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The analgesic efficacy, safety, and compliance of free drug combinations versus fixed dose combinations of aceclofenac and diazepam were compared.

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Abstract
The ever-increasing elderly population expects and deserves a fulfilling and active existence with minimal reliance on "managed care". This necessitates an intact and robust musculoskeletal system. However, age-related musculoskeletal diseases are a leading cause of global morbidity and result in substantial expenditures for the health and social care systems. Age is the most significant risk factor for degenerative joint disease. Osteoarthritis (OA) is a degenerative disease caused by a collection of mechanical abnormalities affecting the joints, articular cartilage, and subchondral bone. Osteoarthritis is derived from the Greek terms "Osteo" (bone) and "Ortho" (joints) and "Itis" (inflammation). OA is characterized by the progressive onset of joint pain, edema, instability, rigidity, and loss of range of motion (Louthrenoo W. et al., 2007).The joints most frequently affected are the knees, hips, hands, and spine.

INTRODUCTION

OA has a gradual onset, with symptoms typically not appearing until the age of 45 to 50. Inflammation is the result of polymorphonuclear leucocytes releasing lysosomal enzymes and oxygen free radicals, according to the evidence. This leads to an increase in articular cartilage degeneration, joint pain, rigidity, and movement restriction (Dieppe, 1978). In osteoarthritis, subchondral osteoblasts have an abnormal phenotype, increased alkaline phosphatase, increased osteocalcin release, decreased parathyroid hormone and PGE2-dependent cAMP formation, increased Urokinase plasminogen, IGF-1, and altered collagen metabolism.With the improvement of health care facilities in developing nations, the elderly population is also growing. Consequently, the prevalence of age-related diseases such as osteoarthritis is anticipated to rise, necessitating a greater emphasis on health care. Besides the progressive character of the disease, pain and inflammations are a major concern for both patient and physician. Reducing symptoms, minimizing functional disability, halting the progression of structural changes, and ultimately delaying or avoiding arthroplasty are the primary goals of OA treatment. "The best treatment for knee OA is prevention" (Joern W et al., 2010).

Common analgesics for osteoarthritis include nonsteroidal anti-inflammatory drugs (NSAIDs) and inhibitors of the cyclooxygenase (COX) enzyme (Louthrenoo W et al., 2007). However, the use of NSAIDs may increase the risk of GIT adverse effects, and because they have no effect on the underlying pathogenesis of articular diseases, they play a minimal role in modifying disease progression.

Recently, there has been an increase in the use of disease-modifying osteoarthritic medications (DMOAD) whose primary action is to prevent articular cartilage breakdown (Mahajan A, et al., 2006).These medications have a gradual onset of action after 4-6 weeks, but their symptomatic effects persist for 4-8 weeks after treatment cessation. Glucosamine, chondritinsulphate, chemically modified tetracycline, and diacerein are drugs in this class.In larger clinical trials, tetracyclines have yet to demonstrate their structure-modifying activity (Mahajan A. et al., 2005).Patients who participated in trials conducted by GAIT demonstrated that Glucosamine and Chondritin supplements did not significantly reduce pain or enhance function (Sawitzke AD, et al., 2008).

Diacerein is a commonly used DMOAD with excellent pain-alleviating properties. The disease-modifying effect of a treatment becomes evident between two and four weeks after its initiation and reaches a significant value between four and eight weeks later.

4-6 weeks, but persists for several weeks after administration cessation. (Mehdi B. et al., 2007) However, the pain-

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relieving influence of treatment is promptly apparent. It inhibits directly IL-1 synthesis, release, and IL-1-induced activities.IL-1 serves a crucial function in the pathophysiology and cartilage destruction of osteoarthritis. IL-1 also promotes expression of inducible nitric oxide synthase and the production of joint-degrading prostaglandins E2, IL-6, and IL-8 from osteoarthritic chondrocytes. By inhibiting IL-1, diacerein retards all OA-initiated pathological processes.Diacerein inhibits the expression of cartilage degrading enzymes induced by IL-1. It also increases expression of TGF -1 and TGF -2, thereby promoting matrix synthesis and turnover in articular chondrocytes and accounting for diacerein's disease-modifying properties. A further potential benefit of using diacerein in the treatment of OA is that it does not inhibit the synthesis of prostaglandins and, unlike NSAIDs, does not have a detrimental effect on the upper gastro-intestinal mucosa.The most commonly prescribed NSAID is aceclofenac. By virtue of its analgesic and anti-inflammatory properties, aceclofenac provides increased symptomatic alleviation in a variety of excruciating conditions (Dooley M., et al., 2001). Aceclofenac has significant therapeutic effects on rheumatoid arthritis and osteoarthritis and a high tolerability level. Aceclofenac belongs to the class of irreversible, nonselective COX enzyme inhibitors.

The anti-inflammatory agent aceclofenac inhibits both cox-1 and cox-2 enzymes. After administration, aceclofenac reduces PGE2 production in the synovial fluid of patients with acute knee pain and suppresses PGE2 production by polymorphonuclear leukocytes or mononuclear cells in the blood of patients with osteoarthritis. Aceclofenac reduces inflammation and pain by blocking the substances that cause inflammation, pain, rigidity, tenderness, edema, and an increase in body temperature.

It takes a few weeks for aceclofenac to reduce inflammation, but the first dose relieves discomfort. The stimulatory effects of aceclofenac on cartilage matrix synthesis may be related to the drug's ability to inhibit IL-1 activity. There is evidence that aceclofenac stimulates the synthesis of IL-1 receptor antagonist in articular chondrocytes exposed to inflammatory stimuli, and that 4-hydroxyaceclofenac has chondroprotective properties due to inhibition of IL-1-mediated promatrix metalloproteinase production and proteoglycan release (Saraf S, 2006).

