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200 Kashmiri Patients of osteoarthritis Knee Were Studied And Free Drug Combination Versus Fixed Dose Combination of aceclofenac and Diacerin Were assessed For analgesic Efficacy,Safety and Compliance.

I. INTRODUCTION

The ever-expanding aging population expects and deserves a fulfilling and active life, with low dependence on "managed care". This requires a healthy and well- functioning musculoskeletal system. However, age-related musculoskeletal diseases are a major cause of global morbidity, and result in high costs for health and social care system. Advancing age is a major risk factor for degenerative joint disease. Osteoarthritis (OA) is a degenerative disease resulting from a group of mechanical abnormalities involving joints, articular cartilage and subchondral bone. Osteoarthritis is derived from Greek words "Osteo" meaning the bone, "Ortho" meaning joints and "Itis" which means inflammation. The clinical manifestations in OA are gradual development of joint pain, swelling, instability, stiffness and loss of motion **(Louthrenoo W, et al. 2007).**The joints most commonly affected are the knees, hip and those of the hand and spine.

OA has gradual onset, and symptoms usually don't appear until around the age of 45 to 50 years **.** Evidences suggest that inflammation events are outcome of intervention of polymorphonuclear leucocytes that release lysosomal enzymes and oxygen free radicals. This results in increased articular cartilage destruction, joint pain, stiffness and limitation of movement **(Dieppe p 1978)**. In OA subchondral osteoblasts have abnormal phenotype, elevated alkaline phosphatase, increased release of osteocalcin, reduced parathyroid hormone and PGE2 dependent cAMP formation, elevated Urokinase plasminogen, IGF-1 and altered collagen metabolism.**(Hilal G, et al. 1998, Mansell JP, et al.1998 , Lajeunesse D, et al.1999.)**.These disease cells produce more IL-6 and PGE-2 than normal.

OA affects 35% of adults aged 65 or older **(Lawrence RC, et al. 2008).** Prevalence of OA increases with age, the disease affects 10% of males and 18% of females over 45 and these figures are predicted to rise as the general population ages **(Mobasheri A. 2013, Alhasmi AM. 2014).**

In India overall prevalence of OA is 24.9 % **(Aggarwal V 2003)** and while from Jammu it has been recorded 42.4 %**(Mahajan A, et al. 2003)**. Studies estimate that 80% of population will have radiographic evidence of OA by age 65 years although only 60% of those will be symptomatic **(Dilip K, et al. 2010).**OA is a disease of synovial joints, primarily affecting the knee (33%), hand (30%), feet (21%) and hip (5%) **(Lawrence RC, et al. 1998).** OA is a major cause of pain and disability and among most prevalent form of musculoskeletal disorders **(Polisson R 2001).** Symptomatic knee OA is currently the fourth leading cause of disability worldwide **(Fransen M, et al. 2011).**

With improved health care facilities in developing countries the elderly age population is also increasing. Thus the volume of age related disease like osteoarthritis is expected to increase and shall demand health care priority. Pain, inflammations are important concern both for patient and doctor besides progressive nature of disease. The main objectives in the management of OA are to reduce symptoms, minimize functional disability, limit the progression of structural changes and ultimately delay or avoid arthroplasty. "The best treatment for knee OA is prevention" **(Joern W et al 2010).**

Pharmacological treatment is mostly palliative and non-steroidal anti inflammatory drugs (NSAIDs) including the cyclooxygenase (COX) enzyme inhibitors are common analgesics used in osteoarthrits **(Louthrenoo W et al. 2007).** However, NSAID use may increase the risk of GIT adverse effects and do not affect the underlying pathogenesis of articular diseases thus have a minimal role in modifying disease course.

Recently there has been increase in the use of disease modifying osteoarthritic drugs (DMOAD) whose action are basically aimed at preventing break down of articular cartilage **(Mahajan A, et al.2006)**.These drugs have gradual onset of action after 4-6wks but maintain their symptomatic effect even for a period of 4-8 wks after cessation of treatment. Drugs belonging to this group are glucosamine, chondritin sulphate, chemically modified tetracycline and diacerein.Tetracyclines,in larger clinical trials have yet to prove their structure modifying activity **(Mahajan A, et al. 2005)**.Patients who participated in trials conducted by GAIT, showed there was neither significant pain reduction nor improved function with Glucosamine and Chondritin supplements **(Sawitzke AD, et al 2008)**.

Diacerein is a commonly used DMOAD and in addition possess good pain ameliorating property. Disease modifying effect becomes apparent 2-4 weeks after the start of treatment, reaching significant value

after 4-6 weeks but persists for several weeks after cessation of administration. **(Mehdi B, et al. 2007)** but pain relieving effect is seen immediately after starting treatment. It directly inhibits IL-1 synthesis, release and down modulate IL-1 induced activities.IL-1 plays fundamental role in osteoarthritis patho-physiology and cartilage destruction. IL-1 also promotes expression of inducible nitric oxide synthase, increase release of prostaglandins E2, IL-6, IL-8 in osteoarthritic chondrocytes, which promote joint degradation. Hence, by inhibiting IL-1 diacerein retards all pathological processes initiated in OA.Diacerein inhibits IL-1 induced expression of cartilage degrading enzymes. It also enhances expression of TGF β-1 and TGF β-2 thus favoring matrix synthesis and turnover in articular chondrocytes, thereby accounting for disease modifying property of diacerein. A further potential advantage of using diacerein in OA treatment is that it does not affect synthesis of prostaglandins and thereby does not have deleterious effect on the upper gastro-intestinal mucosa like NSAIDs **(Petrillo M, et al. 1991).**Aceclofenac is most commonly prescribed NSAID. Aceclofenac is an effective analgesic and anti-inflammatory agent, through these properties it provides greater symptomatic relief in a variety of painful conditions **(Dooley M, et al. 2001).** Aceclofenac has marked therapeutic effects on rheumatoid arthritis and osteoarthritis and good level of tolerability. Aceclofenac belongs to the group of non selective reversible inhibitors of COX enzyme.

Aceclofenac inhibits both cox-1 and cox-2 enzymes. Aceclofenac also reduce PGE2 production in the synovial fluid of patients with acute knee pain and suppress PGE2 production by blood polymorphonuclear leukocytes or mononuclear cells from patients with osteoarthritis after its administration. Aceclofenac works by blocking the chemicals that cause inflammation, pain, stiffness, tenderness, swelling and increase in temperature and helps to reduce inflammation and pain.

Aceclofenac takes a few weeks to reduce inflammation but relieves pain after first dose. Aceclofenac shows stimulatory effects on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL-1 activity. There is evidence that Aceclofenac stimulates synthesis of IL-1 receptor antagonist in articular chondrocytes subjected to inflammatory stimuli and that 4-hydroxyaceclofenac has chondroprotective properties attributable to suppression of IL-1 mediated promatrix metalloproteinase production and proteoglycan release **(Saraf S, 2006).**

FDC are very popular in clinical practice mainly because of improved patient compliance, decreased pill burden. However, irrational prescribing of FDC is a major health concern in India as such combinations are equally harmful. Many a time FDCs available in market lack therapeutic rationale for their use leading to wasteful expenditure **(Roy V, et al. 2011, Desai P, et al. 2013, Goswami N,et al. 2013).**

Of late the Fixed dose combinations (FDC) have shown increased use with a belief to offer better patient compliance, convenience, clinical effectiveness and less cost (**Amitava M, et al. 2012).** These advantages of FDC products along with the possibilities of greater clinical efficacy due to additive or synergistic effect of each active component, even open up the possibility of reduced dose of each active component and decrease in occurrence of side effects thus make FDCs attractive option. Number of FDC are available for OA treatment and one of most frequently used FDC is Aceclofenac and Diacerein combination. These FDC however, remain minimally researched in term of the claimed rationality, efficacy, safety and compliance in patients of OA in comparison to drugs when given alone.

While reviewing literature, number of studies regarding pharmacotherapy of OA are available exploring various possibilities. However, to the best of our knowledge we fail to cite any study evaluating efficacy, safety, compliance of Fixed dose combination of Aceclofenac and Diacerein and its comparison to these drugs given as free drug combination. Hence, the current study was under taken to address the rationality of this fixed dose Combinations in comparison to free drug combination at the same dose.

II. STUDY DESIGN

A randomized, open label, prospective clinical study was conducted in the Hajahad clinics,prince ,Dar and wani clinics. All principles of bioethics were followed.Following were the criteria for the selection of patients:

III. INCLUSION CRITERIA

Early unilateral or bilateral OA knee. Newly diagnosed or Patients diagnosed as having early OA taking drugs other than those under investigation were included after 2 weeks standardization.Either sex between 45-65 years of age.Patients with or without stable co-morbid condition.Ambulatory patients.
Should not be allergic to medicinal components

IV. EXCLUSION CRITERIA

Deranged LFT, RFT
APD/Peptic ulcers

Old long standing` H/O of OA knee.
Traumatic Arthritis.
Other Rheumatalogical disorders.
Bony Deformity.

The patients reporting to the Orthopedics OPD were screened for early OA knee, according to EULAR (European League Against Rheumatism) evidence based Recommendations, which include following signs and symptoms. **(Alhasmi AM. 2014).**

In early cases of OA typical symptoms of knee OA are pain, which often worsen towards the end of the day, relieved by rest; feeling of "giving away", only mild morning or inactivity stiffness and impaired function. In adults aged > 40 years with knee pain, there is only short-lived morning stiffness, functional limitation and one or more typical examination findings. Typically, the patient may grasp around the knee, indicating deep pain in the joint or bone. On physical examination, findings indicative of knee OA include crepitus, painful and/ or restricted movement, bony enlargement and absent or modest effusion.

Prior to intervention, a detailed clinical history. Physical examination and baseline investigations were carried out. Patients who were on drugs other than the drugs under investigation were standardized for 2 weeks by stopping the ongoing treatment and substituting it with local treatment e.g. hot fomentation and local exercises. The selected patients were enrolled for the study depending on the various inclusion and exclusion criteria. The patients were randomized and assigned to either of the two regimens.

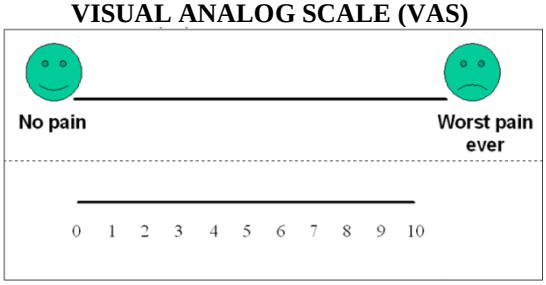
Group A comprised of patients who were put on Individual drugs given as free drug combination Aceclofenac (100mgs) followed by Diacerein (50mgs) after 1 hour twice daily orally for 6 weeks.

Group B comprised of patients who were put on fixed dose combination of Aceclofenac (100mgs) + Diacerein (50mgs) twice daily orally for 6 weeks**.**

During 6 weeks study period, all the patients were clinically evaluated and laboratory investigations were done.

