm Communications Ltd; 2011 [updated 2 February 2011; cited 2011 December 15]; Available from: http://www.medicines.org.uk/emc/medicine/24186/SPC/tramadol%20hydrochloride%2050mg%20caps ules/.
26. Y. Samhitha Reddy et al, Tolerability of Aceclofenac Verses Diclofenac in Osteoarthritis Patients Attending a Secondary Care Hospital in Anantapuramu, Indo Am. J. P. Sci, 2017; 4(05).