FDC are widely used in clinical practice due to increased patient compliance and reduced tablet burden. However, irrational prescribing of FDC is a significant health concern in India due to the fact that such combinations are equally hazardous. Frequently, FDCs on the market lack a therapeutic rationale for their use, resulting in unnecessary spending (Roy V, et al. 2011, Desai P, et al. 2013, GoswamiN,et al. 2013).

Fixed dose combinations (FDC) have recently gained popularity due to the belief that they offer improved patient compliance, convenience, clinical efficacy, and lower costs (Amitava M, et al., 2012). These benefits of FDC products, in addition to the possibility of greater clinical efficacy due to the additive or synergistic effect of each active component, as well as the possibility of reduced doses of each active component and a reduction in the incidence of side effects, make FDCs an attractive option. Aceclofenac and Diacerein combination is one of the most commonly used FDC for the treatment of osteoarthritis. The asserted rationale, efficacy, safety, and compliance of these FDC in comparison to medications given alone in OA patients, however, have been the subject of minimal research.

Reviewing the literature reveals a number of studies investigating various pharmacotherapeutic possibilities for OA. However, to the best of our knowledge, there is no study comparing the efficacy, tolerability, and compliance of the fixed dose combination of aceclofenac and diacerein to the free drug combination. In light of this, the current study was conducted to determine the efficacy of fixed dose combinations versus unrestricted drug combinations at the same dose.

STUDYDESIGN

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

INCLUSIONCRITERIA

Initial unilateral or bilateral knee OA. After 2 weeks of standardization, newly diagnosed or early-stage OA patients taking medications other than those under investigation were included.Both sexes between the ages of 45 and 65.Patients with or without a co-morbid condition that is stable.Patients who are mobile.

Should not be allergic to pharmaceutical ingredients

In early cases of osteoarthritis, the typical symptoms of knee OA include pain, which often worsens at the end of the day and is alleviated by rest; a sensation of "giving away"; moderate morning or inactivity

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stiffness; and impaired function. Knee pain is limited to brief morning discomfort, functional limitation, and one or more typical examination findings in adults older than 40. Typically, the patient will clutch around the knee, signifying severe joint or bone discomfort. On physical examination, signs of knee osteoarthritis include crepitus, excruciating and/or restricted movement, bony enlargement, and a lack of or minimal effusion.

Prior to intervention, a thorough clinical history is required. The patient underwent a physical examination and baseline investigations. Patients who were taking medications other than those under investigation were standardized for two weeks by discontinuing their current treatment and replacing it with local treatment, such as heated fomentation and local exercises. Patients were recruited in the investigation in accordance with the inclusion and exclusion criteria. The patients were randomly assigned to one of the two treatment regimens.

Group A consisted of patients who were administered the free drug combination Aceclofenac (100 mg) followed by Diacerein (50 mg) twice daily orally for six weeks.

Patients in Group B were administered a fixed dose combination of Aceclofenac (100 mg) and Diacerein (50 mg) twice daily orally for six weeks.

During the six-week trial period, all patients were evaluated clinically and underwent laboratory tests.

Efficacyparameterswereevaluatedbythe followingscales:

VISUAL ANALOG SCALE (VAS) WESTERN ONTARIO AND MCMASTER UNIVERSITIESOSTEOARTHRITISINDEX(WOMAC)GLOBAL ASSESSMENTSCALE(GAS)

VISUALANALOGSCALE (VAS)

VAS (Numerical rating scale) is a common form of response option in health outcome studies and is frequently used to assess pain intensity via questionnaires. It was initially released in the early 1920s. It is used for adolescents older than 10 as well as adults. The gauge is supported by terms characterizing the intensity of agony. A numeric scale with 11 points, with 0 signifying no pain and 10 representing the worst agony imaginable. It measures subjective characteristics or attitudes toward pain. This scale may be administered orally, over the telephone, or in writing. The number indicated by the respondent to rate pain intensity is noted. The scores range from 0 to 10. Higher scores indicate more intense discomfort. It takes 1 minute to accomplish the scale. It is simple to administer and assess the scale. There are minimal language translation difficulties when using this scale across cultures and languages. VAS can be utilized as either a single-item scale (e.g., discomfort) or as an option for multiple-item scales. (Gillan A, et al. 2011, Kersten P, et al. 2012, Salaffi F, et al. 2004).With this scale, high test-retest reliability has been observed.VAS has shown sensitivity to variations in pain. (Joyce CR, et al. 1975, Ferraz MB, et al. 1990).

I. WESTERNONTARIOANDMCMASTERUNIVERSITIESOSTEOARTHRITISINDEX(WOMAC)

WOMAC is one of the most extensively used self-report measures of symptoms and function in the lower extremities. The scale has been examined for nearly three decades in numerous contexts and patient populations. The original purpose of the WOMAC score was to evaluate the efficacy of treatment according to the treatment method. Patients are surveyed to complete the WOMAC questionnaire, which consists of 24 questions organized into three categories of pain, rigidity, and function with a total of 96 points. Each query is worth 0 points if there is no answer.

no problem, 1 point for modest problems, 2 points for moderate problems, 3 points for severe problems and 4 points for extreme problems. Consequently, a larger WOMAC score denotes poor performance, and a score is deemed outstanding if it falls below 14, good if it falls between 15 and 28, middling if it falls between 29 and 38, and poor if it exceeds 38 points. WOMAC is available in 65 different languages. The gauge requires 12 minutes to complete. The original purpose of the WOMAC score was to evaluate the efficacy of a treatment method. The WOMAC instruments have been employed extensively in clinical trials. The sensitivity, validity, and responsiveness are well-established. (Bellamy N et, al. 1986, McConnell S et, al. 2001, Rogers JC et, al. 2003). The WOMAC questionnaire comprises of 24 questions and is completed by interviewing patients. (ANNEXURE 1)

GLOBALASSESSMENTSCALE(GAS)

The Global Assessment scale measures the patient's perception of pain as being the worst or the worst. On improvement, the patient should perceive themselves as improved. Numbered gauges are more difficult to interpret.