Efficacy parameters were evaluated by the following scales:
VISUAL ANALOG SCALE (VAS) WESTERN ONTARIO AND MCMASTER UNIVERSITIES OSTEOARTHRITIS INDEX (WOMAC) GLOBAL ASSESSMENT SCALE (GAS)

VISUAL ANALOG SCALE (VAS)



VAS (Numeric rating scale) is a common form of response option in health outcome studies, often used to measure pain intensity based on questionnaires. It was first published in the early 1920s. It is used for children above 10 years old and adults. The scale is anchored by terms describing pain severity. An 11 point –numeric scale with 0 representing one pain extremes (e.g. no pain) and 10 representing the other pain extreme (e.g. worst possible pain). It is a measurement for subjective characteristics or attitude to pain. This scale can be administered verbally, telephonically or in writing. The number that the respondent indicates to rate pain intensity is recorded Scores range from 0-10. Higher scores indicate greater pain intensity. The scale takes < 1 minute to complete. The scale is easy to administer and score. Minimal language translation difficulties occur while using this scale among different cultures and languages. VAS can be used as a single item scale (e.g. pain) or a type of option for multiple item scales. **(Gillan A, et al. 2011, Kersten P, et al. 2012, Salaffi F, et al. 2004).**High test-retest reliability has been seen with this scale.VAS has demonstrated sensitivity to changes in pain. **(Joyce CR, et al. 1975, Ferraz MB, et al. 1990).**

V. WESTERN ONTARIO AND MCMASTER UNIVERSITIES OSTEOARTHRITIS INDEX (WOMAC)

WOMAC is one of the most widely self report measures of lower extremity symptoms and function. The scale has been studied over a period of almost 30 years in many different context and patient populations. WOMAC score was first developed to evaluate the efficacy of treatment according to the treatment method. The WOMAC questionnaire is filled out by surveying the patients and consists of 24 questions grouped into three categories of pain, stiffness and function with a total of 96 points. Each question is given 0 points in case there is

no problem, 1 point for mild problems, 2 points for moderate problems, 3 points for severe problems and 4 points for extreme problems. Therefore, a higher WOMAC score indicates poor results and the score is judged as excellent if it is below14, good if it is between 15 and 28, fair if it is between 29 and 38 and poor if it is above 38 points. WOMAC is translated into 65 languages. It takes 12 minutes to complete the scale. WOMAC score wa first developed to evaluate the efficacy of treatment according to the treatment method. The WOMAC scales have been extensively used in context of clinical trials. The sensitivity responsiveness and validity is well established. **(Bellamy N et, al. 1986, McConnell S et, al. 2001, Rogers JC et, al. 2003).** The WOMAC questionnaire is filled out by surveying the patients and consists of 24 questions. (ANNEXURE 1)

VI. GLOBAL ASSESSMENT SCALE (GAS)

Global Assessment scale is the assessment of patient's perception of pain as worst or bad. On improvement a perception of better should be made by the patient. Numeric scales are harder to interpret. Verbal scales have meaning and easier to interpret clinically. The patient may have a feeling of Much worse, worse, the same, better after taking treatment. Global change is assessed within a time frame which may vary from an hour, a day, a month or a year, since last visit, change in medication and start of study. This scale measures patients' Global impression of change (PGIC), regarding pain, function, and quality of life. This scale can combine multiple important outcomes. It allows patients to integrate factors and answers the important clinical questions as well. It is a reliable and validated scale used in clinical trials **(Ehrich EW et, al. 2000)**.

Pain evaluation was done at **Baseline, 2wks, 4wks, 6wks Safety profile** was evaluated on the basis of ADRs during the study period.Biochemical Parameters were evaluated at **Baseline, 6(wks)** are CBC, LFT, RFT

For clinical risk minimization

Intention to treat plan was followed. The study was done under the guidance of a clinician. Drop out among two groups and timing of drop out (Mean time) was noted. If a patient switched over to alternative treatment, it was noted.ADRs resulting in stoppage of treatment were Intolerance rate if any was noted. To take care of any possibility of APD related problem, PPI was added in both arms.

COMPLIANCE was assessed on follow up, pill count or by telephonically.

VII. STATISTICAL ANALYSIS

The data was expressed in Mean ± SEM or n (%).While comparing neck to neck unpaired-test and while comparing various parameters from the baseline the paired-test was used. The data expressed in n (%) was expressed in Chi-square test. The P value<0.05 was considered significant.

Aims And Objectives

1. To evaluate analgesic efficacy, safety and compliance of free drug combination (Aceclofenac followed by Diacerein) in patients of early OA knee.
2. To evaluate analgesic efficacy, safety and compliance of fixed drug combination (Aceclofenac + Diacerein) in patients of early OA Knee.
3. To compare analgesic efficacy, safety and compliance of compliance of free drug combination (Aceclofenac followed by Diacerein) with fixed drug combination (Aceclofenac + Diacerein) in patients of early OA knee.

Obsevation and Results

The present study was a randomized, open label trial to compare the analgesic efficacy, safety and compliance of fixed drug combination (Aceclofenac + Diacerein) with free dose combination (Aceclofenac, Diacerein) in patients of early Osteoarthritis knee. After meeting inclusion and exclusion criteria 200 patients were randomized into 2 groups, each group comprised 0f 100 patients and all the patients completed the study.

Group A Comprised of patients who were put on Free drug combination in which Aceclofenac (100mgs) was given followed by Diacerein (50mgs) after 1 hour orally for a period of 6 weeks twice daily.

Group B Comprised of patients who were given Fixed dose combination of Aceclofenac (100mgs) + Diacerein (50mgs) orally for a period of 6 weeks twice daily.

At the end of the study following observations were made.

Table 1: Showing Age Distribution

Age (years)	Group A N=100	Group B N=100	Total N=200

45-49	20 (20.0%)	32 (32.0%)	52 (26.0%)
50-59	52 (52.0%)	41 (41.0%)	93 (46.5%)
60 -65	28 (28.0%)	27 (27.0%)	55 (27.5%)
P=0.129, Chi –Square test			

Fig 1: Showing Age Distribution

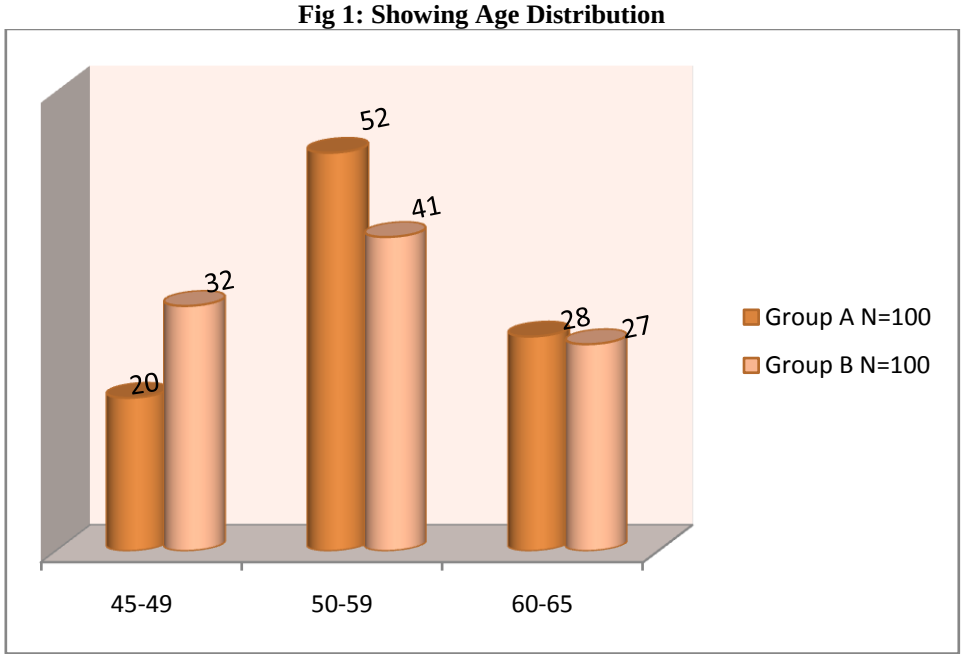


Table 2: Showing Weight (kgs) Distribution

GroupA N=100 Mean± Sd	71.58± 5.582
GroupB N=100 Mean± Sd	70.4± 5.456.

Fig 2: Showing Weight (kgs) Distribution

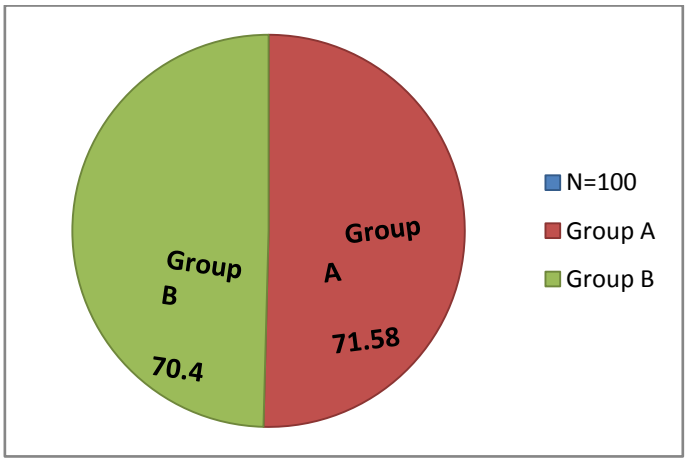


Table 3: Showing Gender Distribution

Gender	Group A N=100	Group B N=100	Total N=200
Male	32 (32.0%)	24 (24.0%)	53 (53.5%)
Female	68 (68.0%)	76 (76.0%)	147 (73.5%)

Fig 3: Showing Gender Distribution

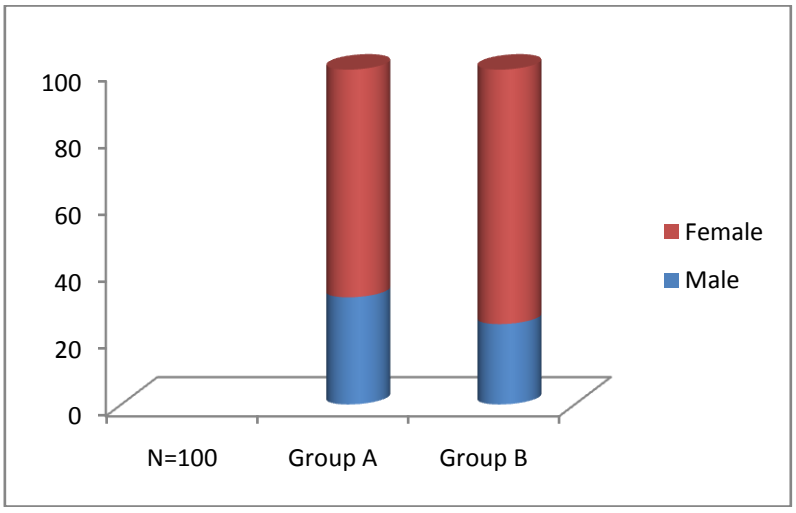
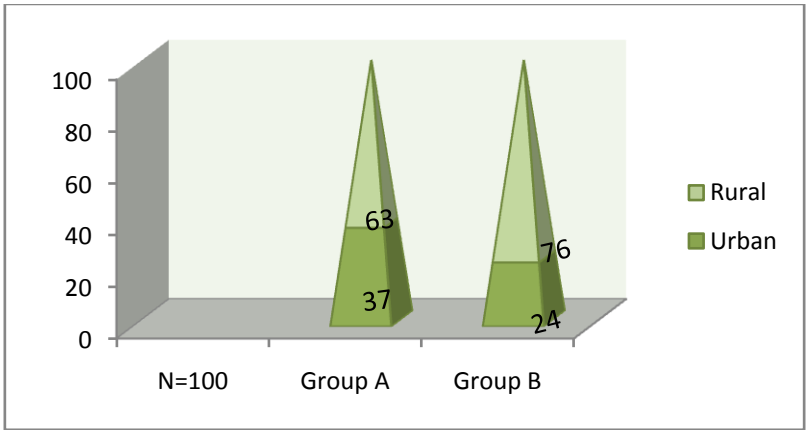


Table 4: Showing Demographic Profile

Demographic Profile	Group A N=100	Group B N=100	Total N=200
Urban	37 (37.0%)	24 (24.0%)	61 (30.5%)

Rural	63 (63.0%)	76 (76.0%)	139 (69.0%)
P=0.065, Chi-square test with continuity correction			

Fig 4: Showing Demographic Profile



Age Distribution

Patients between 45-49 years were 52 (26%), comprised of 20 Group A and 32 Group B. Maximum 93 patients 46.65% were in the age group of 50-59 years comprised of 52 in Group A and 41 in Group B. Patients between 60-69 years of age were 55(27.5%) and out of which 28 and 27 patients were in Group A and Group B respectively. **(Table 1)**

Weight Distribution

Patients in Group A had Average weight of 71.58 ± 5.582 while patients in Group B showed Average weight of 70.4 ± 5.456. **(Table 2)**

Gender Distribution

Maximum patients of Osteoarthritis were females 147 (73.5%).Females present in Group A were 68 and 79 in Group B. Total males were 53 (26.5%) comprised of 32 in Group A and 21 in (Group B).Male and Female Ratio was 1:2.7. **(Table 3)**

Demographic profile

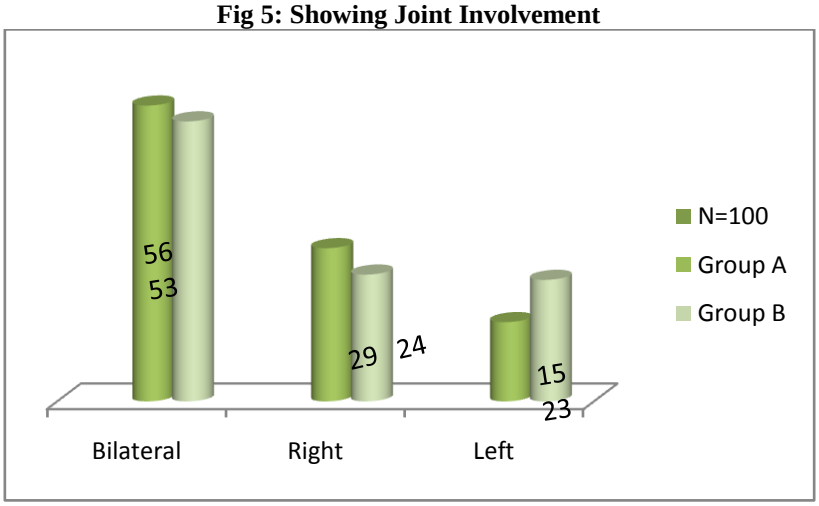
Maximum patients comprising of 139 (69.5%) were from rural background, comprised of 63 in Group A and 79 in Group B. Patients from urban background were 61 (30.5%) out of which Group A had 37 and Group B had 24. **(Table 4)**

Table 5: Showing Joint Involvement

Joint involvement	Group A N=100	Group B N=100	Total N=200
Bilateral	56 (56.0%)	53 (53.0%)	109 (54.5%)
Right	29 (29.0%)	24 (24.0%)	53 (26.5%)
Left	15 (15.0%)	23 (23.0%)	38 (19.0%)

P=0.327, Chi-square test			

Fig 5: Showing Joint Involvement



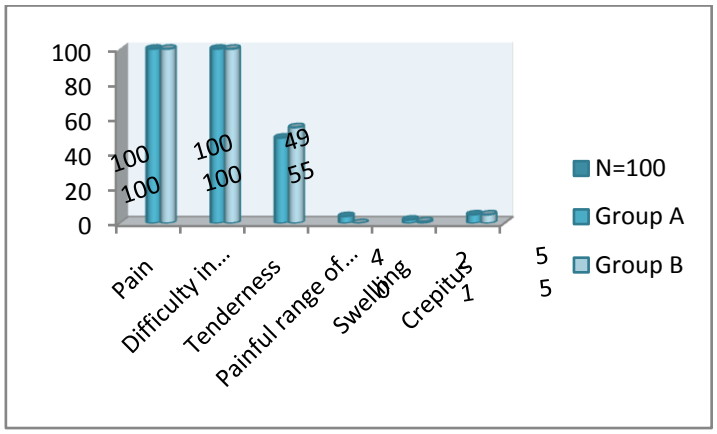
Joint Involvement

Maximum number of patients comprised of 109 (54.5%) had bilateral Osteoarthritis of knees. Group A had 56 while 53 patients were in Group B. Right sided Osteoarthritis was more common and affected 53 patients (26.5%) comprised of 29 in Group A while Group B had 24. While left sided Osteoarthritis was present in 38 patients (19%) with 15 patients in Group A and 23 in Group B.

Table 6: Showing Chief Complaints

Chief Complaints	Group A N=100	Group B N=100
Pain	100 (100.0%)	100 (100.0%)
Difficulty in squatting	100 (100.0%)	100 (100.0%)
Tenderness	49 (49.0%)	55 (55.0%)
Painful range of movements	4 (4.0%)	0 (0.0%
Swelling	2 (2.0%)	1 (1.0%)
Crepitus	5 (5.0%)	5 (5.0%)

Fig 6: Showing Chief Complaints



Chief Complaint

All patients in both groups had pain and difficulty in squatting (100%).Total of 125 patients complained of tenderness comprising of 49 in Group A and 55 in Group B.Painful range of movement was present in 4 patients of Group A only. 2 patients of Group A and 1 patient of Group B reported with swelling. Crepitus was present in 5 patients in each group.

VIII. SCALES EVALUATING PAIN PARAMETER

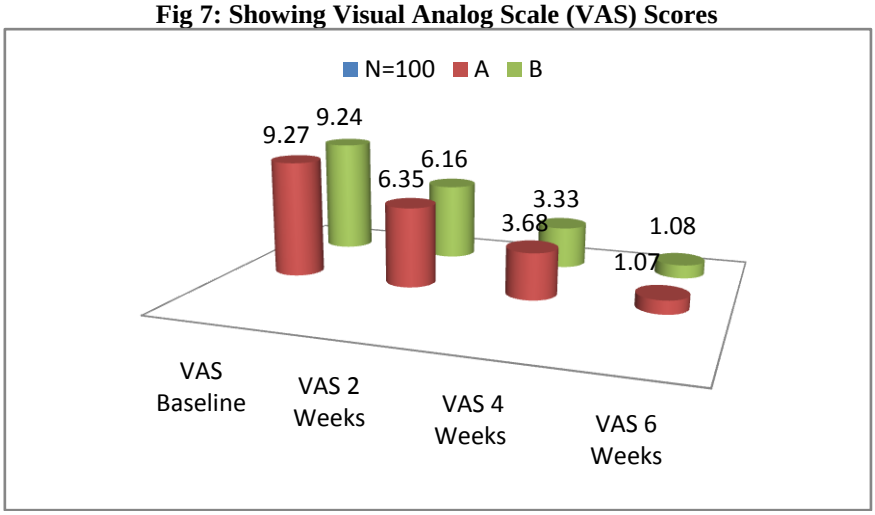
VISUAL ANALOG SCALE (VAS) Visual Analog Scale is a psychometric response scale which is based on responses to questionnaires and measures subjective characteristics or attitudes to pain. The two ends of scale are graded between 10 to 0. The end with 10 gradations represents severe pain while other end graded as 0 representing no pain. Shift of response from 10 towards 0 grades indicate decrease in pain.

Table 7: Showing Visual Analog Scale (VAS) Scores

Group N=100 Mean± SEM	VAS Baseline	VAS 2 Weeks	VAS 4 Weeks	VAS 6 Weeks	
A	9.27 ± 1.118	6.35 ± 1.527	3.68 ± 1.476	1.07 ± 1.416	P<0.0001(H.S)
B	9.24 ± 1.155	6.16 ± 1.561	3.33 ± 1.436	1.08 ± 1.289	P<0.0001(H.S)
	P>0.05(N.S)	P>0.05(N.S)	P>0.05(N.S)	P>0.05(N.S)	

H.S- Highly Significant: p< 0.01 vs. baseline (using Paired t-test)
N.S- Non Significant: p> 0.05 vs. other groups (using Unpaired t-test)

Fig 7: Showing Visual Analog Scale (VAS) Scores



Treatment in both groups lead to significant decline in pain score on VAS scale. (Group A) showed mean visual analog score at baseline as 9.27± 1.118 which reduced to 6.35± 1.527 at 2 weeks, 3.68± 1.476 at 4 weeks and 1.07± 1.416 at 6 weeks. The comparison with baseline score with post drug scores at 2, 4, 6 weeks revealed highly significant effect in reducing pain. ($P < 0.0001$) at all levels (Group B) revealed baseline visual analog score of 9.24± 155 which decreased to 6.16± 1.561 at 2 weeks, 3.33± 1.436 at 4 weeks and 1.08± 1.28 at 6 weeks. Significant decline in visual analog score on comparison with baseline score was found at all levels ($P < 0.0001$).

On comparing the two groups of treatment no significant differences was seen at baseline ($p=0.8521$), at 2 weeks ($p=0.3853$), at 4 weeks ($p=0.0908$) and at 6 weeks ($p=0.9584$) meaning thereby that both drug regimes were equally efficacious in reducing pain.