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Verbal evaluations have meaning and are simpler for clinicians to interpret. After receiving treatment, a patient may feel Much worse, worse, the same, or improved. Since the last visit, medication change, and the beginning of the study, global change is evaluated over a time frame that can range from one hour to one year. This scale assesses the Global impression of change (PGIC) of patients in relation to pain, function, and quality of life. This scale is capable of combining multiple crucial outcomes. It enables patients to integrate factors and provides answers to crucial clinical concerns. In clinical trials, it is a dependable and validated scale (Ehrich EW et al., 2000).
Pain was evaluated at baseline, 2 weeks, 4 weeks, and 6 weeks. The safety profile was evaluated based on ADRs reported during the study period.CBC, LFT, and RFT biochemical parameters were evaluated at baseline and 6 weeks.

STATISTICALANALYSIS

The data was presented as Mean SEM or n (percentage).The unpaired test was used for head-to-head comparisons, whereas the paired test was used to compare parameters from the baseline. The n (percent) data was expressed using the Chi-square test. P0.05 was considered to be statistically significant.
Purposes And Objectives

1. Evaluate the analgesic efficacy, tolerability, and adherence of a free drug combination (Aceclofenac followed by Diacerein) in early OA knee patients.
To assess the analgesic efficacy, tolerability, and adherence of a fixed drug combination (Aceclofenac + Diacerein) in patients with early osteoarthritis of the knee.
To compare the analgesic efficacy, tolerability, and adherence of the free drug combination (Aceclofenacfollowed by Diacerein) with the fixed drug combination (Aceclofenac + Diacerein) in patients with early osteoarthritis of the knee.
Obstruction and Outcomes
This randomized, open-label study compared the analgesic efficacy, tolerability, and compliance of a fixed drug combination (Aceclofenac + Diacerein) with a free dose combination (Aceclofenac, Diacerein) in patients with early osteoarthritis of the knee. After meeting inclusion and exclusion criteria, two hundred patients were randomly assigned to two groups, each containing one hundred patients; all patients completed the study.
Group A patients were administered a free drug combination consisting of Aceclofenac (100 mg) followed by Diacerein (50 mg) after 1 hour orally, twice daily for 6 weeks.
Group B consisted of patients who were administered a fixed dose combination of Aceclofenac (100 mg) and Diacerein (50 mg) orally twice daily for six weeks.
In conclusion, the following observations were made.

Table1:ShowingAgeDistribution

Age(years)	**Group AN=100**	**Group BN=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%)

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P=0.129,Chi –Squaretest

Fig1:ShowingAgeDistribution

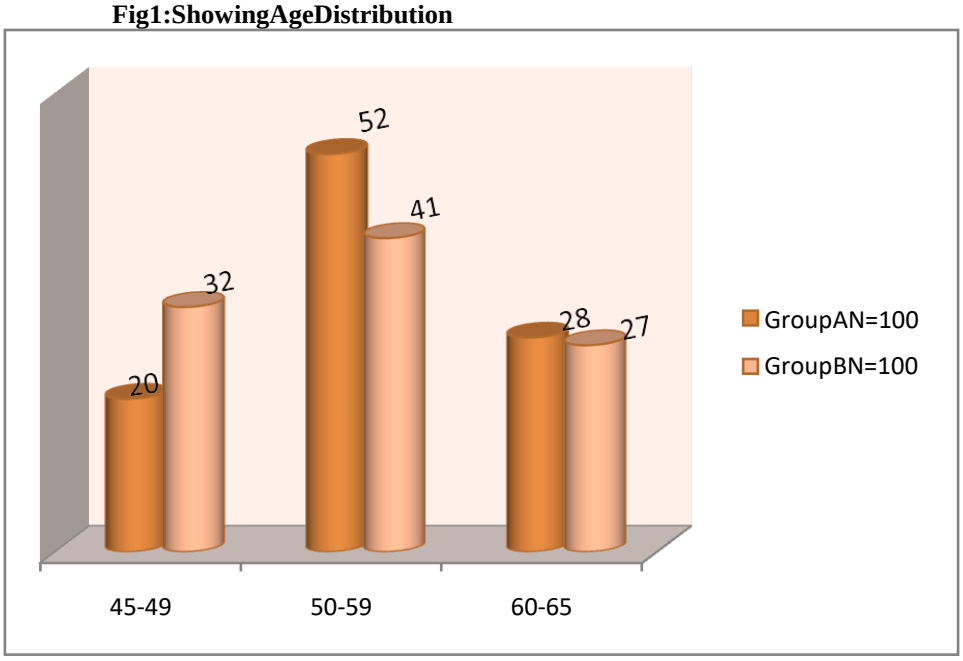

Table2:ShowingWeight(kgs)Distribution

GroupAN =100 Mean±Sd	71.58± 5.582
GroupBN =100 Mean±Sd	70.4±5.456.