IX. WESTERN ONTARIO AND MCMASTER UNIVERSITIES ARTHRITIS INDEX (WOMAC) SCALE

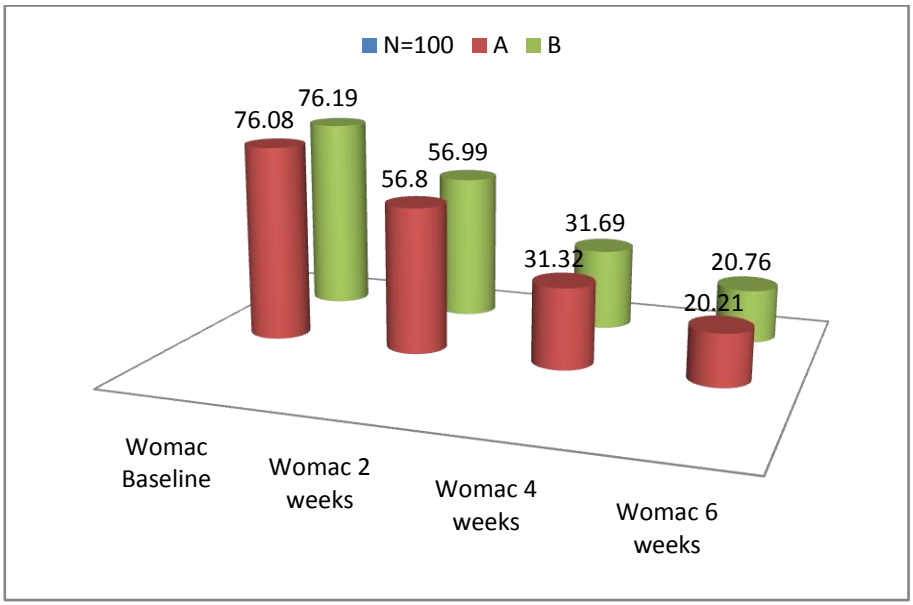
WOMAC scale is based on standardized questionnaires to evaluate the condition of patients with Osteoarthritis, including pain, stiffness and physical functioning of the joints.Womac score ranges from 0 to 96. Pain(score ranges 0-20), stiffness (score ranges 0-8) and functional limitation (score ranges 0-68).

Table 8: Showing Womac Scale Scores

GROUP N=100 Mean± SEM	Womac Baseline	Womac 2 weeks	Womac 4 weeks	Womac 6 weeks	
A	76.08 ± 8.752	56.8 ± 8.521	31.32 ± 4.845	20.21 ± 3.581	P<0-0001(H.S)
B	76.19 ± 8.160	56.99 ± 8.322	31.69 ± 4.361	20.76 ± 3.219	P<0.0001(H.S)
	P>0.05(N.S)	P>0.05(N.S)	P>0.05(N.S)	P>0.05(N.S)	

H.S- Highly Significant: p< 0.01 vs. baseline (using Paired t-test)N.S- Non Significant: p> 0.05 vs. other groups (using Unpaired t-test)

Fig 8: Showing Womac Scale Scores



Womac scores revealed decrease in levels, in both groups. In (Group A), the baseline score was 76.08±8.752 which declined to 56.8± 8.521 at 2 weeks, 31.32± 4.845 at 4 weeks, and 20.21± 3.581 at 6 weeks. Intra group comparison revealed highly significant effect at all post drug levels when compared with baseline score. (P<0.0001).

In (Group B), the baseline score of 76.19± 8.160 which fell to 56.99± 8.322 at 2 weeks, 31.69± 4.361 at 4 weeks and 20.76±.3-219 at 6 weeks. There was highly significant improvement in post drug scores when compared with baseline scores. (P<0.0001).

Inter group comparison of Womac score revealed n significant difference between two groups as indicated by values at baseline (p=0.9268), at 2 weeks (p=0.8734), at 4 weeks (p=0.5709) and at 6 weeks (p= 0.2547) indicating equally efficacy of both groups.

X. SCALE EVALUATING WELL BEING OF PATIENTS

GLOBAL ASSESSMENT SCALE-Assessed patients' perception of pain and was graded as **MuchWorse, Worse,The same and Better** during the treatment period. Global Assessment scale was assigned score of -1(Much Worse), 0(Worse), -1 to 0(The same) and 1(Better).

Table 9a: Showing Global Assessment Scale (GAS) Scores

GROUP N=100 Mean± SEM	**GAS Baseline**	**GAS 2 Weeks**	**GAS 4 Weeks**	**GAS 6 Weeks**	
A	-0.87 ± 0.337	0.5 ± 0.502	0.87 ± 0.337	0.99 ± 0.1	P<0.0001(H.S)
B	-0.85 ± 0.358	0.44 ± 0.537	0.86 ± 0.348	0.98 ± 0.14	P<0.0001(H.S)
	P>0.05(N.S)	P>0.05(N.S)	P>0.05(N.S)	P>0.05(N.S)	

H.S- Highly Significant: p< 0.01 vs. baseline (using Paired t-test)
N.S- Non Significant: p> 0.05 vs. other groups (using Unpaired t-test)

Fig 9a: Showing Global Assessment Scale (GAS) Score

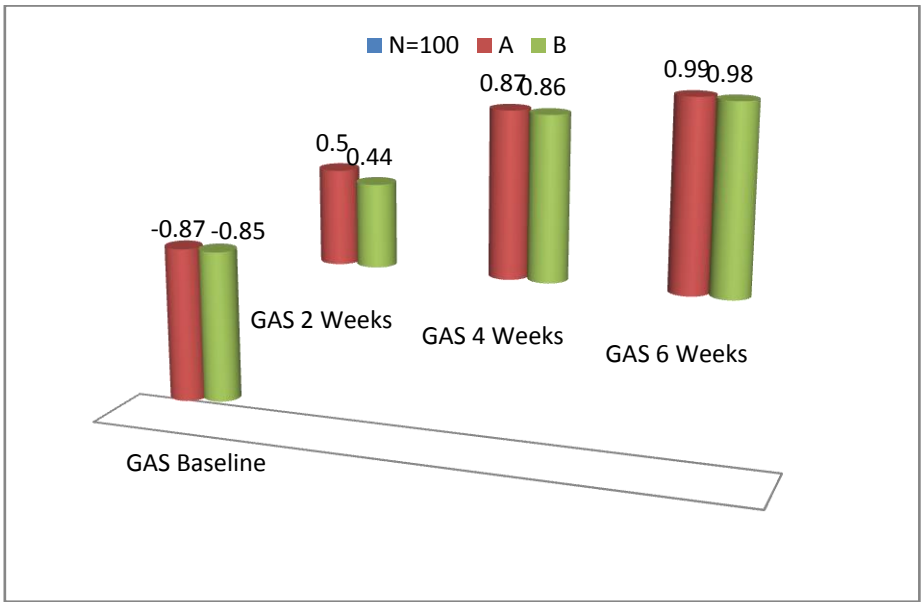
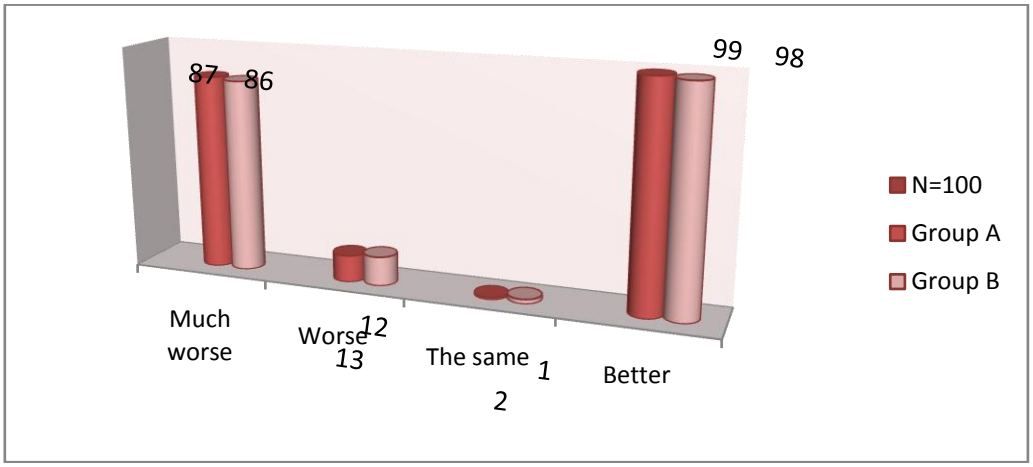


Table 9b: Showing Global Assessment Scale Patient Distribution

Group	Much worse	Worse	The same	Better
A	87	12	1	99
B	86	13	2	98

Fig 9b: Showing of Global Assessment Scale Patient Distribution



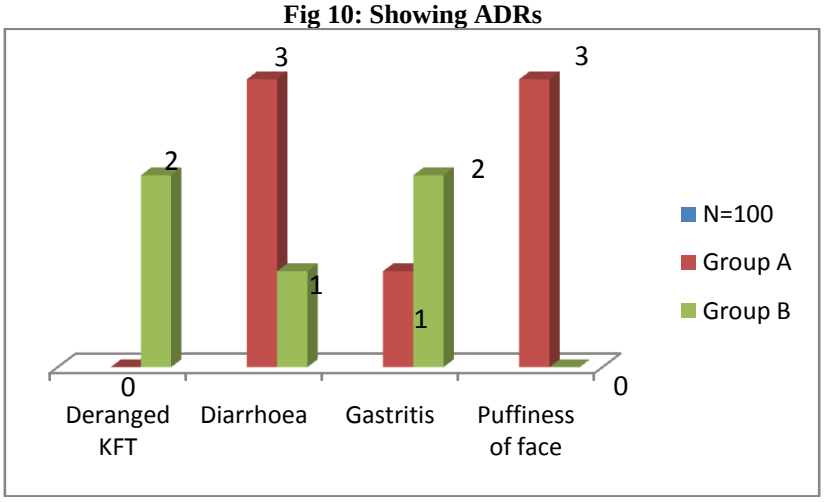
In Group A the baseline scores were -0.87± 0.337 which improved to 0.5± 0.502 at 2 weeks, further improved to 0.87± 0.337 at 4 weeks and at 6 weeks to 0.99± 0.1.This improvement was significant at all levels compared to baseline values. (P< 0.0001).In Group B the baseline scores of -0.85± 0.358 improved to 0.44± 0.537 at 2 weeks, 0.86± 0.348 at 4 weeks and to 0.98± 0.14 at 6 weeks. Significant improvement at all post drug score level as shown by highly significant (P<0.0001).Inter group comparison did not show any significant difference between the values at baseline (p=0.685), at 2 weeks (p=0.415), at 4 weeks (p=0.837) and at 6 weeks (p=0.526) showing both drug regimes to be equally efficacious.In Group A, 99 patients perceived feeling of

better after taking medication when assessed on Global Assessment Scale where as only 1 patient reported with The same perception of pain even after taking medication. In Group B, 98 patients reported as better after taking medication while 2 patients reported with The same perception of pain after taking medication when assessed on Global Assessment Scale.

Table 10: Showing ADRs

ADR	**Group A** N=100	**Group B** N=100	**Total** N=200
Deranged KFT	0 (0.0%)	2 (2.0%)	2 (1.0%)
Diarrhoea	3 (3.0%)	1 (1.0%)	4 (2.0%)
Gastritis	1 (1.0%)	2 (2.0%)	3 (1.50%)
Puffiness of face	3 (3.0%)	0 (0.0%)	3 (1.50%)
	7 (7.0%)	5 (5.0%)	12 (6.0%)
P=0.766,Chi-square test with continuity correction			

Fig 10: Showing ADRs



Both regimes were well tolerated .Only 12 ADRs were reported. ADRs were present in 7 patients in Group A and in 5 patients in Group B.Diarrhoea was the common ADR present in 3 patients in Group A and in 1 patient in Group B.Gastritis was present in 3 patients, 2 patients belonged to Group B and 1 patient to Group A. Puffiness of face was reported as ADR by 3 patients in Group A, while deranged KFT was seen in only 2 patients of Group B.Inter group Comparision failed to reveal any significant difference between two groups, (P=0.766).

LABORATORY PARAMETERS

Table 11a: Showing Laboratory Parameter (Group A)

Laboratory Parameters Group A (N=100)	
Parameter	**P-Value (Paired t-test)**
Haemoglobin	0.593
Total leucocyte count	0.674
Polymorphs	0.737
Lymphocytes	0.391
Monocytes	0.326

Eiosinophils	0.769
Bilirubin	0.602
SGOT	0.602
SGPT	0.297
ALKP	0.906
Blood urea	0.535
Creatinine	0.500

Fig 11a: Showing Laboratory Parameters (Group A)

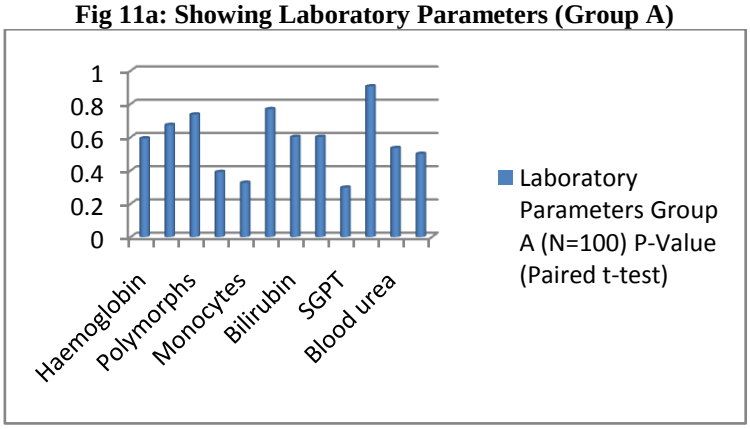
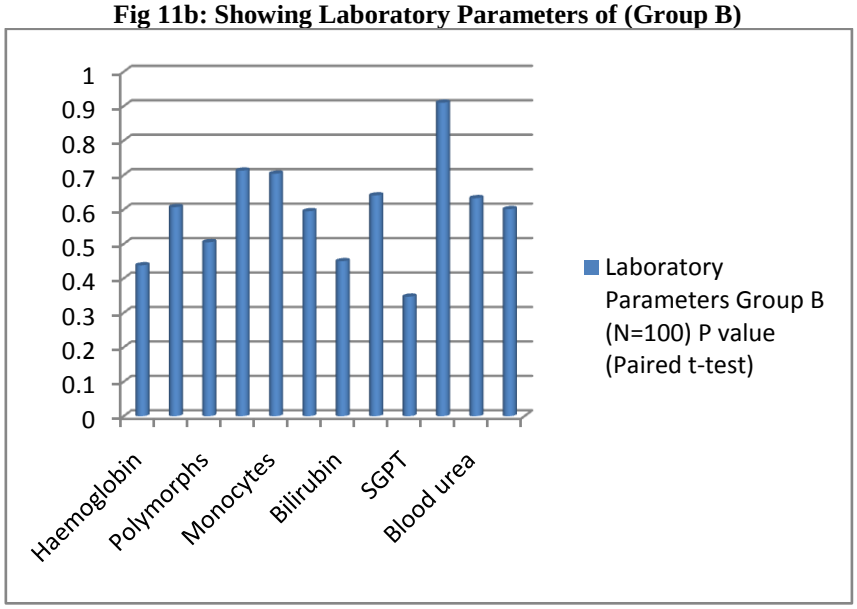


Table 11b: Showing Laboratory Parameters of (Group B)

Fig 11b: Showing Laboratory Parameters of (Group B)



Patients in both groups were evaluated at baseline and at 6 weeks for lab parameters. The values obtained revealed that all values were within normal limits at baseline and no significant change was obtained after 6 weeks of medication.

XI. COMPLIANCE

Compliance was assessed by follow up, pill count, telephonically during the entire span of study. Patients in both groups showed 100% compliance to the drug regimes. There was no dropout of any patient in either group during the study. No patient switched over to other medications. All patients completed the study.

XII. DISCUSSION

Osteoarthritis (OA) is the most common of the musculoskeletal diseases. It is a progressive degenerative disease, characterized by the loss of articular cartilage, accompanied by subchondral bone

remodeling, osteophytes formation at joint margins and synovial membrane inflammation. Clinical manifestations include joint pain, stiffness and loss of movement. Incidence of OA is 10% in males and 18% in females and occurs after 45 years of age. **(Mobasheri A. 2013, Alhasmi AM. 2014).**

There is evidence that the inflammatory events increase the destruction of articular cartilage and result in gradual development of joint pain, stiffness and restricted movements. The inflammation targets synovial membrane (Synovitis) in OA and its early distribution is confined to areas adjacent to sites of chondropathy and is associated with an acceleration of cartilage degradation (chondrolysis). The inflammation is brought about by cartilage matrix mettaloproteinases (MMPs) and reactive oxygen species (ROS) leading to for cartilage breakdown and release of microcrystals, osteochondral fragment breakdown. In the advanced OA, Synovitis invades across the synovial membrane, and progresses to fibrosis and villi hypertrophy. Mechanical stress directly damages cartilage or activate chondrocytes to produce abnormal level of matrix mettaloproteinases and products of extracellular matrix degradation in the joint cavity **(Henrotin Y, et al 2014).** The polymorphonuclear leucocytes and mononuclear cells release lysosomal enzymes and oxygen free radicals. In OA changes include subchondral osteoblasts, elevated alkaline phosphatase, increased release of osteocalcin, decreased parathyroid hormones and PGE dependent cyclic AMP formation, elevated urokinase plasminogen, IGF-1 and altered collagen metabolism. The diseased cells produce more IL-6 and PGE2 levels. OA as it is a inflammatory change suggests role of NSAIDs in management by combating the proinflammatory mediators.

At present OA is not curable, the main objectives in the management of OA are to provide pain relief, improve quality of life, mobility and walking and delay progression of OA. These objectives can be achieved by both non-pharmacological and pharmacological interventions. Non-pharmacological interventions include general measures like, patient education, lifestyle adjustment, weight loss and exercises. Pharmacological intervention primarily centers around NSAIDs and disease modifying osteoarthritic drugs (DMOADS).The treatment of knee OA should be tailored according to risk factors, severity of pain and other associated factors. NSAIDs are useful for long term use, if effective. Opioids analgesics can be used effectively if NSAIDs fail to provide relief. DMOAD or SYSADOA are also effective in symptomatic treatment with advantage of halting progress of disease. Intra-articular injection of corticosteroids is indicated to treat joint effusion and severe pain (**Joern M, et al. 2010).** If these treatment modalities fail, invasive intervention like lavage or arthroplasty can be resorted.Among all conservative drugs used for treatment of OA knee, NSAIDs are the most widely prescribed. **(Lansas A, et al. 2011).** These drugs provide symptomatic relief rather than actually preventing the progression of disease, besides having adverse effects on long term use on cartilage and gastrointestinal tract.

Recently, agents have been introduced that provide symptomatic relief by targeting underlying pathology in cartilage and subchondral bone and retard the progression of the disease. Such drugs classified as disease modifying osteoarthritic drugs (DMOAD).They are expected to retard, stabilize or even reverse pathological changes that occur in OA, thereby limiting progression of the disease.**(Johanne M, et al. 2010).**

Poor adherence to the medication regimes, especially in the chronic diseases affect the clinical outcome as the expected benefits may not be achieved. Fixed dose combinations (FDCs) have advantage and are important in combating chronic diseases by reducing non-compliance significantly. Besides FDC products have possibility of greater clinical efficacy due to additive effects of each active ingredient which may lead to even possibility of reduction of dose of each active ingredient and thereby minimizing side effects. FDA defines Fixed dose combination as a product composed of any drug, device or a biological product **(Sreedhar D, et al. 2006).**The Fixed dose combination are acceptable only when dosage of each ingredient meets the requirement of a defined population group and when the combination has advantage over single compound administered separately in therapeutic effect, safety or compliance. **(Chandler SG, et al. 2008).**The ratonality of FDC should be based on certain aspects**. (Poudel A, et al. 2008).** The drug in combination should act by different mechanism. Pharmacokinetics must not be widely different. Combination should not have superadded toxicity of the ingredients. It would be recommended if one of the ingredients takes care of toxicity of the other.

Currently number of FDCs are available for management of OA.Studies have compared the efficacy and safety of different FDCs **(Sripal B, et al. 2007, Bhavik D, et al. 2012).**However none of the study till date compared the Fixed drug combination of Aceclofenac and Diacerein with the Free drug combination of these drugs Aceclofenac followed by Diacerein with a time interval in-between.

Therefore taking above into account, the current study was undertaken to evaluate the most commonly used Fixed dose combination of NSAID (Aceclofenac) with DMOAD (Diacerein) for the efficacy, tolerability and compliance with Free drug combination of Diacerein and Aceclofenac when taken 1 hour apart in patients of early OA knee. In the present study, 200 patients of early OA knee diagonosed on EULAR guidelines. (**Johanne M, et al. 2010) w**ere enrolled. These patients were randomized into two groups , in Group (A) patients were put on free drug combination of Aceclofenac (100mgs) followed by (50mgs) Diacerein taken 1 hour apart twice daily orally for 6 weeks , while in Group (B) the patients were treated on fixed dose combination of Aceclofenac (100mgs) and Diacerein (50mgs) twice daily orally for 6 weeks.

Current study results revealed, the maximum numbers of patients were in the age group of 50-59 years. These trends were similar to**Torri G, et al. (1994)** where average age of the patients who had OA Knee was between 56.72± 10.66 to 57± 10.12. Similar results were reported by **Patil PR, et al. (2012)** where average age of patients was between 52.80± 4.55 to 53.61± 5.64. **Kurubaran G, et al. (2014)** estimated Prevalance of 70%-80% of OA in population aged 55 years and older.**Awan MMY, et al. (2014)** have also showed average age of patients between 56.04± 10. 78 to 56.35± 8.51 with OA knee.