Fig2:ShowingWeight(kgs)Distribution

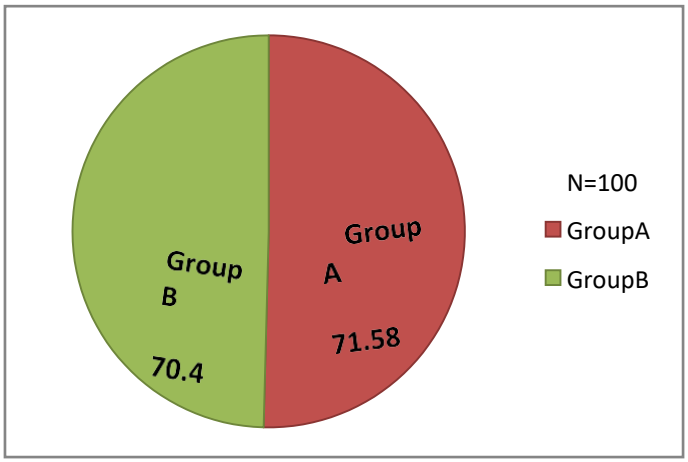

Table3:ShowingGenderDistribution

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

Fig3:ShowingGenderDistribution

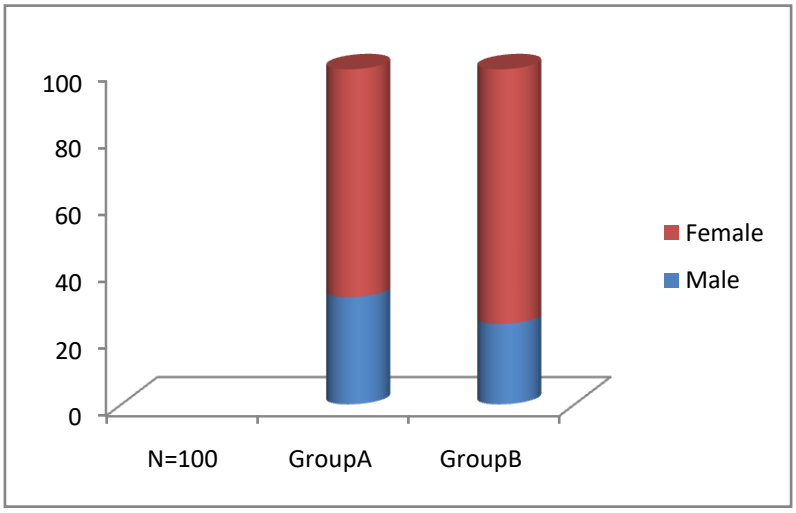

Table4:ShowingDemographicProfile

Demographic Profile	Group AN=100	Group BN=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-squaretestwithcontinuitycorrection			

Fig4:ShowingDemographicProfile

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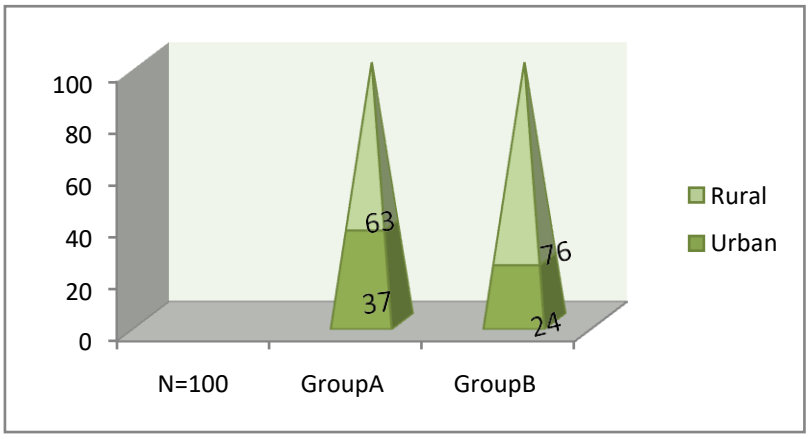

AgeDistribution

There were 52 (26%) patients between the ages of 45 and 49, 20 from Group A and 32 from Group B. Maximum 93 patients, or 46.65%, were between the ages of 50 and 59, with 52 in Group A and 41 in Group B. There were 55 patients between the ages of 60 and 69 (27.5%), and 28 and 27 patients in Group A and Group B, respectively. (Table 1)

Mass Distribution

Group A patients had an average weight of 71.58 5.582 while Group B patients had an average weight of 70.4 5.456. (Table 2)

Gender Distribution

147 (73.5%) of Osteoarthritis patients were females.There were 68 women in Group A and 79 in Group B. The total number of males was 53 (26.5%), with 32 in Group A and 21 in Group B.The ratio of men to women was 1:2.7. (Table 3)

Statistical profile

The majority of patients, 139 (69.5%), were from rural areas, with 63 in Group A and 79 in Group B. There were 61 patients from an urban background (30.5%), with 37 in Group A and 24 in Group B. (Table 4)

Table5:ShowingJointInvolvement

Jointinvolvement	**Group AN=100**	**Group BN=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%)

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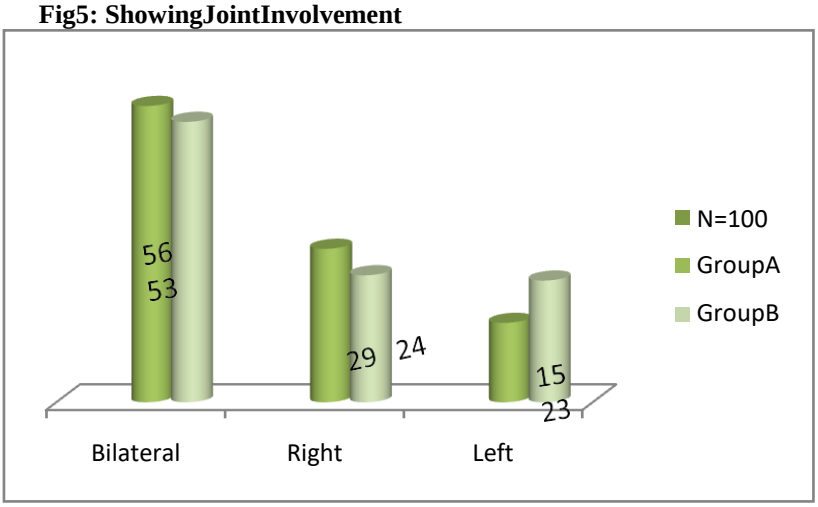
P=0.327,Chi-squaretest			

Fig5: ShowingJointInvolvement



JointInvolvement

The greatest proportion of patients, 109 (54.5%), had bilateral knee osteoarthritis. Group A had 56 patients, while Group B had 53. Osteoarthritis of the right side was more prevalent, affecting 53 patients (26.5%), including 29 in Group A and 24 in Group B. Osteoarthritis of the left side was present in 38 patients (19%), including 15 patients in Group A and 23 patients in Group B.