OA is described as the disease of old. With age, joints become vulnerable for OA. The body's ability to repair cartilage deteriorates with increasing age as the osteoarthritic cartilage is chemically different from normal cartilage of the same age. As chondrocytes age, they lose their ability to make repairs and produce more cartilage. This process plays an important role in the development and progression of OA.

In the present study average weight among patients of Group A was 71.5 ± 5.582, while in Group B it was 70.4 ± 5.456. These finding are similar to the studies done by **Torri G, et al. (1994), Pham T, et al. (2004)**.The body weight of patients was between 70.52± 10.49 to 71.48± 9.04 in the first study; whereas the weight of the patients in the second study was between 76.8±14.0 to 78.0± 13.9.

The association between the Body Mass Index (BMI) and knee OA is of great importance, since knee OA has strong correlation with the highly inflammatory metabolic environment found in obesity. Cytokines associated to the adipose tissue adiponectine, leptine and resistine, can influence OA through the direct degradation of the articular cartilage or by controlling local inflammatory processes. Obesity increases mechanical stress on joints. Whereas the weight loss reduces the pain and improves the physical function of the OA patients. (**Marcia UDR, et al. 2013).**

In present study females were found to be more affected with Male: Female Ratio of =1: 2.7. Similar findings were reported by number of authors showing higher occurrence of OA among females ranging between 52 to 87% **Torri G, et al. (1994), Guaida EB, et al. (2007), Awan MMY, et al. (2014), Moon YW, et al. (2014).** Female gender is at higher risk for developing OA. Higher Prevalance of OA in females is because of hormonal factors affecting women during menopausal phase. Women with co morbid osteoporosis are also at higher risk of developing OA**. (Zhuo Q, et al. 2012).**

Demographic profile showed higher prevalence of OA in rural population than urban population. **Andrianakos AA, et al. (2006), Xiaozheng K, et al. (2009)** in their studies showed similar results. OA .It may be explained on the basis that people in rural areas do jobs that require heavy physical work. Knee OA has been associated with occupations, involving knee bending, squatting, kneeling and heavy lifting with obesity adding to the risk. Joint cartilage breaks down often because of mechanical stress or biochemical alteration causing the bone underneath to fail.

Bilateral involvement of Joints in both groups was more common in current study. Among unilateral OA right joint was involved more in both groups. These findings are similar to **Joren W, et al. 2010** as their results showed that right Knee OA was 23% as compared to 16.3% on left side.

Chief complaints reported by patients in both groups were pain (100%), difficulty in squatting (100%), tenderness 49% in Group A and 55% in Group B respectively, painful range of movements 4% in Group A only and swelling in 2% and 1% in Group A and Group B respectively. These findings are in concurrence with **Dilip KR, et al. (2010)** in which patients presented with knee pain, bony tenderness, swelling, and difficulty in squatting (stiffness).Results of study done by **Alhasmi AM.(2014)** are in concurrence with our study as patients reported with complaints of pain knees, bony swelling, bony tenderness, stiffness.

Both the groups did not show significant change in routine hematological and biochemical parameters carried out at the baseline and at the end of the study. These results are similar that were seen in the study **Bhavik D, et al. (2012).**This showed that all patients in both the groups had good tolerability to respective drug regimes for full study period of 6 weeks.

During study period, 12 Adverse drug reactions occurred. In Group A there were 7 while in Group B 5 ADRs were present. Similar findings were also reported by **Sharma A, et al. (2008), Brahmachari B, et al. (2009), Dilip K, et al (2010). Patil PR, et al. (2012).**All the patients completed the study that shows that ADRs were clinically insignificant (P=0.766).

Compliance to medication is of paramount importance as non compliance can lead to poor efficacy, resistance to a drug endangering not only individual but community at large.FDC have gained acceptance in clinical setup as they improve patient compliance **(Geiter, et al. 1987. Su and Perng. 2002. Eron, et al. 2000. Taylor and Shoheiber. 2003. Dezii. 2000. NDC dataset. 2003. Melikian, et al. 2002).** In the current study compliance was evaluated by examining the complete adherence rate/In-complete adherence rate and Switch to other medication, which was assessed by follow up, pill count or telephonically. In the present study 100% adherence rate was seen. No dropout was seen during study period in both regimes nor any switch over to other medication was present.

In present study**,** pain parameters showed improvement in both groups on Visual analog scale, Womac scale and Global assessment scale. The post drug values decreased in both groups at all levels (P value<0.0001)

on all scales, however on inter group comparison both drug regimes were equally efficacious on all scales as their was no statistical difference amongst them (P value > 0.05).

Review of the literature revealed no study where fixed dose combination or free drug combination of Aceclofenac and Diacerein were compared. However, there are number of studies comparing the drugs under investigation with other analgesics.

Aceclofenac has been reported by various authors to be effective in improving pain as demonstrated by findings on VAS scale, WOMAC scale and Global assessment scale. It has been shown to be effective than Piroxicam **(Torri G, et al. 1994).** Nabumetone **(Paul S, et al. 2009).** Diclofenac **(Ward DE, et al. 1995. Pareek A, et al. 2006. Patil PR, et al. 2012. Pareek A, Chandurkar N 2013. Awan MMY, et al. 2014).** Ibuprofen **(Klair JP. 2009).** Paracetamol **(Guaida EB, et al. 2007).** Celecoxib **(Soria MA, et al. 2006).**

Superiority of Aceclofenac is attributed to its stimulatory effects on cartilage matrix synthesis by inhibiting IL-β.There is evidence that Aceclofenac stimulates IL-1 receptor antagonist in human articular chondrocyte subjected to inflammatory stimuli and has chondroprotective properties because of suppression IL-1β mediated promatrix metalloproteinase production and proteoglycan release. Stimulation of glycosaminoglycan synthesis occurs by Aceclofenac in OA cartilage which prevents its deterioration. Aceclofenac exhibits excellent therapeutic effects by easy penetration into inflammatory tissue, such as joint and suppressing prostaglandin production. Aceclofenac inhibits COX-2 selectively not affecting stomach mucosal prostaglandin production thus reducing GIT side effects and a high tolerance. Therefore Aceclofenac has been considered useful for long term use.**(Hinz B, et al. 2003 Gowda KV, et al. 2006).**Aceclofenac reduces pain, symptomatic severity and improves functional capacity of injured joint, especially in cases of knee OA.**(Dooley M, et al. 2001).**

Similarly authors have found Diacerein to be effective in improving pain parameters of patients on VAS scale, WOMAC scale, and Global Assessment scale though it is primarily DMOAD.It has been documented superior to Placebo **(Pham T,et al. 2004 Brahmachari B, et al. 2009 Bartels EM, et al. 2009 Dilip KR, et al. 2010).** Piroxicam **(Louthrenoo W, et al. 200).** Aceclofenac **(Loitongbam LSS, et al. 2013).**

Efficacy of Diacerein can be explained by its anti-inflammatory effect through inhibition of interleukin-1B.Diacerein reduces fibrinolytic synovial fibroblasts and inhibits chemotaxis and super oxide anion production. Diacerein reduces collangenase in the intraarticular cartilage which occur in the body during destructive inflammation. Diacerein being a IL-1 inhibitor with symptom and structure modifying properties in OA.In bone remodelling both osteoblasts and osteoclasts contribute significantly. Altered bone formation occurs if there is difference in the activity of two cells. Diacerein and Rhein act on osteoclasts and reduced MMP-13 and Cathepsin K **(Boileau, et al. 2008).**MMP-13 and Cathepsin K work in conjunction in bone resorption. Reduction in activity of these enzymes leads imbalance between bone formation and resorption. Diacerein and Rhein block survival of mature osteoclasts proliferation and differentiation of pre- osteoclasts into mature osteoclasts and finally reducing number of osteoclasts. This effect of Diacerein Is because of its ability to increase PGE2 in human subchondral bone osteoblasts **(Pelletier, et al. 2001).**High PGE2 levels inhibit bone resorption and human OA subchondral bone osteoblasts expressing low levels of PGE2 enhanced formation of osteoclasts, whereas those expressing higher levels did not.**(Kwan T, et al. 2008).**

Pain should be treated promptly and effectively to restore the patient to full function and preserve quality of life as it negatively affects productivity. There are number of analgesics available combining two agents in one fixed dose combination. Combining two analgesics agents may provide an additive or synergistic effect of the two components. This can positively affect the analgesic efficacy of the drugs. A combination analgesic regimen may be considered especially effective when the individual agents have different analgesic mechanism and act synergistically. These fixed dose combinations are convenient, reduce the pill burden, and may require lower dosages of the individual compounds.

Fixed dose combinations have shown good efficacy and tolerability in OA knee in number of studies **(Choi, et al 2007. Corsinovi, et al 2009. Pareek, et al 2010. Doherty, et al 2011).** However, there is a paucity of the research evaluating FDC of Aceclofenac and Diacerein. Review of literature revealed a single study, evaluating the FDC of Aceclofenac and Diacerein on pain parameters **(Bhavik D, et al. 2012)** with FDC of Celecoxib and Diacerein . Their results were similar to the current study as the FDC of Aceclofenac + Diacerein showed improvement in pain, as all the 13 patients that completed study reported an excellent response to the drug regime.We have not come across even a single study where Fixed drug combination of Aceclofenac and Diacerein has been compared with Free drug combination of Aceclofenac and Diacerein. In the current study we have compared Fixed dose combination with the Free drug combination of these drugs. Such a study could have answered the advantages or disadvantages of FDC of Aceclofenac and Diacerein over the free drug combination in terms of efficacy, safety and compliance. The result of the current study has failed to demonstrate the superiority of either of group over each other in patients of early OA knee thereby indicating that current FDC of (Aceclofenac + Diacerein) is not irrationally marketed.

From the foregoining discussion we conclude that FDC of Aceclofenac and Diacerein when compared with Free drug combination of Aceclofenac and Diacerein given for 6 weeks in patients of early OA knee have similar clinical outcome in efficacy, safety and compliance.

XIII. LIMITATIONS

The present study suffers from few limitations. The study was conducted for a short period of six weeks duration. The study was done only in patients of early OA Knee and was not a placebo control study. To evaluate Diacerein in the short period for its disease modifying effect was not possible. However, current study focused on analgesic evaluation of Diacerein. No comparison was done with individual drugs as the research question centered around the comparison of FDC with free drug combination. Compliance was more based on subjective inference, rather than on analytic estimation of the drugs, as the department lacked the drug evaluation facilities.

XIV. SUMMARY AND CONCLUSION

- A randomized open label, prospective clinical study comparing analgesic efficacy, safety and compliance of fixed dose combination (Aceclofenac + Diacerein) with free drug combination (Aceclofenac, Diacerein) in patients of early OA knee was conducted over a period of one year.
- Total 200 patients were included after meeting inclusion criteria. They were randomized into two groups – 100 patients in Group A (free drug combination) received orally Aceclofenac (100mgs) followed by Diacerein (50mgs) with a time interval of 1 hour twice daily for 6 weeks while 100 patients in Group B (fixed dose combination) received orally Aceclofenac(100mgs) + Diacerein(50mgs) twice daily for 6 weeks. Parameters evaluated were age, weight, gender, demographic profile, clinical presentation, joint involvement, pain, compliance, adverse drug events and laboratory parameters during study period. All patients completed the study as there was no drop out.
- The majority of the patients were in the age group of 50-59, with average weight between 70.04± 5.456 to 71.58± 5.582 kgs. There was female predominance (73.5%) with rural background (69.5%).
- Patients presented with chief complaint of pain, difficulty in squatting, tenderness, painful range of movement and swelling. Maximum patients reported with bilateral invovelment of joints (54.5%). In unilateral involvement right joint was involved more.
- Compliance was 100% in all patients. There was no drop out, or switch over to other medications. Laboratory parameters in all patients remained within normal limits.
- Adverse events were observed in 12 patients only. 7 patients reported adverse events in Group A while 5 reported adverse events in Group B. Pain parameters of patients in Group A (Free drug combination) on VAS, WOMAC, GAS scales, on intra-group comparison showed significant improvement $P<0.0001$. Similar results were seen in Group B (Fixed dose combination) $P<0.0001$ when intra group comparison of the values was done. Inter-group comparison showed both drug regimes to be equally efficacious $P>0.05$.

XV. CONCLUSION

Current study demonstrated equal efficacy, safety and compliance of the both drug regimes of free drug combination (Aceclofenac, Diacerein) and fixed dose combination (Aceclofenac + Diacerein) in patients of early OA knee. None of the drug regimes showed superiority over other.

REFERENCES

[1] Aggaral V. Prevalance of Rheumatic diseases in India. JK Science. 2003; 5(2): 48-49.
[2] Alhasmi AM. Knee Osteoarthritis related pain: a narrative review of diagnosis and treatment. International Journal of Health Sciences, Qassim University.2014; 8(1): 86-104.
[3] Amitava M, Yunhui WU. Challenges & oppurtunities in achieving Bioequivalence combination for fixed dose combination products. AAPS J. 2012; 14(3): 646-55.
[4] Andrianakos AA, Kontelis LK, Karamitsos DG, et al.Prevalance of symptomatic knee, hand and hip osteoarthritis in Greece. The ESORDIG study. Journal of Rheumatology. 2006; 33(12): 2507-2514.
[5] Awan MMY, Ahmad I, Aziz A. Efficacy and safety of Aceclofenac in the treatment: A randomized double –blind comparative clinical trial versus Diclofenac. Professional Med J.2014; 21(3): 471-476.
[6] Bartel EM, Bliddal H, Schondorff PK, et al.Symptomatic efficacy and safety of Diacerein in the treatment of Osteoarthritis: a meta-analysis of randomized placebo-controlled trails. Osteoarthritis and Cartilage. 2009; 18(3): 289-296.
[7] Bellamy N, Buchanan WW. A preliminary evaluation of the dimensionality and clinical importance of pain and disability in osteoarthritis of the hip and knee. Clin Rheumatol. 1986; 5: 231-41.
[8] Bhavik D, Amit K, Rakeshkumar R. A randomized, active controlled, clinical trial to assess the efficacy and safety of Celecoxib+ Diacerein fixed dose combination in adult Indian patients- suffering from Osteoarthritis. Innovative journal of medical & health science. 2012; 2: 31-34.
[9] Blonde L, Wogen J, Krellick C, et al. Greater reductions in AIC in type 2 diabetic patients new to therapy with glyburide/ metformin tablets as compared to glyburide co-administered with metformin. Diabetes Obes Metab. 2003; 5: 424-31.

[10] Boileau C, Tat SK, Pelletier JP, et al. Diacerein inhibits the synthesis of resorptive enzymes and reduces osteoclastic differentiation/survival in osteoarthritic subchondral bone: a possible mechanism for a protective effect against subchondral bone remodelling. Arthritis Res Ther. 2008;10 R71.

[11] Brahmachari B, Chatterjee S, Ghosh A. Efficacy and Safety of Diacerein in early Osteoarthritis: a randomized placebo-controlled trail. Clin Rheumatol. 2009; 28(10).

[12] Chandler S. Gautam & Lekha S. Fixed dose drug combinations (FDCs): rational or irrational: a view point. Br J Clin Pharmacol. 2008 65:5 / 795–79.

[13] Chopra A, Patil J, Bilampelly V, et al. Prevalance of rheumatic disease in rural population in Western India: A WHO-ILAR-COPCORD study. J Assoc physicians India. 2001; 49: 240-46.

[14] Coggen D, Reading I, Croft P, et al. Knee Osteoarthritis and obesity. Int. J. Obes. Relat. Metab. Disord. 2001; 25(5): 622-7.Desai P, Patel S, Shah R, et al. A comprehensive evaluation ofrationality of cough and cold medicines available in Indian market. J Indian Med Assoc. 2013 Feb; 111(2):94-8.

[15] Dezii CM. A retrospective study of persistence with single pill combination therapy vs. concurrent two pill therapy in patients with hypertension. Manag Care.200; 9(9): 2-6.

[16] Dieppe P. Inflammation in Osteoarthrits. Rheumatol Rehabil. 1978; 59-63.

[17] Dilip k, Shobana M, Jagdiswar R. Evaluation of Efficacy & Safety of Diacerein in Osteoarthritis of knee joint. International Journal of Pharma & Bio sciences. 2010; 1(3): 1-12.

[18] Dooley M, Spencer CM, Dunn CJ. Aceclofenac: a reappraisal of its use in the management of pain and rheumatic disease. Drugs. 2001; 61:1351-78.

[19] Dougadaos M, Nguyem M, Berdah L, et al. Evaluation of the structure modifying effect of Diacerein in hip osteoarthritis: ECHODIAH, a three year, placebo-controlled trail. Evaluation of the chondromodulating effect of Diacerein in OA of the hip. Arthritis Rheum. 2001; 44: 2539-47.

[20] Ehrich EW, Davies GM, Watson DJ, et al. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities Osteoarthritis Index Questionnaire and Global Assessment in patients with Osteoarthritis. J. Rheumatol. 2000; 27(11): 2635-41.

[21] Eron JJ, Yetzer ES, Ruane PJ, et al. Efficacy, safety and adherence with twice – daily combination lamivudine/zidovudine tablet formulation, plus a protease inhibitor, in HIV infection. AIDS. 2000; 14:671-681.

[22] Ferraz MB, Quaresma MR, Aquino LR, et al. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J.Rheumatol. 1990; 17: 1022-4.

[23] Feson DT, Ahange y, Anthony JM, et al. Weight loss reduces the risk for symptomatic knee Osteoarthritis in women. Annals of Internal Medicine. 1992; 116: 535-39.

[24] Fransen M, Bridgett L, March l, et al. The epidemiology of Osteoarthritis in Asia.Internatinal journal of Rheumatic Diseases.2011; 14(2): 113-121.

[25] Geiter LJ, O Brien RJ, Combs DL, et al. Preliminary results of an evaluation of a combination tablet of isoniazid, rifampin and pyrazinamide.Tubercle.1987; 68(2): 41-46.

[26] Gillian AH, Samra M, Tetyana K, et al. Measures of adult pain: Visual Analog Scale Pain (VAS pain), Numeric Rating Scale (NRS pain), McGill Pain Questionnaire (MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP).Arthritis & Research.2011; 63(11): 240-252.

[27] Goswami N, Gandhi A, Patel P, et al. An evaluation of knowledge,attitude and practices about prescribing fixed dose combinationsamong resident doctors. Perspect Clin Res. 2013 Apr;4(2):130-5.

[28] Gowda KV, Rajan DS, Mandal U, et al. Evaluation of bioequivalence of two formulations containing 100 milligrams of Aceclofenac.Drug Dev Ind Pharm.2006; 32: 1219-25. `

[29] Grau M, Guasch J, Montero JL, et al. Pharmacology of the potent new non-steriodal anti inflammatory agent Aceclofenac .Arzneim-Forsch. 1991a; 41: 1265-76.

[30] Grau M, Montero JL, Guasch J, et al. The pharmacology profile of Aceclofenaca new non-steriodal anti-inflammatory & analgesic drug. Agents Action. 1991b; 32: 125-29.

[31] Guaida EB, Ivorra JR, Mola EM, et al. Aceclofenac vs. paracetmol in the management of symptomatic Osteoarthritis of the knee: a double blind 6-week randomized controlled trail. Osteoarthritis and Cartilage. 2007; 15(7): 900-908.

[32] Gupta N. Efficacy and Safety of Diacerein and Diclofenac in knee Osteoarthritis in Indian patients. A prospective Randomized open label study. Journal of Biomedical Sciences. 2012; 1(1).

[33] Hilal G, Martel PJ, Pelletier JP, et al. Osteoblast like cells from human subchondral osteoarthritic bone demonstrates an altered phenotype in vitro: possible role in subchondral bone sclerosis. Arthritis Rheum .1998; 41(5):891-9.

[34] Hinz B, Auge D, Rau T, et al. Simultation determination of Aceclofenac and three of its metabolites in human plasma by high – performance liquid chromatography. Biomed Chromatogr.2003; 17: 268-75.

[35] Joern W, Micheal P, Klaus U, et al. The Epidemiology, Etiology, Diagnosis and Treatment of Osteoarthritis of the knee. Dtsch Arztebl int. 2010; 107(9): 152-62.

[36] Johanne MP, Jean PP, et al. Effects of diacerein at molecular level in the osteoarthritis disease process. Therapeutic Advances in Musculoskeletal Disease.2010; 2(2): 95-104.

[37] Joyce CR, Zutshi DW, Hrubes VF, et al. Comparison of fixed interval and visual analogue scales for rating chronic pain. Eur J Clin Pharmacol. 1975; 8: 415-20.

[38] Klair JP. A comparative Study of efficacy and Tolerability of Ibuprofen Vs Aceclofenac in Osteoarthritis of Knee Joint. Annals of Medicine & Healthcare. 2009: 236.

[39] Kersten P, Ayse A, Kucukdeveci, et al. The use of the visual analogue scale (VAS) in rehabilitation outcomes Rehabil Med.2012; 44: 609-610.

[40] Kurubaran G, Michael JM, Vasudeva MCR, et al. Level and Determinants of knowledge of Symptomatic Knee Osteoarthritis among Railway Workers in Malaysia. Biomed Research International.2014; Article ID 370273: 1-9.

[41] Kwan TS, Pelletier JP, Lajeunesse D, et al. The differential expression of osteoprotegerin (OPG) and receptor activator of nuclear factor kappa B ligand (RANK) in human osteoarthritic subchondral bone osteoblasts is an indicator of the metabolic state of these disease cells. Clin Exp Rheumatol.2008;26:295-304.

[42] Lajeunesse D, Hilal G, Pelletier JP et al. Subchondral bone morphological and biochemical alterations in Osteoarthritis. Osteoarthritis Cartilage. 1999; 7(3): 321-2.