Table6:ShowingChiefComplaints

ChiefComplaints	**Group AN=100**	**Group BN=100**
Pain	100(100.0%)	100(100.0%)
Difficultyinsquatting	100(100.0%)	100(100.0%)
Tenderness	49(49.0%)	55(55.0%)
Painfulrangeofmovements	4(4.0%)	0(0.0%
Swelling	2(2.0%)	1(1.0%)
Crepitus	5(5.0%)	5(5.0%)

Fig6:ShowingChiefComplaints

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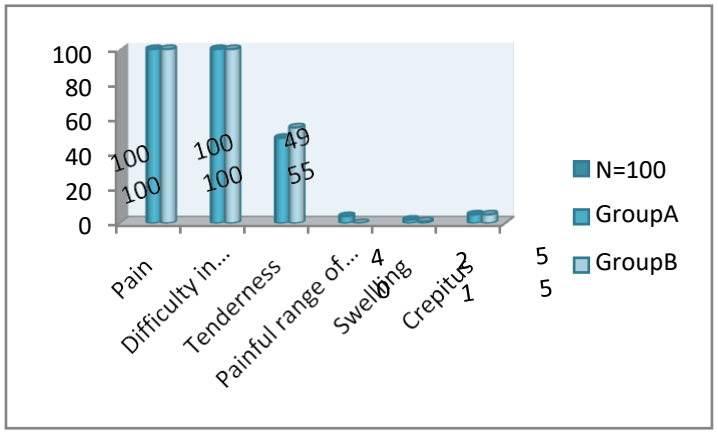

ChiefComplaint

Allpatientsinbothgroupshadpainanddifficultyinsquatting(100%).Totalof125patientscomplained of tenderness comprising of49in Group A and 55 in Group B.Painful range of movement waspresent in 4 patients of Group A only. 2 patients of Group A and 1 patient of Group B reported with swelling.Crepituswaspresentin5patientsineach group.

SCALESEVALUATINGPAINPARAMETER

VISUAL ANALOG SCALE (VAS) Visual Analog Scale is a psychometric response scale which is based onresponses to questionnairesandmeasures subjective characteristics or attitudes to pain.The two ends of scaleare graded between 10 to 0. The end with 10 gradations represents severe pain while other end graded as 0representingnopain.Shiftofresponse from10 towards0 gradesindicatedecrease inpain.

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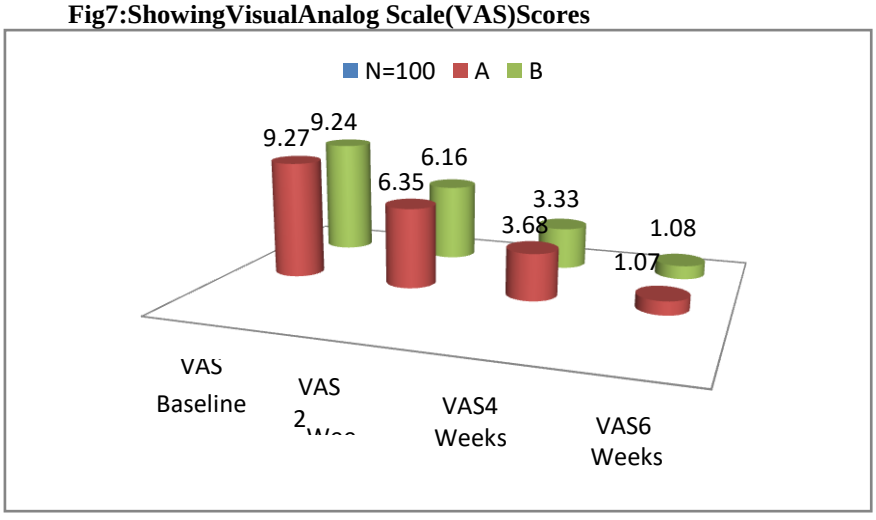
Table7:ShowingVisualAnalog Scale(VAS)Scores

Group N=100 Mean± SEM	VAS Baseline	VAS 2Weeks	VAS 4Weeks	VAS 6Weeks	
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-NonSignificant:p> 0.05vs.othergroups(usingUnpairedt-test)

Fig7:ShowingVisualAnalog Scale(VAS)Scores



Treatment in both groups lead to significant decline in pain score on VAS scale. (Group A) showedmean 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 4weeks and 1.07± 1.416 at 6 weeks. The comparison with baseline score with post drug scores at 2, 4, 6 weeksrevealed highly significant effect in reducing pain. (P < 0.0001) at all levels (Group B) revealed baselinevisualanalogscoreof9.24±155whichdecreasedto6.16±1.561at2weeks,3.33±1.436at4weeksand1.08± 1.28 at 6 weeks. Significant decline in visual analog score on comparison with baseline score was found at alllevels(P< 0.0001).

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On comparing the two groups of treatment no significantdifferenceswas seen at baseline (p=0.8521), at 2weeks (p=0.3853), at 4 weeks (p=0.0908) and at 6 weeks (p=0.9584) meaning thereby that both drug regimeswereequallyefficaciousinreducingpain.

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II. WESTERN ONTARIO AND MCMASTER UNIVERSITIESARTHRITISINDEX(WOMAC) SCALE

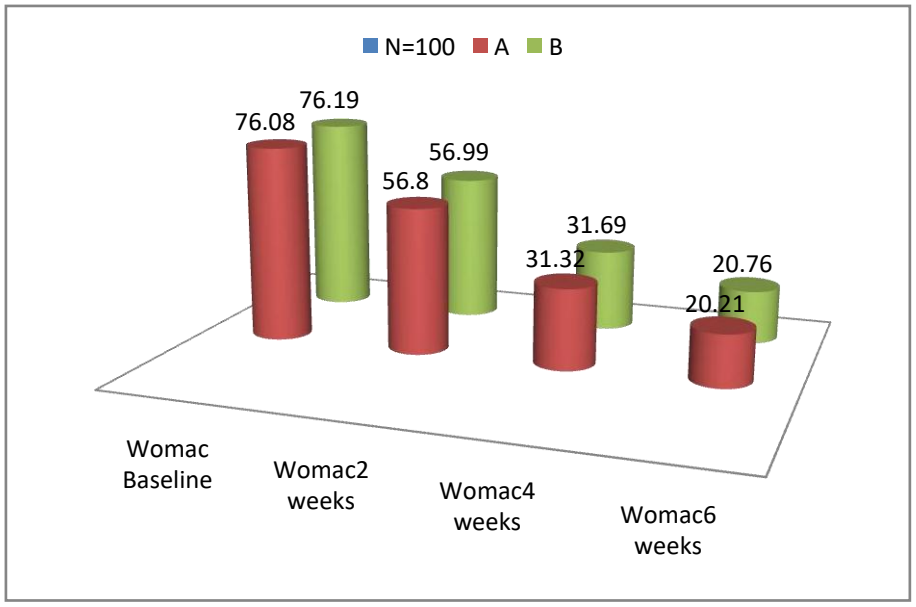
WOMAC scale is based on standardized questionnaires to evaluate the condition of patients withOsteoarthritis, including pain, stiffness and physical functioning of the joints.Womac score ranges from 0 to 96.Pain(scoreranges0-20),stiffness(score ranges0-8)andfunctionallimitation(score ranges0-68).

Table8:ShowingWomacScaleScores

GROUP N=100 Mean± SEM	Womac Baseline	Womac2 weeks	Womac4 weeks	Womac6 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(usingUnpairedt-test)

Fig8:ShowingWomacScaleScores



Womac scores revealed decrease in levels, in both groups. In (Group A), the baseline score was

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76.08±8.752which 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 groupcomparison revealedhighlysignificant effectatall postdruglevelswhen comparedwith baselinescore.(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 weeksand 20.76±.3-219 at 6 weeks. There was highly significant improvement in post drug scores when comparedwithbaseline scores.(P<0.0001).

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

DISCUSSION

Osteoarthritis (OA) is the most prevalent disease affecting the musculoskeletal system. It is a progressive degenerative disease marked by the loss of articular cartilage and the development of subchondral bone.

remodeling, osteophyte formation at the joint margins, and inflammation of the synovial membrane. The clinical manifestations include joint pain, rigidity, and immobility. After 45 years of age, 10% of males and 18% of females develop osteoarthritis. (Mobasheri A. 2013, Alhasmi AM. 2014).

There is evidence that inflammatory events accelerate the degeneration of articular cartilage, resulting in the progressive onset of joint pain, rigidity, and movement restrictions. In OA, synovial membrane (Synovitis) is the target of inflammation, and its early distribution is confined to areas adjacent to sites of chondropathy and is associated with an acceleration of cartilage degradation (chondrolysis). Inflammation is caused by cartilage matrix mettaloproteinases (MMPs) and reactive oxygen species (ROS), which result in cartilage degradation, microcrystal release, and osteochondral fragment destruction. Synovitis invades the synovial membrane and progresses to fibrosis and hypertrophy of the villi in advanced OA. Mechanical stress directly damages cartilage or activates chondrocytes to generate an anomalous level of matrix mettaloproteinases and extracellular matrix degradation products in the joint cavity (Henrotin Y, et al 2014). Leucocytes and monocytes release lysosomal enzymes and oxygen free radicals. Subchondral osteoblasts, elevated alkaline phosphatase, increased osteocalcin release, decreased parathyroid hormones and PGE-dependent cyclic AMP formation, elevated urokinase plasminogen, IGF-1, and altered collagen metabolism are a few of the alterations that occur in OA. The diseased cells produce higher levels of IL-6 and PGE2. As OA is an inflammatory condition, NSAIDs may play a role in its management by inhibiting proinflammatory mediators.

As OA is currently incurable, the primary goals of OA treatment are to alleviate pain, enhance quality of life, mobility, and walking, and slow disease progression. These goals are attainable through both non-pharmacological and pharmacological interventions. Non-pharmaceutical interventions include measures such as patient education, lifestyle modification, weight loss, and exercise. Pharmacological intervention focuses predominantly on NSAIDs and disease-modifying osteoarthritis medications (DMOADS). The treatment of knee OA should be individualized based on risk factors, pain severity, and other factors. If efficacious, NSAIDs are beneficial for long-term use. If NSAIDs fail to alleviate pain, opioid analgesics can be used effectively. DMOAD or SYSADOA are also effective in symptomatic treatment, with the added benefit of preventing disease progression. Corticosteroid intra-articular injection is recommended for the treatment of joint effusion and severe pain (Joern M, et al., 2010). In the event that these treatment modalities fail, invasive interventions such as lavage or arthroplasty may be considered.Among all conservative medications used to treat OA knee, NSAIDs are the most commonly prescribed. (Lansas A, et al. 2011). In addition to having detrimental long-term effects on cartilage and the gastrointestinal tract, these medications provide symptomatic relief rather than preventing the progression of disease.

Recently, agents that provide symptomatic alleviation by targeting underlying pathology in cartilage and subchondral bone and slow the progression of the disease have been developed. These medications are categorized as disease-modifying osteoarthritis drugs (DMOAD). They are anticipated to retard, stabilize, or even rectify pathological changes that occur in OA, thereby limiting disease progression.