[43] Lawrence RC, Falcon DT, Helmick CG, et al. Estimates of the Prevalance of arthritis and other rheumatic conditions in the united states. Arthritis Rheum. 2008; 58: 26-35.

[44] Loitongbam LSS, Handa G,Sing U, et al. Efficacy of Diacerein in the treatment of Osteoarthritis of Knee.IJPMR.2013; 24(4): 92-8.

[45] Louthrenoo W, Nilganuwong S, Aksaranugraha, et al. The efficacy, safety & carry over effect of Diacerein in the treatment of painful knee Osteoarthritis: a randomized, double-blind, NSAID-controlled study. Osteoarthritis Research Society International. 2007; 15: 605-614.
[46] Mahajan A, Jasrotia DS, Manhas AS, Jammal SS. Prevalance of Rheumatic disorders in Jammu.JK science. 2003; 5 (2): 63-66.
[47] Mahajan A, Kulbir S, Vishal R, et al. Diacerein: A symptomatic slow acting drug for Osteoarthritis. JK science. 2006; 8(3): 173-75.
[48] Mansell JP, Bailey AJ. Abnormal cancellous bone collagen metabolism in Osteoarthritis Clin Invest. 1998; 101(8):1596-1603.
[49] March IM, Bachmeier CJ. Economics of osteoarthritis global prespective.Bailleres clinical Rheumatology. 1997; 11: 817-34.
[50] Marcia UDR, Gustavo CDC, Alexandre FP. Current concepts in osteoarthritis.Acta Ortop Bras. 2013; 2 (12): 120-2.
[51] McConell S, Kolopack P, Davis AM. The Western Ontario and Mcmaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arithritis Rheum. 2001; 45(5): 453-461.
[52] Mehdi B, Singh Pk, Prakash A, Sen R, et al. Diacerein: A new Disease Modulating Agent in Osteoarthritis. IJPMI 2007; 18(2): 48-52.
[53] Melikian C, White TJ, Vanderplas A, et al. Adherence to oral antidiabetic therapy in a managed Care organization: a comparison of monotherapy, combination therapy and fixed dose Combination therapy. Clin Ther.2002; 24: 460-467.
[54] Mobasheri Al. The Future of Osteoarthritis Therapeutics: Targeted Pharmacological Therapy. CurrRep. 2013; 15(364): 1-13
[55] Pareek A, Chandurkar N. Comparison of gastrointestinal safety & tolerability of Aceclofenac with diclofenac: a multicentreic, randomized, double blind study in patients with osteoarthritis. Curr Med Res Opin. 2013; 29(7): 849-59.
[56] Pareek A, Chandurkar N, Gupta A, et al. Efficacy & safety of Aceclofenac-cr & Aceclofenac in the treatment of knee osteoarthritis: a 6-week, comparative, randomized, multicentric, double-blind study. J Pain. 2011; 12(5): 546-53.
[57] Pareek A, Chandurkar N, Oak J, et al. Efficacy & safety of Aceclofenac in the treatment of osteoarthritis double-blind comparative clinical trial versus diclofenac-an Indian experience. Curr Med Res Opin. 2006; 22(5): 977-88.
[58] Patil PR, Jaida J, Palani A, et al. A comparative study of efficacy and safety of Diclofenac and Aceclofenac in the treatment of Osteoarthritis patients.Journal of drug delivery and Therapeutics. 2012; 2(4): 139-143.
[59] Paul S, Das N, Ghosh S. The effects of Aceclofenac & nabumetone in Osteoarthritis. JNMA J Nepal Med Assoc. 2009; 48(174): 121-5.
[60] Pavelka K, Trc T,Karpas K,et al. The efficacy and safety of diacerein in the treatment of painful osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo-controlled study with primary end points at two months after the end of a three-month treatment period. Arthritis Rheum.2007: 56(12): 4055-64.
[61] Pelletier JP, Yaron M, Harooui B, et al. Efficacy & safety of Diacerein in Osteoarthritis of the knee: a double- blind placebo controlled trail. The Diacerein study group .Arthritis Rheum. 2000; 43: 2339-48.
[62] Pelletier JP,Lajeunesse D, Reboul P, et al. Diacerein reduces the excess synthesis of bone remodelling factors by human osteoblasts cells from osteoarthritic subchondral bone.J Rheumatol. 2001; 28: 814-24.
[63] Perez M, Calero E, Rodriquez M, et al. Comparison of Aceclofenac with piroxicam in the treatment of Osteoarthritis. Clin rheumatol. 1997; 16(2): 154-9.
[64] Petrillo M, Montrone F, Adrizzone S, et al. Endoscopic evaluation of di-acetylrehin induced gastric mucosal lesion. Curr Ther Res. 1991; 49: 10-15.
[65] Pham T, Henanff A, Ravaud Ph et al. Evaluation of the symptomatic & structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with Diacerein & placebo in a year randomized controlled study in symptomatic knee Osteoarthritis. Ann Rheum Dis. 2004; 63: 1611-17.
[66] Philip J, Gregory, Chris F. Dietary Supplements as Disease-Modifying Treatments in Osteoarthritis: A Critical Appraisal.P&T.2014; 39: (6) 436-452.
[67] Polisson R. Innovative therapies in Osteoarthritis. Curr Rhematol Rep. 2001; 3(6): 489-95.
[68] Pottie P, Presle N, Terlain B, et al. Obesity and Osteoarthritis: more complex than predicted.Ann.Rheum.Dis. 2006; 65: 1403-5.
Poudel A, Palaian S, Shankar PR, et, al.. Irrational fixed dosecombinations in Nepal: need for intervention. Kathmandu Univ Med J (KUMJ). 2008 Jul-Sep;6(23):399-405.
[69] Pramod R, Jyothermal J, Anuradha P et al. A Comparative study of efficacy & safety of Diclofenac &Aceclofenac in the treatment of Osteoarthritis patients. Journal of drug delivery & therapeutics. 2012; 2(4).
[70] Rajesh SB, Chandralekha N, Harsharaj. Diacerein efficacy in knee osteoarthritis: Pain and Structure. International Journal of Recent Trends in Science And Technology.2014;9 (3): 411-412.
[71] Rintelen B, Neumann K, Leeb B. A met analysis of controlled clinical studies with Diacerein in the treatment of Osteoarthritis. Archieves of Internal Medicine. 2013; 166(17): 1-3.
[72] Rogers JC, Irrgang JJ. Measures of adult lower extremity functions. Arithritis Care Res. 2003; 49(5S): S67-S84.
, Malhotra R, Tayal V, Bansal A, et al. Fixed-dose combinations forcough and common cold in India: an assessment of availability and rationality. Fundam Clin Pharmacol. 2011 Apr; 25(2):258-66.
[73] Salaffi F, Stancati A, Silvestri CA, et al. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale.Eur J Pain.2004; 8: 283-91.
[74] Sathish A, Kinjal P. The effect of Etodolac and Aceclofenac in patients with Osteoarthritis of knee. A comparative study. International Journal of Health & Pharmaceutical Sciences.2013;2(2) :2013.
[75] Saraf S. Aceclofenac: A potent Non-Steroidal Anti-inflammatory Drug. Pharmaceutical information.net. 2006 May; 45.
[76] Sawitzke AD, Shi H, Finco MF, et al. The effect of Glucosamine &/or Chondritin sulfate on the progression of the knee Osteoarthritis: a report from the glucosamine/Chondritin arthritis intervention trial. Arthritis & Rheumatism. 2008; 58(10): 3183-91.
[77] Sharma A,Rathod R, Baliga VP. An open prospective study on post marketing evaluation of the efficacy and tolerability of Diacerein in Osteoarthritis of the knee (DOK).J Indian Med Assoc.2008: 106(1):54-6,58.
[78] Sripal B, Gayathri K, Sanobar P, et al. Fixed- dose Combinations improves Medication Compliance: A Meta Analysis. The American Journal of Medicine. 2007; 120: 713-19.
Sreedhar D, Subramanian G, Udupa N. Combination drugs: arethey rational? Curr Sci 2006; 91: 406.
[79] Soria MAA, Largo R, Santilana J, et al. Long term NSAID treatment inhibits COX-2 synthesis in the synovial membrane of patients with Osteoarthritis: differential proinflammatory cytokine profile between Celecoxib and Aceclofenac. Annals of Rheumatic diseases. 2006; 65: 998-1005.
[80] Su WJ, Perng RP. Fixed dose combination chemotherapy (Rifater/Rifinah) for active pulmonary tuberculosis in Taiwan: a two year follow-up.Int J Tuberc Lung Dis.2002; 6: 1029-101032.

[81] Tanamas SK, Wyethilake P, Wluka AE, et al. Sex hormones and structural changes in Osteoarthritis: a systemic review. Maturitas. 2011; 69(2): 141-56.
[82] Taylor AA, Shoheiber O. Adherence to antihypertensive therapy with fixed dose amlodipine besylate/benazepril HCL versus comparable component–based therapy. Congest Heart Fail.2003;9: 324-332.
[83] Torri G, Vignati C, Agrifoglio E, et al. Aceclofenac versus Piroxicam in the management of Osteoarthritis of the knee: A double blind controlled study. Current Therapeutic Research.1994; 55(5): 576-583.
[84] Valdes AM, Spector TD. The contribution of genes to Osteoathritis. Rheum. Dis. Clin. North Am. 2008: 34(3): 581-603.
[85] Verbruggen G. Chondroprotective drugs in degenerative joint disease. Rheumatology (Oxford) 2006; 45(2): 129-38.Epub 2005 Nov 8.
[86] Ward DE, Veys EM, Bowdler JM, Roma J. Comparison of Aceclofenac with diclofenac in the treatment of Osteoarthritis. Clin Rheumatol. 1995; 14(6): 656-62.
[87] Yamazaki R, Kawai S, Matsumoto T et al. Hydrolytic Activity is Essential for Aceclofenac to Inhibit Cyclooxygenase in Rheumatoid Synovial Cells. The Journal of Pharmacology & experimental Therapeutics. 1999; 289(2):
[88] Yaron M, Shiraz I, Yaron I. Anti-interleukin -1 effects of Diacerein % Rhein in human Osteoarthritis synovial tissue & cartilage cultures. Osteoarthritis Research Society International. 1999; 7(3): 272-80.
[89] Young WM, Seung BK, Tae KK, et al. Efficacy and Safety of Aceclofenac Controlled Release in patients with knee Osteoarthritis: A 4-week multicenter, randomized, comparative clinical study. Knee Surgery and Related Research. 2014; 26(1): 33-42.
[90] Yves H, Laurence P, Cecile L. Targeting the synovial angiogenesis as a novel treatment approach to osteoarthritis. Therapeutic Advances in Musculoskeletal Disease.2014; 6(10): 20-34. Zhuo Q, Yang W, Chen J, et al. Metabolic syndrome meets osteoarthritis. Nat Rev Rheumatol.