Inadequate adherence to medication regimens, particularly in the case of chronic diseases, negatively affects the clinical outcome, as the anticipated benefits may not be realized. Fixed dose combinations (FDCs) are advantageous and crucial in the fight against chronic diseases because they substantially reduce noncompliance. In addition, FDC products have the potential for increased clinical efficacy due to the additive effects of each active ingredient, which may even allow for a reduction in the dose of each active ingredient and a consequent reduction in adverse effects. The FDA defines Fixed dose combination as a product composed of any drug, device, or biological product (Sreedhar D, et al., 2006). Fixed dose combination are acceptable only when the dosage of each ingredient meets the requirements of a defined population group and when the combination has an advantage over a single compound administered separately in terms of therapeutic effect, safety, or compliance. (Chandler SG, et al., 2008).The rationality of FDC should be determined by a number of factors. (Poudel A, et al. 2008). The drugs should act by distinct mechanisms when combined. Pharmacokinetics must not differ significantly. The combination should not increase the toxicity of the constituents. It would be preferable if one ingredient neutralized the toxicity of the other.

Studies have compared the efficacy and safety of various FDCs (Sripal B, et al. 2007, Bhavik D, et al. 2012).However, no study has 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.

In light of the foregoing, the current study was designed to compare the efficacy, tolerability, and compliance of the most commonly used Fixed dose combination of NSAID (Aceclofenac) and DMOAD (Diacerein) with the Free drug combination of Diacerein and Aceclofenac when taken 1 hour apart in patients with early osteoarthritis of the knee. In this investigation, 200 patients with early knee OA were diagnosed according to EULAR guidelines. (Johanne M, et al. 2010) were enrolled. These patients were assigned randomly to two categories, Group A

Patients in Group (A) received a free drug combination of Aceclofenac (100mgs) and Diacerein (50mgs) taken 1 hour apart twice daily orally for 6 weeks, whereas patients in Group (B) received a fixed dose combination of Aceclofenac (100mgs) and Diacerein (50mgs) twice daily orally for 6 weeks.

According to the findings of the present investigation, the greatest number of patients fell between the ages of 50 and 59. These trends mirrored those of Torri G et al. (1994), who found that the average age of OA Knee patients was between 56.72 10.66 and 57 10.10. Patil PR, et al. (2012) reported similar findings, where the average age of patients ranged from 52.80 4.55 to 53.61 5.50. Kurubaran G, et al. (2014) estimated Prevalence of 70%-80% of OA in populations aged 55 years and older.Awan MMY, et al. (2014) also demonstrated that the average age of patients is between 56.04 10. 78 to 56.35 8.51 due to knee OA.

OA is characterized as the aging disease. Joints age and become susceptible to OA. The capacity of the body to restore cartilage declines with age because osteoarthritic cartilage is chemically distinct from normal cartilage of the same age. As chondrocytes age, they lose the capacity to produce more cartilage and make repairs. This process plays a significant role in the progression and development of OA.

In the present study, the average weight of Group A patients was 71.5 5.582, while that of Group B patients was 70.4 5.454. These findings are comparable to those of Torri G, et al. (1994) and Pham T, et al. (2004).The body weight of patients in the first study ranged from 70.52 10.49 to 71.48 9.04, whereas the weight of patients in the second study ranged from 76.814.0 to 78.0 13.9.

The relationship between Body Mass Index (BMI) and knee osteoarthritis (OA) is extremely significant, as knee OA has a strong correlation with the highly inflammatory metabolic environment associated with obesity. Adiponectine, leptine, and resistine, cytokines associated with adipose tissue, can influence OA through the direct degradation of articular cartilage or by regulating local inflammatory processes. Obesity increases joint mechanical tension. In contrast, weight loss decreases pain and enhances physical function in OA patients. (Marcia UDR, et al. 2013).

In the present investigation, a Male:Female Ratio of 1:2.7 was discovered to affect females more than males. Torri G, et al. (1994), Guaida EB, et al. (2007), Awan MMY, et al. (2014), and Moon YW, et al. (2014) all reported findings indicating a higher incidence of OA in females, spanning between 52 and 87%. Female gender is at higher

risk for developing OA. The higher prevalence of OA in women is due to hormonal factors that affect women during menopause. Women with co morbid osteoporosis are also more likely to develop OA. (Zhuo Q, et al. 2012).

The demographic profile of rural populations revealed a higher prevalence of OA than urban populations. In their respective investigations, Andrianakos AA, et al. (2006) and Xiaozheng K, et al. (2009) found comparable outcomes. It may be explained by the fact that people in rural locations perform physically demanding tasks. Knee osteoarthritis has been linked to jobs requiring knee flexion, squatting, kneeling, and hard hauling, with obesity increasing the risk. Frequently, joint cartilage deteriorates due to mechanical stress or biochemical alteration, causing the underlying bone to fail.

In the current investigation, bilateral involvement of Joints was more common in both categories. In both groups, the right joint was engaged more in unilateral OA. These results are comparable to those of Joren W. et al. (2010), in which the prevalence of OA in the right knee was 23% compared to 16.3% in the left knee.

Patients in both groups reported pain, difficulty squatting, tenderness (49% in Group A and 55% in Group B, respectively), excruciating range of motion (4% in Group A only), and edema (2% in Group A and 1% in Group B, respectively). These findings are consistent with those of Dilip KR, et al. (2010), in which patients complained of knee pain, bony tenderness, swelling, and difficulty squatting (stiffness).Results of study conducted by Alhasmi AM.(2014) are consistent with our findings, as patients reported knee pain, bony swelling, bony tenderness, and stiffness.

Routine hematological and biochemical parameters measured at the beginning and conclusion of the study showed no significant differences between the two groups. Similar results were observed in the study by Bhavik D., et al. (2012).This demonstrated that all patients in both groups tolerated their respective drug regimens well for the entire 6-week study period.

During the study period, there were 12 adverse drug reactions. In Group A, there were seven ADRs while in Group B, there were five. Sharma A, et al. (2008), Brahmachari B, et al. (2009), and Dilip K, et al. (2010) reported similar findings. All patients completed the study showing that ADRs were clinically insignificant (P=0.766) conducted by Patil PR et al. in 2012.

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 present study, compliance was evaluated by comparing the Complete Adherence Rate/Incomplete Adherence Rate and Switch to Other Medication, which was assessed by follow-up, pill count, or telephone. In this investigation, 100 percent adherence was observed. Neither discontinuation of treatment nor switching to an alternate medication was observed during the course of the study.

In the present investigation, pain parameters improved on the Visual analog scale, Womac scale, and Global assessment scale for both groups. Post-drug values decreased at all levels in both groups (P 0.0001)

On all scales, however, there was no statistically significant difference between the two drug regimens when compared between groups (P value > 0.05).

Aceclofenac and Diacerein have not been compared in either a fixed dose combination or a free drug combination in any published study. However, a number of studies have compared the investigated substances to other analgesics.

Various authors have reported that aceclofenac is effective at alleviating pain, as evidenced by findings on the VAS scale, WOMAC scale, and Global assessment scale. Torri G, et al. (1994) demonstrated that it is more efficacious

than Piroxicam. Nabumetone (Paul S, et al. 2009). Diclofenac (Ward DE et al. 1995.Pareek A et al. 2006. Patil PR et al. 2012. Pareek A et al. 2013. Chandurkar N et al. 2014). Ibuprofen (Klair JP. 2009).Paracetamol (Guaida EB, et al. 2007). Celecoxib (Soria MA, et al. 2006).

Aceclofenac's superiority is attributable to its stimulatory effects on cartilage matrix synthesis by inhibiting IL-.There is evidence that Aceclofenac stimulates IL-1 receptor antagonist in human articular chondrocytes subjected to inflammatory stimuli and has chondroprotective properties due to suppression of IL- 1-mediated promatrix metalloproteinase production and proteoglycan release. Aceclofenac stimulates glycosaminoglycan synthesis in OA cartilage, thereby preventing its degeneration. By easily penetrating inflammatory tissue, such as joint tissue, and inhibiting prostaglandin production, aceclofenac demonstrates outstanding therapeutic effects. Aceclofenac selectively inhibits COX-2 without impacting gastric mucosal prostaglandin production, thereby diminishing GIT adverse effects and promoting a high tolerance. Therefore, Aceclofenac has been deemed suitable for long-term use.(Hinz B, et al. 2003 Gowda KV, et al. 2006).Aceclofenac reduces pain, symptomatic severity, and enhances the functional capacity of injured joints, particularly in cases of knee osteoarthritis.(Dooley M, et al. 2001).

It has been shown to be more effective than placebo (Pham T,et al. 2004; Brahmachari B, et al. 2009; Bartels EM, et al. 2009; Dilip KR, et al. 2010). (Louthrenoo W, et al., 200) Piroxicam.Aceclofenac (Loitongbam LSS, et al. 2013).

Diacerein's anti-inflammatory effect can be explained by its inhibition of interleukin-1B. Diacerein reduces fibrinolytic synovial fibroblasts and inhibits chemotaxis and super oxide anion production. Diacerein inhibits the enzyme collangenase in intraarticular cartilage, which is produced during destructive inflammation. Diacerein is an IL-1 inhibitor with structure-modifying properties in OA. Both osteoblasts and osteoclasts contribute significantly to bone remodelling. If the activity of two cells is dissimilar, bone formation is altered. Diacerein and Rhein inhibit MMP-13 and Cathepsin K in osteoclasts (Boileau et al., 2008).MMP-13 and Cathepsin K function together in bone resorption. A decrease in the activity of these enzymes causes an imbalance in bone formation and resorption. Diacerein and Rhein inhibit the survival of mature osteoclasts, proliferation and differentiation of pre-osteoclasts into mature osteoclasts, and osteoclast number. This effect of Diacerein is due to 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.

As pain has a negative impact on productivity, it should be treated promptly and effectively to restore the patient to full function and preserve their quality of life. There are a number of analgesics that combine two agents into a single fixed dose. When two analgesics are combined, their effects may be additive or synergistic. This can enhance the analgesic effectiveness of the medications. When the individual agents have distinct analgesic mechanisms and act synergistically, a combination analgesic regimen may be deemed particularly effective. These fixed dose combinations are convenient, reduce the tablet burden, and may necessitate reduced doses of the constituent compounds.

Several studies (Choi, et al. 2007, Corsinovi, et al. 2009, Pareek, et al. 2010, Doherty, et al. 2011) have demonstrated the efficacy and tolerability of fixed dose combinations in OA knee (Corsinovi, et al. However, research evaluating the FDC of Aceclofenac and Diacerein is limited. A literature search revealed a solitary study comparing the FDC of Aceclofenac and Diacerein on pain parameters with the FDC of Celecoxib and Diacerein (Bhavik D, et al., 2012). The FDC of Aceclofenac + Diacerein showed improvement in pain, as all 13 patients who completed the study reported an excellent response to the drug regimen. We have not come across a single study that compares the Fixed drug combination of Aceclofenac and Diacerein with the Free drug combination of Aceclofenac and Diacerein. In this study, we compared the Fixed dose combination to the Free drug combination of these medications. Such a study could have determined the efficacy, safety, and compliance advantages or disadvantages of FDC Aceclofenac and Diacerein over the free drug combination. The current study failed to demonstrate superiority of either group over the other in patients with early osteoarthritis of the knee, indicating that the current FDC of (Aceclofenac + Diacerein) is not being marketed irrationally.

From the foregoining discussion we conclude that FDC of Aceclofenac and Diacerein when comparedwith Free drug combination of Aceclofenac and Diacerein given for 6 weeks in patients of early OA

knee havesimilarclinicaloutcome inefficacy, safetyandcompliance.

CONCLUSION

In patients with early osteoarthritis of the knee, both the free drug combination (Aceclofenac, Diacerein) and the fixed dose combination (Aceclofenac + Diacerein) exhibited comparable efficacy, tolerability, and compliance. None of the pharmacological regimes demonstrated superiority.

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